## RESEARCH

# Effect of insulin resistance on CAC scores in cancer survivors

N. Jacobi[1*], S. Ortman[2], L. Buda[2] and Daniel Duprez[3]

## Abstract

**Background** Many ca. survivors exhibit signs of IR, an important risk factor for the development of CAD. CAC scans offer a risk assessment of CV disease before cardiac damage has occurred. We investigated how IR affects CAC scores in cancer survivors.

**Objectives** The aim of this study was to show that CAC scores differ significantly between insulin-sensitive- and -resistant cancer survivors.

**Methods** We enrolled 90 cancer survivors of a large community hospital from March 2021 to January 2022 into this pilot study. Patients were subdivided into three groups: insulin-sensitive (IS), insulin-resistant/prediabetic and insulin-resistant/diabetic. All patients received a CAC scan.

**Results** 70% of asymptomatic survivors overall and 81% of asymptomatic IR patients show CAD on CAC scans. 17 CAC scans in the IS group, 6 CAC scans in the IR/prediabetic group and 5 CAC scans in the IR/diabetic group showed an Agatston score of 0. The p-value between the three groups was statistically significant ($p = 0.005$) whereas the IR/prediabetic- and the IR/diabetic group did not differ statistically from each other. The mean MESA 10-year CHD risk with CAC was 7.8. There was a highly significant difference between the 3 groups ($p < 0.001$). The two IR groups did not differ statistically ($p = 0.076$).

**Conclusions** Survivors with IR including prediabetes have less frequent zero CAC scores than insulin-sensitive survivors. Our study also showed that IR including prediabetes significantly increases the MESA 10-yr. CHD Risk with CAC in cancer survivors. This trial highlights the importance of screening survivors for IR and draws attention to the association of IR to CAC not only in diabetes but also in prediabetes. The high fraction of asymptomatic survivors with CAD is concerning and calls for further investigation. CAC scans are an inexpensive and efficient way of screening asymptomatic cancer survivors for CAD.

**Keywords** Insulin resistance, Hyperinsulinemia, CAC scans, Cancer survivors, Coronary artery disease, Coronary heart disease

*Correspondence:
N. Jacobi
jacob260@umn.edu
[1]Department of Hematology, Oncology, Hennepin Healthcare, Minneapolis, MN, USA
[2]Department of Medicine, Hennepin Healthcare, Minneapolis, MN, USA
[3]Department of Cardiology, University of Minnesota, Minneapolis, MN, USA

## Background

Hyperinsulinemia/insulin resistance (IR) in general, not only diabetes, is an important risk factor for the development of coronary artery disease (CAD) [1–5]. An important goal is to detect CAD before events such as angina, myocardial infarction (MI) and cardiac interventions have taken place. CAC scans offer an assessment of CAD in the asymptomatic patient before cardiac damage has occurred. High CAC scores increase the risk for cardiac events within the next 10 years. Framingham data has shown that 50% of coronary events are not predicted from traditional cardiac risk factors [6]. CAC scores are highly predictive for future cardiac events in asymptomatic patients according to their risk category (low, intermediate and high) [7–10]. Thus, CAC scores offer valuable information regarding a patient's risk of developing symptomatic CAD in addition to known cardiac risk factors.

Cancer survivors are typically monitored for long-term effects caused by their treatment. A major focus is on the risk of cardiomyopathy from chemotherapy and/or radiation [11]. However, CAD can also develop due to shared risk factors or as a consequence of cancer treatment (e.g. radiation). Cancer survivors are at particular risk for cardiovascular events. Their prevalence of CAC is significantly higher than in patients without cancer [12]. It has to be suspected that this is in part due to the high incidence of IR in this population.IR is not only a risk factor for CAD but also for certain types of cancers. For example, breast cancer risk is not only increased in patients with DM but also in patients who are still in the prediabetic phase [13]. Marked IR increases the incidence of breast cancer and all-cause mortality after breast cancer in postmenopausal women in the Women's Health Initiative [14]. Hyperinsulinemia and IR are associated with an increased risk of lung cancer [15]. Similar findings have been discovered in prostate-, colon- and pancreatic cancer [16–19]. Insulin leads to proliferation and reduction of apoptosis in colorectal cancer, shown in cell lines and animal models [20–22].

We set out to investigate the association of IR with CAC scores in cancer survivors.

## Methods

### Patients

Patients were recruited from the survivorship clinic of Hennepin Healthcare. Inclusion criteria was a previous history of cancer. Exclusion criteria were a history of CAD including angina, MI, percutaneous transluminal coronary angioplasty (PTCA) with and without stent placement, coronary artery bypass graft (CABG) and pregnancy.

### Trial design

All patients were tested for fasting insulin, fasting glucose, HgbA1c and had a lipid panel. Only those patients whose laboratory results did not indicate diabetes or prediabetes underwent an oral glucose tolerance test (oGTT).

Data were collected on demographics with age, gender, race, height, weight and BMI. Cardiac risk factors were determined (current and previous nicotine use, family history of heart attacks, current and previous history of diabetes and prediabetes). The patients' systolic and diastolic blood pressure at the time of recruitment was documented. We calculated the Framingham cardiovascular 10-year risk score and the ACC/AHA clinical atherosclerotic cardiovascular disease (ACSVD) 10-year risk score for every patient. Additionally, we collected information on any other history of heart disease besides CAD.

We documented whether patients were on exogenous insulin. Data were obtained on lipid lowering drugs and antihypertensive use.

We obtained data on tumor characteristics such as histology, stage and recurrence. We put special emphasis on documenting cardiotoxic treatments such as chemotherapy (e.g., anthracyclines) and radiation to the left chest or both. We also gathered data on the use of aromatase inhibitors, androgen biosynthesis inhibitors and tyrosine kinase inhibitors.

### Trial conduction

Patients were recruited from March 2021 until January 2022. They were assessed according to our inclusion- and exclusion criteria. After obtaining informed consent, study participants underwent baseline laboratory tests. They were subdivided into one of three groups according to their oGTT- and HgbA1c results (insulin-sensitive, insulin-resistant/prediabetes and insulin-resistant/diabetes). All patients underwent a CAC scan shortly after baseline laboratory results were completed.

### Statistical analysis

Clinical and demographic measures were summarized descriptively and compared between the three groups using one-way *ANOVA* for continuous, non-CAC/MESA related measures, and Fisher's Exact test for categorical measures. Due to the skewness among the CAC and MESA scores, the Kruskal-Wallis test was used for these measures. A subgroup comparison was made between the IR-prediabetic and IR diabetic groups using *t*-tests, Mann-Whitney U, or Fisher's Exact tests, as appropriate. P-values less than 0.05 were considered statistically significant. R (R Core Team) Version 4.0 was used for all analyses.

Jacobi *et al. Cardio-Oncology*      (2023) 9:21

Page 3 of 8

## Results

We enrolled 90 patients into our study. 32 patients were insulin-sensitive, 29 patients were insulin-resistant/prediabetic and 29 patients were insulin-resistant/diabetic. Mean age of all trial participants was 64.1 and did not differ significantly among the three groups. 57.8% of patients were female, 42.2% were male. There was no significant gender difference between the three groups. Mean BMI was 29.1 across all study participants but differed significantly across the three groups. Mean BMI in the IS group was 26.5, in the IR/prediabetic group 28.4 and in the diabetic group 32.8 which was statistically significant (p=0.002). The distribution of race differed significantly across the three groups (Table 1).

Mean weight was 79.6 kg across all study participants, and the difference among the three groups was statistically different (74.2 kg in IS group, 77.1 kg in IR/prediabetic group and 88.1 kg in IR/diabetic group, p=0.006). The three groups were similar in smoking status, pack years, family history of heart attack, diagnosis of hyperlipidemia and being on antihypertensives (Table 1). The study participants had similar systolic and diastolic blood pressure levels (Table 1).

There was a statistical difference among the Framingham CV Risk for men (overall mean 23.3 (SD 13.3), p=0.38). Women also showed statistically different values with an overall mean of 10.6 (8.0), p<0.001) (Table 1). The ACC/AHA risk score showed an overall mean of 15 (12.3). The three groups were statistically different (IS 8.5, IR/prediabetic 14.1, IR/diabetic 23, p<0.001). The three groups were comparable regarding previous cardiac history (Table 2).

The patients did not differ in their total cholesterol- and LDL levels. However, there was a significant difference between the three groups regarding HDL (69.5 IS, 54.6 IR/prediabetic, 51.1 IR/diabetic, p<0.001). There was a difference between patients in terms of being on lipid lowering drugs (IS 15.6%, IR/prediabetic 24. % and IR/diabetic 65. %, p<0.001).

Mean fasting insulin across all study participants was 23 U/ml (35.4) in all 3 groups. As expected, there was a statistical difference between the IS group (8.8), the IR/prediabetic group (22.4) and the IR/diabetic group (39.3, p<0.003). Similar findings were observed with fasting glucose where the mean was 114.5 mg/dl (40.4) in all three groups. The IS group had a mean fasting glucose of 94.4 mg/dl, the IR/prediabetic group had a mean of 112.1, and the IR/diabetic group had a mean of 139.2, p<0.001. We also calculated the HOMA-IR (Homeostatic Model Assessment for Insulin Resistance) by measuring fasting insulin- and glucose. The HOMA-IR formula determines the degree of IR. A level above 2 signifies IR. The overall mean of HOMA-IR was overall 5.8 (8.9), the mean in the IS group was 2.1, the mean in the IR/prediabetic

group was 6.7 and the mean in the IR/diabetic group was 9.1 (p=0.006). Along the same lines, HgbA1c had a mean of 6.1% (1.5) with 5.2% in the IS group, 5.7% in the IR/prediabetic group and 7.5% in the IR/diabetic group (p<0.001). The oral glucose tolerance test had a mean of 94.7 in the IS group and 162.7 in the IR/prediabetic group (Table 3).

Mean baseline CAC among all three groups was 169.5 (359.8). The overall median was 27.5 (0.0, 2316.0). The IS group had a mean of 202.4 (520.6), the IR/prediabetic group showed a mean of 183.9 (257.5), and the IR/diabetic group had a mean of 119.0 (202.4), p=0.029. The medians of the three groups were 0.0 (0.0, 2316.0), 74.0 (0.0, 977.0) and 39.0 (0.0, 969.0), respectively. There was no statistical difference between the IR/prediabetic- and the IR/-diabetic group (p=0.404).

70% of asymptomatic survivors overall and 81% of asymptomatic IR patients show CAD on CAC scans. The IS group showed 17 zero (53.1%) and 15 (46.9%) non-zero CAC scan values, the IR/prediabetic had 6 zero (20.7%) scans and 23 (79.3%) non-zero scans, and the IR/diabetic group contained 5 (17.2%) patients with zero scans whereas 24 (82.8%) CAC scans were non-zero, p=0.005. The IR/prediabetic- and the IR/diabetic group did not differ statistically from each other (p=0.999). The difference in non-zero CAC score values among all 3 groups was not statistically significant (p=0.388) (Fig. 1).

The total mean MESA baseline percentile was 49.3%. The IS group had a mean of 36.2%, the IR/prediabetic group a mean of 56.3% and the IR/diabetic group a mean of 58.8% which was not statistically different (p=0.168).

The mean MESA 10-year CHD risk with CAC was 7.8. There was a highly significant difference between the 3 groups: the IS group had a mean of 5.3, the IR/prediabetic group had a mean of 7.3, and the IR/diabetic group had a mean of 11.0, p<0.001. The two IR groups did not differ statistically (p=0.076) (Table 4).

## Discussion

Our study showed that IR including prediabetes reduces a cancer survivor's probability of having a zero CAC scan. The statistical difference between the two IR groups in regard to the probability of having a non-zero CAC scan was not significant in our trial. IR including prediabetes also significantly increased the MESA 10-yr risk with CAC. There was no statistical difference between the two IR groups. Other authors have shown that IR increases CAC scores in a normal patient population. Similar to our small trial on cancer survivors, an increase in number of non-zero scans in association with HOMA-IR was observed in large number of non-diabetic patients in the MESA trial. Like in our study there was no association with extent of calcification [23]. This was in contrast to patients in the Framingham Offspring study where extent

**Table 1** Patient Characteristics and Cardiac Risk Factors

| | Insulin Sensitive (N = 32) | IR - Prediabetic (N = 29) | IR - Diabetic (N = 29) | Total (N = 90) | P-value |
|---|---|---|---|---|---|
| Age | | | | | 0.071 |
| Mean (SD) | 60.9 (10.5) | 66.1 (9.8) | 65.5 (8.2) | 64.1 (9.7) | |
| Range | 45.0–87.0 | 43.0–82.0 | 49.0–82.0 | 43.0–87.0 | |
| Gender - Male | 11 (34.4%) | 15 (51.7%) | 12 (41.4%) | 38 (42.2%) | 0.395 |
| Race | | | | | < 0.001 |
| African/AA | 8 (25.0%) | 4 (13.8%) | 13 (44.8%) | 25 (27.8%) | |
| Asian | 1 (3.1%) | 1 (3.4%) | 1 (3.4%) | 3 (3.3%) | |
| Caucasian | 23 (71.9%) | 18 (62.1%) | 8 (27.6%) | 49 (54.4%) | |
| Hispanic | 0 (0.0%) | 6 (20.7%) | 7 (24.1%) | 13 (14.4%) | |
| Height (m) | | | | | 0.284 |
| Mean (SD) | 1.7 (0.1) | 1.6 (0.1) | 1.6 (0.1) | 1.7 (0.1) | |
| Range | 1.5–1.9 | 1.5–1.8 | 1.4–1.9 | 1.4–1.9 | |
| Weight (kg) | | | | | 0.006 |
| Mean (SD) | 74.2 (13.1) | 77.1 (16.4) | 88.1 (21.6) | 79.6 (18.1) | |
| Range | 52.0–103.4 | 50.3–131.0 | 59.4–136.8 | 50.3–136.8 | |
| BMI | | | | | < 0.001 |
| Mean (SD) | 26.5 (5.2) | 28.4 (5.7) | 32.8 (7.7) | 29.1 (6.7) | |
| Range | 19.6–39.7 | 18.9–48.1 | 22.1–50.6 | 18.9–50.6 | |
| BMI (categorical) | | | | | 0.029 |
| Normal | 14 (43.8%) | 7 (24.1%) | 4 (13.8%) | 25 (27.8%) | |
| Overweight | 12 (37.5%) | 11 (37.9%) | 9 (31.0%) | 32 (35.6%) | |
| Obese | 6 (18.8%) | 11 (37.9%) | 16 (55.2%) | 33 (36.7%) | |
| Smoking Status | | | | | 0.809 |
| Missing | 1 | 3 | 0 | 4 | |
| Current | 5 (16.1%) | 4 (15.4%) | 2 (6.9%) | 11 (12.8%) | |
| Former | 9 (29.0%) | 9 (34.6%) | 11 (37.9%) | 29 (33.7%) | |
| Never | 17 (54.8%) | 13 (50.0%) | 16 (55.2%) | 46 (53.5%) | |
| Pack Years | | | | | 0.362 |
| Mean (SD) | 23.4 (17.1) | 42.0 (56.5) | 22.0 (36.0) | 29.0 (39.5) | |
| Range | 0.5–70.0 | 0.4–200.0 | 1.0–130.0 | 0.4–200.0 | |
| Hyperlipidemia | 22 (68.8%) | 21 (72.4%) | 22 (75.9%) | 65 (72.2%) | 0.802 |
| Family Hx Heart Attack | 10 (31.2%) | 4 (13.8%) | 10 (34.5%) | 24 (26.7%) | 0.170 |
| Total Cholesterol | | | | | 0.117 |
| Mean (SD) | 196.3 (42.8) | 186.0 (45.5) | 172.4 (45.4) | 185.3 (45.1) | |
| Range | 99.0–299.0 | 91.0–281.0 | 88.0–277.0 | 88.0–299.0 | |
| HDL | | | | | < 0.001 |
| Mean (SD) | 69.5 (19.6) | 54.6 (13.3) | 51.1 (13.9) | 58.8 (17.8) | |
| Range | 42.0–115.0 | 27.0–76.0 | 31.0–81.0 | 27.0–115.0 | |
| Systolic BP | | | | | 0.687 |
| Mean (SD) | 126.8 (15.5) | 130.1 (16.4) | 129.9 (18.9) | 128.9 (16.8) | |
| Range | 94.0–164.0 | 96.0–162.0 | 98.0–160.0 | 94.0–164.0 | |
| Diastolic BP | | | | | 0.256 |
| Mean (SD) | 75.8 (11.3) | 72.1 (12.5) | 71.2 (10.1) | 73.1 (11.4) | |
| Range | 52.0–100.0 | 44.0–98.0 | 50.0–93.0 | 44.0–100.0 | |
| On Lipid Lowering Drugs | 5 (15.6%) | 7 (24.1%) | 19 (65.5%) | 31 (34.4%) | < 0.001 |
| Framingham CV Risk (Men) | | | | | 0.038 |
| Mean (SD) | 16.9 (8.5) | 20.8 (10.0) | 30.0 (15.9) | 23.3 (13.3) | |
| Range | 4.4–27.8 | 10.5–46.9 | 10.6–61.0 | 4.4–61.0 | |
| Framingham CV Risk (Women) | | | | | < 0.001 |
| Mean (SD) | 7.1 (4.1) | 9.1 (3.9) | 17.5 (11.4) | 10.6 (8.0) | |
| Range | 2.5–17.9 | 2.3–16.7 | 4.5–47.2 | 2.3–47.2 | |
| ACC/AHA (ASCVD) | | | | | < 0.001 |
| Mean (SD) | 8.5 (8.3) | 14.1 (10.0) | 23.0 (13.7) | 15.0 (12.3) | |
| Range | 0.8–36.3 | 1.2–35.1 | 3.8–61.6 | 0.8–61.6 | |

P-values come from ANOVA for continuous measures, and Fisher's Exact Test for categorical measures

Jacobi *et al. Cardio-Oncology*        (2023) 9:21

Page 5 of 8

**Table 2** Cancer treatment

|  | Insulin Sensitive (N = 32) | IR - Prediabetic (N = 29) | IR - Diabetic (N = 29) | Total (N = 90) | P-value |
|---|---|---|---|---|---|
| Cardiotoxic Treatment | 13 (40.6%) | 5 (17.2%) | 7 (24.1%) | 25 (27.8%) | 0.120 |
| Radiation L chest | 13 (40.6%) | 4 (13.8%) | 4 (13.8%) | 21 (23.3%) | 0.020 |
| Cardiotoxic Chemo | 9 (28.1%) | 1 (3.4%) | 4 (13.8%) | 14 (15.6%) | 0.027 |
| Cardiotoxic Chemo + Radiation | 7 (21.9%) | 0 (0.0%) | 1 (3.4%) | 8 (8.9%) | 0.005 |
| Cardiac Damage from Chemo | 1 (3.1%) | 0 (0.0%) | 0 (0.0%) | 1 (1.1%) | 0.999 |

P-values come from Fisher's Exact test

**Table 3** Lab results

|  | Insulin Sensitive (N = 32) | IR - Prediabetic (N = 29) | IR - Diabetic (N = 29) | Total (N = 90) | P-value |
|---|---|---|---|---|---|
| Cholesterol |  |  |  |  | 0.117 |
| Mean (SD) | 196.3 (42.8) | 186.0 (45.5) | 172.4 (45.4) | 185.3 (45.1) |  |
| Range | 99.0–299.0 | 91.0–281.0 | 88.0–277.0 | 88.0–299.0 |  |
| HDL |  |  |  |  | < 0.001 |
| Mean (SD) | 69.5 (19.6) | 54.6 (13.3) | 51.1 (13.9) | 58.8 (17.8) |  |
| Range | 42.0–115.0 | 27.0–76.0 | 31.0–81.0 | 27.0–115.0 |  |
| LDL |  |  |  |  | 0.287 |
| Mean (SD) | 107.1 (37.4) | 105.5 (41.2) | 92.5 (37.7) | 101.9 (38.9) |  |
| Range | 41.0–195.0 | 30.0–191.0 | 6.0–163.0 | 6.0–195.0 |  |
| Exogenous Insulin | 0 (0.0%) | 0 (0.0%) | 17 (58.6%) | 17 (18.9%) | < 0.001 |
| Fasting Insulin |  |  |  |  | 0.003 |
| Mean (SD) | 8.8 (4.3) | 22.4 (31.3) | 39.3 (49.7) | 23.0 (35.4) |  |
| Range | 2.6–21.6 | 2.6–168.0 | 3.0–172.0 | 2.6–172.0 |  |
| Fasting Glucose |  |  |  |  | < 0.001 |
| Mean (SD) | 94.4 (7.3) | 112.1 (16.3) | 139.2 (61.3) | 114.5 (40.4) |  |
| Range | 79.0–106.0 | 73.0–141.0 | 6.9–291.0 | 6.9–291.0 |  |
| HOMA-IR |  |  |  |  | 0.006 |
| Mean (SD) | 2.1 (1.1) | 6.7 (10.9) | 9.1 (10.2) | 5.8 (8.9) |  |
| Range | 0.6–5.0 | 0.8–58.5 | 0.8–48.1 | 0.6–58.5 |  |
| HgbA1c |  |  |  |  | < 0.001 |
| Mean (SD) | 5.2 (0.2) | 5.7 (0.4) | 7.5 (1.9) | 6.1 (1.5) |  |
| Range | 4.4–5.6 | 4.8–6.2 | 5.2–12.6 | 4.4–12.6 |  |
| oGTT |  |  |  |  |  |
| N | 32 | 11 | 0 | 43 |  |
| Mean (SD) | 94.7 (28.0) | 162.7 (25.1) | - | 112.1 (40.4) |  |
| Range | 47.0–138.0 | 125.0–199.0 | - | 47.0–199.0 |  |

P-values come from ANOVA for continuous measures, and Fisher's Exact Test for categorical measures

of subclinical CAD was associated with severity of IR [24].

The focus of our trial was on the population of cancer survivors. Cancer survivors disproportionately exhibit IR. One possible reason is the association of certain types of cancer in patients with hyperinsulinemia [13–19].

The similarities between the two IR groups in terms of the risk of having a non-zero CAC scan and the increased risk of the MESA 10-year CHD with CAC raise the question about the importance of screening survivors for IR including prediabetes. The strength of our study lies in the meticulous distinction between the two insulin-resistant groups through various laboratory tests. It should be kept in mind that IR can be missed on conventional laboratory tests such as fasting glucose and HgbA1c. Given the significant number of patients diagnosed with

prediabetes based solely on oGTT in this trial, future effort should be made to evaluate the benefit of screening cancer survivors with oGTT.

Almost 70% of our asymptomatic study participants showed CAD on CAC screening. Moreover, the fraction of asymptomatic IR patients is even higher with 81%. These numbers are certainly concerning and call for further investigation on a larger scale. In view of the increased cardiovascular risk of cancer survivors, some authors have suggested prospective trials on screening survivors with cardiac tomographies (including CAC scans and coronary CT angiography) for surveillance [25]. There is a need for screening cancer survivors for CAD above that of the general population. Yet, monitoring cancer survivors with coronary CT angiographies could lead to financial toxicity for the patients. CAC
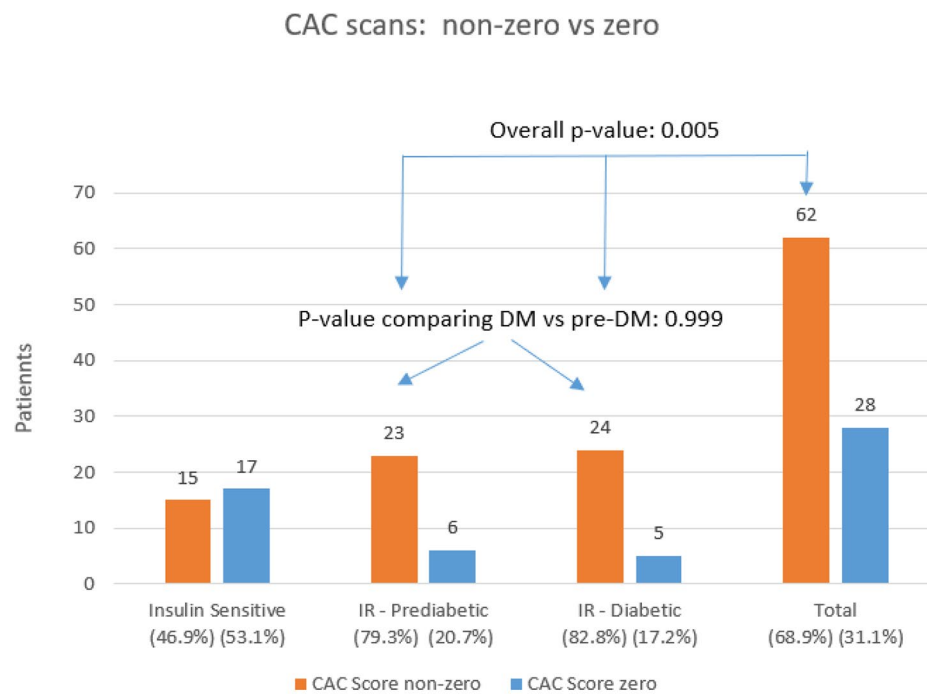
CAC scans:  non-zero vs zero



**Fig. 1** Zero- versus non-zero CAC scans in the IS- and IR groups

scans are a less expensive and efficient way of screening cancer asymptomatic survivors for CAD as shown in this pilot trial.

The CAC consortium has demonstrated that high CAC scores preceding a cancer diagnosis was predictive of having CVD as a supporting cause of death on death certificates. The risk through elevated CAC scores was independent of the Framingham ASCVD sore and general CVD risk factors. The authors also encouraged the utilization of CAC scans as a screening tool for cancer survivors [26]. This is especially important for patients with high CAC scores as it has been shown that in patients with CAC scores>300 death from CAD even surpasses death from cancer [27].

The association between CAC scores and certain types of cancer is notable. A cancer diagnosis is associated with the development of CAC independent of other cardiac risk factors in patients with a zero CAC at baseline [28]. Very high CAC scores are also associated with high incidences of cancer [29]. In addition, CAC scores are associated with an increased risk for lung cancer mortality, especially in current/former smokers and women [30].

Moreover, CAC scans are prognostic of major adverse cardiac events and all-cause deaths in patients with lung cancer without a history of CVD [31]. CAC scores were found to be an independent predictor of CV events and all-cause mortality on low-dose lung CT's [32]. Similar observations were made in breast cancer patients after

adjuvant radiation therapy where high pre-treatment CAC scores were associated with acute coronary events [33].

Many chemotherapeutic agents and left-sided chest irradiation are recognized as cardiotoxic. Yet, left-sided chest radiation has not been shown to increase CAC scores in breast cancer survivors [34].

Further studies are needed to evaluate whether we are overestimating the effect of cardiotoxic treatment and/or radiation and underestimating the effect of IR on CAD in cancer survivors.

## Conclusions

In our trial, asymptomatic cancer survivors show a high rate of CAD on CAC scans. IR including prediabetes and not only diabetes increased the risk of a non-zero CAC scan in cancer survivors. IR including prediabetes also significantly increased the 10-year MESA CHD risk with CAC. Prediabetes appears to be a more significant cardiac risk factor for survivors than anticipated. Further trials should investigate whether cancer survivors need to be tested for IR with yearly oGTT's and furthermore, whether asymptomatic survivors with IR should undergo screening CAC scans.

## Study limitations

This is a single-center pilot study of a specific population of cancer survivors at a safe-haven hospital. Further

**Table 4** CAC results

| | Insulin Sensitive (N = 32) | IR - Prediabetic (N = 29) | IR - Diabetic (N = 29) | Total (N = 90) | Overall P-value | P-value Comparing DM vs. pre-DM |
|---|---|---|---|---|---|---|
| CAC-Agatson Score | | | | | 0.029[a] | 0.404[a] |
| Mean (SD) | 202.4 (520.6) | 183.9 (257.5) | 119.0 (202.4) | 169.5 (359.8) | | |
| Median (Range) | 0.0 (0.0, 2316.0) | 74.0 (0.0, 977.0) | 39.0 (0.0, 969.0) | 27.5 (0.0, 2316.0) | | |
| CAC-Agatson Score* | | | | | 0.005[a] | |
| Mean (SD) | 81.6 (205.2) | 183.9 (257.5) | 119.0 (202.4) | 127.6 (224.4) | | |
| Median (Range) | 0.0 (0.0, 876.0) | 74.0 (0.0, 977.0) | 39.0 (0.0, 969.0) | 23 (0.0, 977) | | |
| CAC-Agatson Score (non-zero) | | | | | 0.388[a] | 0.148[a] |
| N | 15 | 23 | 24 | 62 | | |
| Mean (SD) | 431.7 (702.9) | 231.8 (269.7) | 143.8 (214.9) | 246.1 (412.0) | | |
| Median (Range) | 79.4 (2.0, 2316.0) | 158.0 (0.9, 977.0) | 69.5 (1.0, 969.0) | 94.5 (0.9, 2316.0) | | |
| CAC-Agatson Score (non-zero)* | | | | | 0.321[a] | |
| N | 13 | 23 | 24 | 60 | | |
| Mean (SD) | 188.3 (282.8) | 231.8 (269.7) | 143.8 (214.9) | 187.2 (250.9) | | |
| Median (Range) | 64.0 (2.0, 876.0) | 158.0 (0.9, 977.0) | 69.5 (1.0, 969.0) | 86.2 (0.9, 977.0) | | |
| CAC Score (binary) | | | | | 0.005 | 0.999 |
| Non-zero | 15 (46.9%) | 23 (79.3%) | 24 (82.8%) | 62 (68.9%) | | |
| Zero | 17 (53.1%) | 6 (20.7%) | 5 (17.2%) | 28 (31.1%) | | |
| Mesa baseline %ile | | | | | 0.041 | 0.958 |
| Mean (SD) | 36.2 (41.2) | 56.3 (32.9) | 56.8 (31.9) | 49.3 (36.7) | | |
| Median (Range) | 0.0 (0.0, 99.0) | 64.0 (0.0, 93.0) | 59.0 (0.0, 98.0) | 59.5 (0.0, 99.0) | | |
| Mesa 10-Year CHD risk w/ CAC | | | | | < 0.001 | 0.045 |
| Mean (SD) | 5.3 (6.6) | 7.3 (5.1) | 11.0 (8.3) | 7.8 (7.1) | | |
| Median (Range) | 2.1 (0.9, 27.6) | 5.5 (1.0, 18.8) | 6.6 (1.5, 35.1) | 5.5 (0.9, 35.1) | | |
| Mesa 10-Year CHD risk w/o CAC | | | | | < 0.001 | < 0.001 |
| Mean (SD) | 4.2 (3.6) | 5.7 (3.5) | 10.9 (6.5) | 6.8 (5.5) | | |
| Median (Range) | 2.4 (0.7, 14.4) | 4.9 (0.9, 15.4) | 9.0 (2.3, 24.6) | 5.3 (0.7, 24.6) | | |

P-values come from ANOVA for continuous measures, and Fisher's Exact Test for categorical measures

studies are required to confirm that these data can be extrapolated to all cancer survivors. Moreover, multivariate analyses are called for to validate IR as an independent risk factor. Research is also needed as to the rate of progression of CAC scores in cancer survivors in association with IR.

**Abbreviations**

| | |
|---|---|
| ca. | cancer |
| IR | insulin resistance |
| CAD | coronary artery disease |
| CAC | coronary artery calcium |
| CV | cardiovascular |
| IS | insulin-sensitive |
| oGTT | oral glucose tolerance test |
| MESA | Multi-Ethnic Study of Atherosclerosis |
| MI | myocardial infarction |
| HR | hazard ratio |
| PTCA | percutaneous transluminal coronary angioplasty |
| CABG | coronary artery bypass graft |
| ACSVD | atherosclerotic cardiovascular disease |
| ACC/AHA | American College of Cardiology/American Heart Association |
| BMI | body mass index |
| HgbA1c | hemoglobin A1C |
| CT | computed tomography |

**Author Contribution**
Nicole Jacobi developed and conducted the trial. She analyzed the data and wrote the script. Syndal Ortman co-conducted the trial. Lea Buda was instrumental in putting the trial data in context with current data. Daniel Duprez oversaw the trial and guided the co-authors.

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

**Declarations**

**Ethical approval**
This study was approved by the Human Research Protection Office of Hennepin Healthcare. The IRB approval No is: HSR#18-4477 (04/26/2018).

**Consent to participate and publish**
All patients signed a consent to participate and publish.

**Competing interest**
The authors declare that they have no competing interests.

**Disclosures**
Nothing relevant to disclose for any author.

**References**
1. Laakso M, Kuusisto J. Insulin resistance and hyperglycaemia in cardiovascular disease development. Nat Rev Endocrinol. 2014 May;10(5):293–302.
2. Reaven G. Insulin resistance and coronary heart disease in nondiabetic individuals. Arterioscler Thromb Vasc Biol. 2012 Aug;32(8):1754–9.
3. Pyörälä M, Miettinen H, Laakso M, Pyörälä K. Hyperinsulinemia predicts Coronary Heart Disease Risk in Healthy Middle-aged men. The 22-Year follow-up results of the Helsinki Policemen Study. Circulation. 1998;98:398–404.
4. Young MH, Jeng CY, Sheu WH, et al. Insulin resistance, glucose intolerance, hyperinsulinemia and dyslipidemia in patients with angiographically demonstrated coronary artery disease. Am J Cardiol. 1993 Aug;15(5):458–60.
5. Mozersky RP, Bahl VK, Patel H, et al. Hyperinsulinemia and coronary artery disease risk factors in patients with non-insulin-dependent diabetes mellitus and nondiabetics. J Am Osteopath Assoc. 1996 Oct;96(10):591–6.
6. Greenland P, Smith SC Jr, Grundy SM. Improving Coronary Heart Disease Risk Assessment in Asymptomatic People. Circulation. 2001;104:1863–7.
7. Kondos. GT, Hoff JA, Sevrukov A et al. "Electron-beam tomography coronary artery calcium and cardiac events: a 37-month follow-up of 5635 initially asymptomatic low- to intermediate-risk adults". Circulation. 2003 May 27;107(20):2571-6.
8. Arad Y, Spadaro LA, Goodman K et al. "Predictive value of electron beam computed tomography of the coronary arteries. 19-month follow-up of 1173 asymptomatic subjects". Circulation1996 Jun 1;93(11):1951-3.
9. Budoff M, Young R, Lopez VA, et al. Progression of coronary calcium and incident coronary heart disease events: MESA (multi-ethnic study of atherosclerosis). J Am Coll Cardiol. 2013 Mar;26(12):1231–9.
10. Raggi P, Callister TQ, Shaw LJ. Progression of coronary artery calcium and risk of first myocardial infarction in patients receiving cholesterol-lowering therapy. Arterioscler Thromb Vasc Biol. 2004 Jul;24(7):1272–7.
11. Armenian SH, Lacchetti C. Barac. A., "Prevention and Monitoring of Cardiac Dysfunction in Survivors of Adult Cancers: American Society of Clinical Oncology Clinical Practice Guideline".J Clin Oncol 2017 Mar10;35(8):893–911.
12. Whitlock MC, Yeboah J, Burke GL, Chen H, Klepin HD, Hundley WG. "Cancer and Its Association With the Development of Coronary Artery Calcification: An Assessment From the Multi-Ethnic Study of Atherosclerosis". J Am Heart Assoc. 2015 Nov 9;4(11):e002533.
13. Onitilo AA, Stankowski RV, et al. Breast cancer incidence before and after diagnosis of type 2 diabetes mellitus in women increased risk in the prediabetes phase. Eur J Cancer Prev. 2014 Mar;23(2):76–83.
14. Pan K, Chlebowski RT, Mortimer JE, et al. Insulin resistance and breast cancer incidence and mortality in postmenopausal women in the Women's Health Initiative. Cancer. 2020 Aug;15(16):3638–47.
15. Argirion I, Weinstein SJ, Männistö S, Albanes D, Mondul AM. "Serum Insulin, Glucose, Indices of Insulin Resistance, and Risk of Lung Cancer:, Cancer Epidemiol Biomarkers Prev. 2017 Oct;26(10):1519–1524.
16. Albanes D, Weinstein SJ, Wright ME, et al. Serum insulin, glucose, indices of insulin resistance, and risk of prostate Cancer. JNCI. 2009 Sept;101(18):1272–9.
17. Hsing AW, Chua S, Jr, Gao Y-T et al. "Prostate Cancer Risk and Serum Levels of Insulin and Leptin: a Population-Based Study". JNCI: 2001 May; 93(10): 783–789
18. Limburg PJ, Stolzenberg-Solomon RZ, et al. Insulin, glucose, insulin resistance, and Incident Colorectal Cancer in male smokers. Clin Gastroenterol Hepatol. 2006 Dec;4(12):1514–21.
19. Stolzenberg-Solomon RZ, Graubard PhD, Chari BI. Insulin, glucose, insulin resistance, and pancreatic Cancer in male smokers. JAMA. 2005;294(22):2872–8.
20. Wu X, Fan Z, Masui H, Rosen N, Mendelsohn J. "Apoptosis induced by an anti-epidermal growth factor receptor monoclonal antibody in a human colorectal carcinoma cell line and its delay by insulin".J Clin Invest. 1995Apr; 95(4):1897–1905.
21. Tran TT, Medline A, Bruce WR. Insulin promotion of colon tumors in rats. Cancer Epidemiol Biomarkers Prev. 1996 Dec;5(12):1013–5.
22. Corpet DE, Jacquinet C, Peiffer G, Tache S. Insulin injections promote the growth of aberrant crypt foci in the colon of rats. Nutr Cancer. 1997;27:316–20.
23. Ong K-L, McClelland RL, Rye K-A, et al. The relationship between insulin resistance and vascular calcification in coronary arteries, and the thoracic and abdominal aorta: the multi-ethnic study of atherosclerosis. Atherosclerosis. 2014 October;236(2):257–62.
24. Meigs JB, Larson MG, O'Donnell SCD. Coronary artery calcification in type 2 diabetes and insulin resistance: the Framingham offspring study. Diabetes Care. 2002;25(8):1313–9.
25. Layoun ME, Yang EH, Herrmann J et al. "Applications of Cardiac Computed Tomography in the Cardio-Oncology Population". Curr Treat Options Oncol 2019 May 6;20(6):47.
26. Wang FM, Reiter-Brennan C, Dardari Z, et al. Association between coronary artery calcium and cardiovascular disease as a supporting cause in cancer: the CAC consortium. Am J Prev Cardiol. 2020 Nov;12:4:100119.
27. Whelton SP, Al Rifai M, Dardari Z et al. "Coronary artery calcium and the competing long-term risk of cardiovascular vs. cancer mortality: the CAC Consortium". Eur Heart J Cardiovasc Imaging. 2019 Apr 1;20(4):389–395.
28. Whitlock MC, Yeboah J, Burke MD. Cancer and its Association with the development of coronary artery calcification: an Assessment from the multi-ethnic study of atherosclerosis. J Am Heart Assoc. 2015;4:e002533.
29. Chen W-T, Huang J-H, Hsieh M-H, Chen Y-J. "Extremely high coronary artery calcium score is associated with a high cancer incidence". Int J Cardiol. 2012 Mar 22;155(3):474-5.
30. Dzaye O, Berning P, Dardari ZA, et al. Coronary artery calcium is associated with long-term mortality from lung cancer: results from the coronary artery Calcium Consortium. Atherosclerosis. 2021 Dec;339:48–54.
31. Osawa K, Bessho A, Fuke S, et al. Coronary artery calcification scoring system based on the coronary artery calcium data and reporting system (CAC-DRS) predicts major adverse cardiovascular events or all-cause death in patients with potentially curable lung cancer without a history of cardiovascular disease. Heart Vessels. 2020 Nov;35(11):1483–93.
32. Jacobs PC, Gondrie MJA, van der Graaf Y, et al. Coronary artery calcium can predict all-cause mortality and cardiovascular events on low-dose CT screening for lung cancer. AJR Am J Roentgenol. 2012 Mar;198(3):505–11.
33. Roos CTG. Bogaard. V.A.B., Greuter M.J.W.,. "Is the coronary artery calcium score associated with acute coronary events in breast cancer patients treated with radiotherapy? Radiother Oncol. 2018 Jan;126(1):170–176.
34. Takx RAP, Vliegenthart R, Schoepf UJ, et al. Coronary artery calcium in breast cancer survivors after radiation therapy. Int J Cardiovasc Imaging. 2017 Sep;33(9):1425–31.

**Publisher's Note**