The Insulin Sensitivity Mcauley Index (Mcai) is Associated with 40-Year Cancer Mortality in a Cohort of Men and Women Free of Diabetes at Baseline

Yonatan Moshkovits

Sheba Medical Center at Tel Hashomer: Sheba Medical Center

David Rott

Sheba Medical Center at Tel Hashomer: Sheba Medical Center

Angela Chetrit

Gertner Institute for Health Policy and Epidemiology

Rachel Dankner (✉ racheld1963@gmail.com)

Gertner Institute for Health Policy and Epidemiology <https://orcid.org/0000-0001-6454-6000>

Research

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Abstract

Background: The association between insulin resistance and cancer mortality is not fully explored. We investigated the association between several insulin sensitivity indices (ISIs) and cancer mortality in a cohort of adult men and women free of diabetes. We hypothesized that higher insulin resistance (Q_1 of the McAuley index (MCAi), calculated by fasting insulin and triglycerides, and Q_4 of the Homeostatic Model Assessment (HOMA), calculated by fasting plasma glucose and insulin) will be associated with greater cancer mortality risk.

Methods: A cohort of 1612 men and women free of diabetes during baseline were followed since 1979 through 2016 for cause specific mortality as part of the Israel study on Glucose Intolerance, Obesity and Hypertension (GOH).

Results: Mean age at baseline was 51.5 ± 8.0 years, 804 (49.9%) were males, and 871 (54.0%) had prediabetes. Mean follow-up was 36.7 ± 0.2 years and 47,191 person years were accrued. Cumulative incidence analysis using Cox proportional hazard model and competing risks analysis adjusted for age, sex, country of origin, BMI, blood pressure, total cholesterol, smoking and glycemic status (table 2), revealed an increased risk for cancer death, sub-distribution HR=1.4 (95% CI: 1.1-1.9, $p=0.02$) for individuals in the lower quartile of MCAi (Q_1), denoting higher insulin resistance, compared with the upper quartiles (Q_{2-4}). No statistically significant association was observed between the other insulin resistance surrogates and cancer death.

Conclusion: The MCAi was found to independently associate with an increased risk for cancer mortality in adult men and women free of diabetes. The MCAi may be considered as a long-term prognostic biomarker in diabetes-free adults.

1. Introduction

Cancer remains one of the most common causes for morbidity and mortality in the US and worldwide (1,2). Worldwide, 9.5 million cancer-related deaths were reported in 2018 (3).

In the US, cancer incidence is approximately 442.4 per 100,000 per year (2) and although declining, cancer death rate is 158.3 per 100,000 per year, placing it as the second most common cause of death in the US (1). According to predictions, 606,520 people died from malignancy in the US during 2020. In Israel cancer is also a leading cause of death with 13,050 deaths (25.4% of all cases of death, cumulative risk 9.09) reported in 2018 (4). A number of factors were associated with cancer incidence and carcinogenesis such as smoking (5), Body Mass Index (6), diabetes (7) and sedentary lifestyle (8).

The association between insulin resistance (IR) and cancer remain uncertain. Metabolic alterations were previously found to correlate with both IR and cancer through dietary risk factors (e.g. hypercaloric diet, low fibers etc.) that induces inflammation and oxidative stress, or promote IGF-1 secretion that acts as a

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 that in susceptible individuals, metabolic

abnormalities such as obesity, IR and dyslipidemia would be the initial manifestation of unhealthy diets and lifestyle, whereas carcinogenesis is more prolonged with delayed clinical manifestations (10). A wide epidemiological evidence is showing that diabetes is strongly associated with specific types of cancer (6), mainly pancreatic and liver cancer (11) and the American Diabetes Association and the American Cancer Society issued a consensus report on diabetes association with cancer incidence (12). Nevertheless, the nature of this association is yet to be clarified, and there is a possibility of an indirect association, underlined by the hyperinsulinemic state or by glucose lowering medication use in addition to common risk factors such as obesity (13–15).

The associations between type 2 diabetes, IR and increased fasting glucose plasma levels with malignancy associated mortality were demonstrated in a number of studies (15,16), however these studies were mostly on diabetic participants or with a short follow up period. Furthermore other studies on diabetic participants including meta-analyses did not show such an association with cancer mortality (17).

Insulin resistance can be evaluated indirectly via validated indices, calculated using insulin and glucose blood levels (18–21). Frequently examined indices include the Homeostatic model assessment (HOMA) (21), the Matsuda Insulin Sensitivity Index (MISI) (18), the Quantitative Insulin Sensitivity Check Index (QUICKI) (20) and the McAuley index (MCAi) (19). Albeit values of insulin sensitivity indices (ISIs) denoting IR were associated with an increased risk for specific types of cancer, e.g. prostate (22) and endometrial cancer (23), such an association with malignancy associated mortality is still not established, with contradicting results (16,24,25).

This study aimed to investigate the association between insulin resistance surrogates, i.e. fasting insulin and glucose plasma levels and ISIs, with cancer mortality in an Israeli cohort study-the Glucose Intolerance, Obesity and Hypertension (GOH) study over a 40-year follow-up.

2. Materials And Methods

2.1 Study design and population:

Study population was previously described (26). The cohort was part of the second stage of the Glucose Intolerance, Obesity and Hypertension (GOH) study (27). The study is an ongoing prospective longitudinal study, initially began on 1967 and included a total of 8400 Israeli Jews, stratified according to sex, ethnicity as determined by country of birth or that of the mother for Israeli born (Yemenite, Asian, North Africans, and European-North Americans) as well as birth decade (1912-1921; 1922-1931; 1932-1941). The second phase was performed between 1979 and 1982 and included anthropometric measurements, blood tests and in particular fasting glucose and insulin plasma levels taken during oral glucose tolerance test (OGTT).

Participants with both fasting glucose and insulin plasma levels and free of diabetes were included in the Loading [MathJax]/jax/output/CommonHTML/fonts/TeX/fontdata.js ants who met the inclusion criteria out of 2769

participants primarily examined in the second phase. Information regarding the GOH population and methodology is further detailed elsewhere (24, 27).

Blood glucose was measured using the automated Technicon Autoanalyser II (Technicon Instruments Corp, Tarrytown, NY); Blood insulin was measured using the Phadebas Radioimmunoassay kit (Pharmacia Diagnostics Inc. Piscataway, NJ). Blood test analysis was performed by a single laboratory.

Participants were followed until December 2016 for malignancy associated mortality. Participant's approval was obtained a priori and the study protocol was approved by the Sheba Medical Center's IRB.

2.2 Insulin resistance:

The current study examined IR state as reflected by the following IR surrogates and ISIs: Fasting insulin and glucose plasma levels: both were categorized into quartiles and the upper quartile (Q_4) was compared to lower quartiles (Q_{1-3}) as with the ISIs.

ISIs were calculated as follow (18–21, 28):

Homeostatic model assessment (HOMA)-Insulin resistance (IR) and beta cell function (%B) (21), were calculated as follows:

$$\text{HOMA1 - IR} = \text{FPI} \times \frac{\text{FPG}}{405}$$

$$\text{HOMA1 - \%B} = 360 \times \frac{\text{FPI}}{(\text{FPG} - 63)}$$

Matsuda Insulin Sensitivity Index (MISI) (18):

$$\text{MISI} = \frac{10,000}{\sqrt{(\text{FPG} \times \text{FPI}) \times [\text{mean glucose during OGTT} \times \text{mean insulin during OGTT}]}}$$

MISI mean glucose was calculated using glucose taken at 0, 60 and 120 minutes after an ingestion of 100 gr of glucose during an OGTT. Mean insulin was calculated using insulin taken at 0, 30, 60 and 120 minutes during the OGTT.

Quantitative Insulin Sensitivity Check Index (QUICKI) (20) was calculated as follows:

$$\text{QUICKI} = \frac{1}{\text{LogFPI} + \text{LogFPG}}$$

Mcauley index (MCAi) (19) was calculated as follows:

$$\text{MCAi} = e^{[2.63 - 0.28 * \text{LnFPI} - 0.31 * \text{Lntrig}]}$$

Were FPI refer to fasting insulin levels in $\left[\frac{\text{mU}}{\text{L}}\right]$; FPG refer to fasting glucose levels in $\left[\frac{\text{Mg}}{\text{dl}}\right]$; Trig refer to fasting triglycerides levels in $\left[\frac{\text{mMole}}{\text{L}}\right]$.

ISIs that were not normally distributed were logarithmically transformed using natural log (ln). Lower values of HOMA-%B, MISI, QUICKI and MCAi, and higher values of HOMA-IR depicts insulin resistance.

2.3 Death from cancer:

The primary outcome was a 40-year mortality rate due to malignancy, reported as the primary cause of death, using the International Classification of Diseases (ICD) 9 or ICD 10. Mortality date was reported by the Israeli population registry through December 2016. Surveillance period started on the examination date during phase 2 and ended at the end of the follow-up or death- earliest of these.

2.4. Statistical methods

Chi square test or Fisher's exact test for small cells were performed in order to evaluate differences among ISI quartiles. One-way ANOVA test for normally distributed variables or the Kruskal Wallis test for nonparametric variables were used for continuous covariates, with two-sided p-values (p) set at the 0.05 level of significance in order to evaluate differences between those who remained alive, those who died from cancer and those who died from other causes by the end of the follow-up. The association between ISIs and 40-year malignancy associated mortality rate were examined for cumulative incidence analysis using the Cox proportional hazards model. Study participants were censored at the time of non-cancer deaths or by the end of follow-up, whichever came first. An additional approach used death from non-cancer causes as a competing risk to cancer death (the Fine and Gray method (29)) by calculating the sub-distribution hazard ratio (SHR). This method is based on the Cumulative Incidence Function (CIF) that counts failures from competing events and deaths from the primary endpoint, whereas the competing events in the cumulative incidence method are censored. Each insulin resistance surrogate was evaluated in a separate model. In order to avoid multicollinearity, Spearman's rank correlation coefficient test was performed, excluding covariates with a correlation of 60% or above from the same model. Survival analysis was performed according to cause specific mortality (i.e. deaths from cancer vs survival and non-cancer deaths). Models were adjusted for demographic variables as for known mortality risk factors such as smoking status, blood pressure, BMI, cholesterol and diabetes status. Models are presented with Hazard Ratio (HR) or SHR with 95% confidence intervals (95%CI). The proportional hazards assumption was tested using the log minus log plot and by constructing an interaction variable composed of time-to-event multiplied by the covariate and entering it into the model.

Kaplan Meier survival curves for insulin resistance surrogates were compared using the log-rank test.

Statistical analysis was performed using SPSS version 25.0.

3 Results

3.1. Baseline characteristics:

A total of 1612 subjects were followed until December 2016 for malignancy associated mortality. Table 1 describes the cohort baseline characteristics according to survival status and cause of death. Mean age at baseline was 51.5 ± 8.0 years, 804 (49.9%) were males, 227 (14.1%) were obese (Body Mass index of $\geq 30 \text{ kg/m}^2$) and 871 (54.0%) were diagnosed with prediabetes prior to enrolment.

Table 1

Characteristics of 1,612 men and women free of diabetes at baseline (1979) according to vital status by the end of follow-up (2016)

Baseline characteristic	Vital status by end of follow-up*				P-value
	Total N (%)	Alive Mean $\pm$ SD	Cancer death Mean $\pm$ SD	Non-cancer death Mean $\pm$ SD	
Number	1612	642	264	706	
Age (years), mean $\pm$ SD	51.4 $\pm$ 8.0	46.3 $\pm$ 5.9	53.3 $\pm$ 7.6	55.3 $\pm$ 7.2	<0.001
Sex					<0.001
Male	804 (49.9)	274 (42.7)	149 (56.4)	381 (54.0)	
Female	808 (50.1)	368 (57.3)	115 (43.6)	325 (46.0)	
Origin					0.6
Middle East	428 (26.6)	172 (26.8)	69 (26.1)	187 (23.7)	
North Africa	288 (17.9)	111 (17.3)	48 (18.2)	129 (18.3)	
Yemen	351 (21.8)	134 (20.9)	50 (18.9)	167 (23.7)	
Europe-America	545 (33.8)	225 (35.0)	97 (36.7)	223 (31.6)	
Smoking status ^a					0.05
Ever smoked	634 (39.3)	234 (36.4)	119 (45.1)	281 (39.8)	
Never-Smoker	978 (60.7)	408 (63.6)	145 (54.9)	425 (60.2)	
Glycemic state					<0.001
Normoglycemia	741 (46.0)	346 (53.9)	116 (43.9)	279 (39.5)	
Prediabetes	871 (54.0)	296 (46.1)	148 (56.1)	427 (60.5)	
Blood Pressure (mmHg), mean $\pm$ SD					
Systolic	130.4 $\pm$ 25.7	122.3 $\pm$ 23.6	132.8 $\pm$ 25.1	136.8 $\pm$ 25.7	<0.001
Diastolic	83.4 $\pm$ 14.8	80.6 $\pm$ 15.2	83.5 $\pm$ 12.9	85.9 $\pm$ 15.2	<0.001
Systolic & Diastolic ^b					
Normal	926 (57.4)	454 (70.7)	151 (57.2)	321 (45.5)	<0.001

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Vital status by end of follow-up*					
Intermediate	313 (19.4)	106 (16.5)	52 (19.7)	155 (22.0)	
Hypertension	373 (23.1)	82 (12.8)	61 (23.1)	230 (32.6)	
BMI (Kg / m ²) ^c , median [IQR]	25.3 [4.9]	24.8 [4.1]	25.3 [5.0]	26.0 [5.3]	<0.001
Normal	735 (45.6)	333 (51.9)	121 (45.8)	281 (39.8)	<0.001
Overweight	650 (40.3)	248 (38.6)	109 (41.3)	293 (41.5)	
Obese	227 (14.1)	61 (9.5)	34 (12.9)	132 (18.7)	
Fasting glucose (mg/dl)	97.8 ± 10.2	96.3 ± 9.7	98.4 ± 10.8	98.9 ± 10.3	<0.001
Q ₁₋₃	1108 (68.7)	472 (73.5)	175 (66.3)	461 (65.3)	0.003
Q ₄	504 (31.3)	170 (26.5)	89 (33.7)	245 (34.7)	
Fasting insulin (mU/L)	15.5 ± 10.4	14.9 ± 10.6	15.5 ± 8.8	15.9 ± 10.8	0.001
Q ₁₋₃	1191 (73.9)	491 (76.5)	189 (71.6)	511 (72.4)	0.2
Q ₄	421 (26.1)	151 (23.5)	75 (28.4)	195 (27.6)	
Total cholesterol ^d (mg/dl), mean ± SD	220.5 ± 54.1	216.3 ± 52.5	216.9 ± 54.5	225.7 ± 55.1	0.003
Normal	525 (32.7)	222 (34.6)	96 (36.4)	209 (29.6)	0.06
Borderline-high	501 (31.1)	208 (32.4)	77 (29.2)	216 (30.6)	
High	584 (36.2)	212 (33.0)	91 (34.5)	281 (39.8)	
Triglycerides (mg/dl), median [IQR]	110 [70]	100 [70]	120 [75]	115 [75]	<0.001
MISI †, median [IQR]	3.6 [2.3]	3.5 [2.2]	2.9 [2.1]	3.2 [2.2]	0.3
Ln MISI, mean ± SD	1.3 ± 0.5	1.2 ± 0.5	1.1 ± 0.6	1.1 ± 0.5	0.4
Q ₁	273 (27.7)	87 (21.0)	47 (28.8)	112 (27.5)	0.2
Q ₂₋₄	709 (72.1)	327 (79.0)	116 (71.2)	295 (72.5)	
HOMA-IR ‡, Median [IQR]	3.1 [2.1]	3.0 [2.0]	3.1 [2.2]	3.3 [3]	0.02
Ln HOMA-IR, mean ± SD	1.1 ± 0.6	1.1 ± 0.5	1.2 ± 0.6	1.2 ± 0.6	0.04
Q ₁	1000 (75.5)	500 (78.2)	192 (72.7)	515 (72.9)	0.06

Vital status by end of follow-up*					
Q ₄	403 (25)	140 (21.8)	72 (27.3)	191 (27.1)	
HOMA-%B §, Median [IQR]	142.3 [100.5]	143.3 [105.0]	145.9 [110.2]	140.1 [95]	0.7
Ln HOMA-%B, mean ± SD	4.9 ± 0.6	5.0 ± 0.6	4.9 ± 0.6	4.9 ± 0.6	0.7
Q ₁	402 (24.9)	153 (23.8)	74 (28.0)	175 (24.8)	0.4
Q ₂₋₄	1208 (74.9)	489 (76.2)	190 (72.0)	529 (74.9)	
QUICKI ¶, mean ± SD	0.32 ± 0.03	0.32 ± 0.02	0.32 ± 0.03	0.32 ± 0.03	0.09
Q ₁	401 (24.9)	140 (21.8)	71 (26.9)	190 (26.9)	0.06
Q ₂₋₄	1208 (74.9)	502 (78.2)	192 (72.7)	514 (72.8)	
MCAi, ¥ mean ± SD	3.9 ± 0.9	4.0 ± 0.9	3.9 ± 0.9	3.9 ± 0.9	0.006
Q ₁	395 (24.5)	137 (21.3)	77 (29.2)	181 (25.6)	0.02
Q ₂₋₄	1187 (73.6)	499 (77.7)	182 (68.9)	506 (71.7)	
Between-group differences (alive vs cancer death vs non-cancer deaths) of categorical variables were examined using Chi square test or Fisher's exact test for small cells. Between-group differences of continuous variables were examined using student one-way Anova test for normally distributed variables or the Kruskal Wallis test for nonparametric variables, with two-sided p-values (p) set at 0.05 level of significance.					
‡ HOMA-IR, Homeostatic model assessment -Insulin resistance; § HOMA-%B - Homeostatic model assessment – percent beta cell function; † MISI, Matsuda Insulin Sensitivity Index; ¶ QUICKI, Quantitative Insulin Sensitivity Check Index; ¥ MCAi, Mcauley index.					
^a Smoking status classification: Smoker-currently or past smoker. Nonsmoker-never smoked; ^b Blood pressure categories: Normal, systolic BP <140 mmHg and diastolic BP < 90 mmHg, Intermediate, systolic BP ≥ 140 mmHg or diastolic BP ≥ 90 mmHg, Hypertension, systolic BP ≥ 140 mmHg and diastolic BP ≥ 90 mmHg; ^c BMI categories: Normal < 25 kg/m ² , Overweight, 25-29.9 kg/m ² , Obese- BMI ≥ 30 kg/m ² ; ^d Total cholesterol classification: Normal < 200 mg/dl, Borderline-high, 200–239 mg/dl, High ≥ 240 mg/dl.					

3.2 Cancer related mortality:

Participants were followed until December 2016 for malignancy associated mortality, with a mean follow up of 36.7±0.2 years. During that period, 47,191 person years were accrued, and 970 (60.2%) participants died. Cancer related mortality was the second most frequent cause of death, being the primary cause in 264 (16.4%) participants and in additional 15 participants as the secondary cause.

As presented in Table 1, only origin did not showed a significant difference between vital status groups. Prediabetes was found in 148 (56.1%), 427 (60.5%) and 296 (46.1%) individuals who died from cancer, from other causes, and survivors respectively. Compared to survivors, individuals who died from cancer were predominantly males, smokers and pre-diabetic, with increased blood pressure and BMI as well as with an increased fasting glucose, fasting insulin and total triglycerides plasma levels. Individuals who died were more frequently found in the IR quartiles of Ln MISI, Ln HOMA-IR, Ln HOMA-%B, QUICKI and MCAi.

Individuals who died from other, non-cancer related, primarily cardiovascular causes, were older ($P<0.001$), with increased systolic ($P=0.03$) and diastolic ($P=0.02$) blood pressure, as well as higher total cholesterol ($P=0.03$) compared with individuals who died from cancer (not shown).

Table S-1 [see Additional file 1] describes the distribution of site specific cancer deaths. Almost 1/3 of all malignancies were of the digestive system (35.7%), followed by cancer of the genitourinary system, mostly prostate, then by lung cancer, non-solid tumors, and breast cancer.

The univariate analysis revealed that age, sex, smoking, hypertension, Ln-MISI and MCAi were significantly associated with cancer specific mortality (Table 2). The adjusted multivariable analysis (for age, sex, origin, BMI, blood pressure, cholesterol, smoking and diabetes status) revealed a significantly higher risk for cancer mortality for individuals in the MCAi Q_1 , HR=1.5 (95% CI 1.1-2.0, $p=0.004$), as compared with the MCAi Q_{2-4} .

Table 2

Cox regression models for associations between baseline characteristics of 1,610 men and women free of diabetes at baseline and cancer mortality over a mean follow-up of 36.7 years

Cancer mortality				
Characteristic	Reference category	Univariate HR (95% CI)	Multivariate ^a HR (95% CI)	Competing risk Multivariate ^b SHR (95% CI)
Age	10-year increment	2.1 (1.8-2.5)	2.2 (1.9-2.6)	1.5 (1.3-1.7)
Sex, Male	Female	1.5 (1.2-1.9)	1.3 (0.97-1.7)	1.2 (0.9-1.6)
Origin	Yemen			
Middle East		0.9 (0.6-1.2)	0.9 (0.6-1.2)	0.9 (0.7-1.3)
North Africa		0.9 (0.6-1.2)	0.98 (0.7-1.3)	0.99 (0.7-1.4)
Europe-America		0.96 (0.7-1.4)	1.0 (0.7-1.5)	0.8 (0.6-1.1)
Smoking status, Ever	Never	1.3 (1.0-1.7)	1.2 (0.9-1.6)	1.2 (0.9-1.6)
Glycemic state	Normoglycemia			
Prediabetes		1.3 (0.98-1.6)	1.0 (0.8-1.3)	0.99 (0.8-1.3)
Blood Pressure ^c	Normal			
Intermediate		1.3 (0.9-1.8)	1.0 (0.7-1.4)	1.0 (0.7-1.5)
Hypertension		1.9 (1.4-2.6)	1.0 (0.8-1.4)	1.1 (0.8-1.6)

Adjusted covariates are reported using the final models that included the Mcauley index. ‡ HOMA-IR, Homeostatic model assessment -Insulin resistance; § HOMA-%B - Homeostatic model assessment – percent beta cell function; † MISI, Matsuda Insulin Sensitivity Index; ¶ QUICKI, Quantitative Insulin Sensitivity Check Index; ¥ MCAi, Mcauley index. ^a Multivariable models using cumulative incidence analysis/ cause specific mortality, comparing deaths from cancer with survivals and non-cancer deaths. The analyses were adjusted for: age, sex, origin, BMI, blood pressure, cholesterol, smoking and diabetes status and to the MCAi and not the other insulin sensitivity indices; ^b Sub-distribution hazard ratio using death from non-cancer causes as competing risks (the Fine and Gray method); ^c Blood pressure categories: Normal- systolic BP $\leq$ 140 mmHg and diastolic BP $\leq$ 90mmHg; Intermediate - systolic BP $\geq$ 140 mmHg or diastolic BP $\geq$ 90 mmHg; Hypertension systolic BP $\geq$ 140 mmHg and diastolic BP $\geq$ 90 mmHg; ^d BMI categories: Normal $<$ 25 kg/m², Overweight, 25 – 29.9 kg/m²; Obese- BMI $\geq$ 30 kg/m²; ^e Total cholesterol categories: Normal $<$ 200 mg/dl; Borderline high Loading [MathJax]/jax/output/CommonHTML/fonts/TeX/fontdata.js

Cancer mortality				
BMI (Kg / m ²) ^d	Normal			
Overweight		1.1 (0.8-1.4)	0.9 (0.7-1.2)	1.1 (0.8-1.7)
Obese		1.0 (0.7-1.5)	0.9 (0.6-1.3)	1.2 (0.8-1.8)
Total cholesterol ^e	Normal			
Borderline-high		0.8 (0.6-1.1)	0.8 (0.5-1.0)	0.8 (0.6-1.1)
High		0.9 (0.7-1.3)	0.7 (0.5-0.9)	0.7 (0.5-0.97)
MCAi [¥] , Q ₁	Q ₂₋₄	1.4 (1.1-1.8)	1.5 (1.1-2.0)	1.4 (1.1-1.9)
Ln MISI [†] , Q ₁	Q ₂₋₄	1.4 (1.0-1.9)	1.3 (0.9-1.9)	1.3 (0.9-2.0)
Ln HOMA-IR [‡] , Q ₄	Q ₁₋₃	1.2 (0.9-1.6)	1.2 (0.9-1.6)	1.2 (0.9-1.6)
Ln HOMA-%B [§] , Q ₁	Q ₂₋₄	1.2 (0.9-1.6)	1.1 (0.8-1.5)	1.1 (0.8-1.5)
QUICKI [¶] , Q ₁	Q ₂₋₄	1.2 (0.9-1.5)	1.2 (0.9-1.5)	1.2 (0.9-1.5)
Fasting insulin, Q ₄	Q ₁₋₃	1.2 (0.9-1.5)	1.2 (0.9-1.6)	1.2 (0.9-1.6)
Fasting glucose, Q ₄	Q ₁₋₃	1.2 (0.96-1.6)	1.1 (0.8-1.4)	1.1 (0.8-1.4)
<p>Adjusted covariates are reported using the final models that included the Mcauley index. [‡] HOMA-IR, Homeostatic model assessment -Insulin resistance; [§] HOMA-%B - Homeostatic model assessment – percent beta cell function; [†] MISI, Matsuda Insulin Sensitivity Index; [¶] QUICKI, Quantitative Insulin Sensitivity Check Index; [¥] MCAi, Mcauley index. ^a Multivariable models using cumulative incidence analysis/ cause specific mortality, comparing deaths from cancer with survivals and non-cancer deaths. The analyses were adjusted for: age, sex, origin, BMI, blood pressure, cholesterol, smoking and diabetes status and to the MCAi and not the other insulin sensitivity indices; ^b Sub-distribution hazard ratio using death from non-cancer causes as competing risks (the Fine and Gray method); ^c Blood pressure categories: Normal- systolic BP ≤ 140 mmHg and diastolic BP ≤ 90mmHg; Intermediate - systolic BP ≥ 140 mmHg or diastolic BP ≥90 mmHg; Hypertension systolic BP ≥ 140 mmHg and diastolic BP ≥ 90 mmHg; ^d BMI categories: Normal < 25 kg/m², Overweight, 25 – 29.9 kg/m²; Obese- BMI ≥ 30 kg/m²; ^e Total cholesterol categories: Normal < 200 mg/dl; Borderline high 200–239 mg/dl; High ≥ 240 mg/dl.</p>				

The remaining IR quartiles of the ISIs did not demonstrated such a significant association with cancer mortality, compared with the non-IR quartiles. Age was associated with a significantly higher risk for cancer death.

In line with the cause specific mortality results, a competing risks analysis (the Fine and Gray method)

Loading [MathJax]/jax/output/CommonHTML/fonts/TeX/fontdata.js individuals in the MCAi Q₁, SHR=1.4 (95% CI:

1.1-1.9, $P=0.02$). The remaining surrogates did not show a significant association with cancer mortality similar to the cause specific mortality results.

The Kaplan-Meier survival curves and log-rank test demonstrated a significant shorter times until cancer death for individuals in the IR MCAi quartile (Q_1) as compared to the upper quartiles, $p=0.02$ (not shown).

Adjusted survival curves using Cox regression (figure 1) showed a significant shorter times until cancer death for individuals in the MCAi quartile (Q_1), $p=0.004$ (figure 1).

An interaction between MCAi and glycemic state was not found to be statistically significant (p -interaction = 0.1).

Separate analyses were conducted according to glycemic status (i.e. normoglycemia and prediabetes). In the pre-diabetics group ($n=850$), both cumulative incidence analysis using the Cox proportional hazards model and the competing risk analysis demonstrated an increased risk for cancer mortality for MCAi Q_1 , $HR=1.6$ (95% CI: 1.1- 2.4, $p=0.01$) and $SHR=1.7$ (95% CI: 1.1-2.5, $p=0.01$), as compared with the MCAi Q_{2-4} . Such an association was not observed in the normoglycemic group ($n= 741$).

4. Discussion

In this long-term follow up of 1,612 men and women free of diabetes, a significant association was demonstrated between insulin resistance, as measured by the MCAi, and cancer mortality. No such association was found for the other IR surrogates.

These results reinforce the contribution of IR on the pathophysiology of cancer, exemplified by the 40-50% increased risk for cancer related mortality and specifically in individuals with prediabetes.

A number of previous studies have reported an association between increased fasting glucose plasma levels and cancer mortality (14–16,30). Parekh et al (16) demonstrated, as part of the Third National Health and Nutrition Examination Survey (NHANES III; 1988–1994), with an average follow-up of 8.5 years, that the risk for overall cancer mortality was significantly higher for every 50 mg/dl increase in fasting plasma glucose concentrations ($HR=1.22$; 95% CI: 1.06–1.39). Our findings show a statistically non-significant 10% increased risk for cancer death in individuals in the upper quartile of fasting glucose, similarly to Parekh et al findings. Other studies found hyperinsulinemia to relate with increased risk for cancer incidence and mortality (either by a direct mechanism or by interactions with other hormones such as IGF-1) (16,31–33).

Dankner et al (32) showed on a cohort of 1,695 nondiabetic participants as part of the GOH study, and after a 29 years of follow up, that individuals in the upper quartile of the fasting insulin had a statistically significant borderline increased risk for all-site cancer mortality ($HR=1.37$, 95% CI 0.94–2.00, $P = 0.097$). The current analysis showed a 20% non-significant increased risk for the upper fasting insulin quartile as

compared to the lower quartiles and a significant 50% higher risk in the upper fasting insulin quartile in pre-diabetics.

The role of ISIs as predictors for death in cancer patients remain unestablished, with inconsistent results (16,33). Perseghin et al (33) showed on a cohort of 2,074 individuals and after 15 years of follow up, as part of the Cremona study, a significant but minor association between abnormal HOMA-IR values and death from cancer (HR=1.003, 95% CI 1.002–1.005, $P < 0.001$). Other studies did not show such a significant association (16). Our findings support these results as demonstrated by an increased risk for cancer death among individuals in the IR quartiles of the Ln HOMA-IR in pre diabetics individuals (SHR=1.5, 95% CI: 1.0-2.2).

The MCAi was the only IR surrogate that demonstrated a significant association in the total cohort and exhibited the highest risk for cancer mortality compared with other IR surrogates. These findings emphasize the importance of elevated triglycerides on cancer prognosis. A possible link between increased triglycerides and cancer incidence was demonstrated in a number of studies (34,35) through common lipid metabolism pathways (e.g. Malonyl-CoA synthesis) in oncogenesis and adipogenesis (36). Such a positive association with increased cancer mortality was not observed (37–39) and even correlated with better disease-free survival (40) in breast cancer patients. Further investigation is needed in order to establish triglycerides inter-relationship with cancer progression and prognosis.

In the GOH cohort, an increased risk for all-cause mortality was found in individuals in the IR quartiles of the MCAi, the QUICKI and the HOMA-IR (26). However, the MCAi was the only ISI that showed a significant association with cardiovascular mortality, regardless of the presence of diabetes. The current findings suggest that the MCAi may be used as a surrogate for the long-term increased risk of death for both malignancy and cardiovascular morbidities.

The current study did not include participants with the diagnosis of diabetes due to the potential confounding effect of anti-diabetes medications (39,41), as well as the established association between diabetes and cancer mortality (15,16). For example, medications for the treatment of diabetes such as Metformin were negatively associated with mortality among diabetic patient (39) while exogenous insulin use and Sulfonylureas were associated with an increased risk for cancer mortality (41). However these findings are controversial, due to potential methodological flaws (42). In addition, diabetic patients display distinct characteristics such as relatively low levels of endogenous insulin as part of the disease progression, and higher BMI, which may confound the association. As previously mentioned, an association between hyperinsulinemia and increased risk for cancer death was observed in a number of studies and thus, lower levels of insulin could potentially have a protective effect from cancer mortality (32). Moreover, studies have shown a negative association between the metabolic syndrome, and specifically obesity, with cancer risk, and better outcome in cancer patient, suggesting that the metabolic syndrome and increased BMI may serve as good prognostic markers (43).

Strengths and weaknesses of the study

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While the standard oral glucose tolerance test (OGTT), as recommended by the American Diabetes Association (44), require the oral administration of 75 gr glucose, in the current study the test was carried out using 100 gr of glucose. This was done due to the absence of clear guidelines at the time of the examination (1979–1982). Furthermore, the ingestion of 100gr of glucose has been shown to improve insulin sensitivity and insulin secretion with minimal effect on the results of the OGTT in terms of the plasma glucose levels measured throughout the test (45).

In addition, the Yemenite population was over sampled in the GOH cohort beyond their normal proportion in the general Israeli population, in order to increase the statistical power and examine cardiovascular risk factor in this ethnic minority. The multivariable analysis adjusted for ethnicity to overcome this potential confounding.

Moreover, although ISI's that were examined in the study were previously found to show high correlation with the euglycemic insulin clamp (18–21), this method is still considered the gold standard for quantifying insulin resistance. However, this method is invasive and not applicable in large-scale epidemiological studies.

Furthermore, no information on medication or family history were collected during the late 70's intakes. However, the cohort was mainly composed of healthy and employed subjects. In addition, routine screenings for cancer were not widely used at that time. Finally, the current study did not investigate the association between IR surrogates and cancer site-specific mortality due to the small number of subjects per group.

The study however present some clear advantages such as the long follow-up over approximately 40 years, the equal representation of both men and women in addition to the representation of an ethnically diverse population. Moreover, blood tests were drawn in the healthy state for research purposes only and analyzed by a single laboratory, avoiding variability in the blood tests analysis. Furthermore, the statistical analysis was performed by two different approaches with similar findings, reinforcing the study results.

Conclusion

Our findings demonstrate an association between insulin resistance, as reflected by the lower values of the MCAi, and increased long-term cancer death, in individuals free of diabetes at start of the follow-up. The MCAi may be considered as a prognostic biomarker in healthy adults.

Abbreviations

HOMA-IR, Homeostatic model assessment -Insulin resistance;

HOMA-%B - Homeostatic model assessment – percent beta cell function;

IR, Insulin resistance.

ISI, insulin sensitivity indices.

MISI, Matsuda Insulin Sensitivity Index;

MCAi, Mcauley index.

OGTT, oral glucose tolerance test.

QUICKI, Quantitative Insulin Sensitivity Check Index.

Declarations

Ethics approval and consent to participate:

The Sheba Medical Center Review Board provided approval for this study (approval number 1180). All patients gave their verbal consent to participate in the study during baseline data collection.

Consent for publication:

Not applicable

Availability of data and materials:

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests:

The authors declare that they have no competing interests

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Author contributions:

YM contributed to the data analysis, the interpretation of data and drafting of the manuscript. RD and AC contributed to the acquisition of the data, to the conception and design of the work, to the data analysis and drafting of the manuscript. DR contributed to the conception and design of the work. DR, AC and RD critically revised the manuscript. All authors have read and approved the final manuscript.

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Figures

Figure 1

Adjusted survival curves using the Cox proportional hazard model, according to the Mcauley index low vs. higher quartiles for cancer mortality. a Adjusted for: age, sex, origin, BMI, blood pressure, cholesterol, smoking and diabetes status. Mean survival time for malignancy associated mortality in the lower (higher insulin resistance) MCA quartile (Q1) was 35.8 (95%CI, 34.9–36.7) years and 36.9 (95%CI, 36.5–37.4) years in the upper (lower insulin resistance) MCA quartiles (Q2-4), p = 0.02. Censoring occurred at time of other non-cancer death or end of follow-up.

Supplementary Files

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