

Research Article

Non-Exercise Estimated Cardiorespiratory Fitness and All-Cause Mortality in Cancer Patients

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Abstract

Background: The purpose of the present study was to examine the association between non-exercise Cardiorespiratory Fitness (eCRF) and all-cause mortality in cancer patients.

Methods and Findings: A total of 2,404 participants from the Aerobics Center Longitudinal Study (622 women and 1,782 men) with a cancer diagnosis were followed for mortality. Non-exercise eCRF was calculated in Metabolic Equivalents (METs) with sex-specific algorithms at baseline. Multivariable Cox regression models were used to examine the association between CRF and risk of all-cause mortality. Hazard ratios and 95% confidence intervals were calculated as an index of strength of the association. More than 96% (2,323) of the 2,404 participants survived, while 81 (3.4%) died. In the multivariable adjusted model, each 1-MET increment was associated with a 17% decreased risk of all-cause mortality. Compared with the reference group, those in the middle CRF group had a 58% lower risk of death and those in the upper CRF group had a 78% lower risk of death than those in the lower CRF group (Ptrend=0.0002).

Conclusion: CRF estimated using a non-exercise formula (non-exercise eCRF) is inversely associated with all-cause mortality in cancer patients.

Keywords: Cardiorespiratory Fitness; Non-Exercise; Mortality; Cancer Survivors

Introduction

Cancer is one of the leading causes of death on a global scale, accounting for approximately 10 million deaths in 2020 or one in six deaths in that year. Between 2015 and 2050, it is projected, partly due to the increasing growth and age of the world population, that the annual number of cancer cases will increase 49%, from 1,534,500 in 2015 to 2,286,300 in 2050 [1]. Additionally, nearly one-third of cancer deaths can be traced to tobacco use, high Body Mass Index (BMI),

alcohol consumption, poor diet, and lack of Physical Activity (PA) [2].

These risk factors, among others, are also major determinants of Cardiorespiratory Fitness (CRF), which is a measure of the capacity of the cardiopulmonary system to effectively transport oxygen and nutrients to active skeletal muscles for adenosine triphosphate resynthesis. It is essentially an objective estimation of a person's physiological functioning [3]. CRF has been established as a predictor of mortality from Cardiovascular (CV) disease (CVD) and it is usually measured via an Exercise Tolerance Test (ETT) in a healthcare setting. Therefore, the American Heart Association has proposed it as a clinical vital sign due to overwhelming evidence of its application to general CV health [4]. However, research has evaluated the accuracy of non-exercise estimated CRF (eCRF) as an alternative to exercise-based and its significance as a predictor of mortality from various diseases. This is primarily due to the cost and time burdens involved in exercise tests [5].

Recent studies have demonstrated significant relationships between non-exercise eCRF and health outcomes, including mortality

and incident hypertension, stroke and depression [5-8]. However, no prior study has investigated the association between non-exercise eCRF and all-cause mortality in cancer patients. We previously demonstrated that PA, a major determinant of CRF, was not associated with cancer survival, whereas Resistance Exercise (RE) was a significant predictor [9]. A prior analysis from the same cohort, however, demonstrated that higher CRF measured by ETT was a predictor of cancer survival [10]. Since ETT is not routinely performed clinically in cancer survivors to more precisely measure CRF, the purpose of this study was to examine the association between non-exercise eCRF and all-cause mortality among a group of cancer survivors. Existing data on the patient population, including men and women, was taken from the Aerobics Center Longitudinal Study (ACLS). The non-exercise estimation was derived from a formula using readily available medical records, including variables such as BMI, Resting Heart Rate (RHR) and Blood Pressure (BP) [11]. The formula could potentially be used as a valid alternative for assessing the risk of all-cause mortality in cancer patients.

Methods

Study Design and Participants

We used data from the ACLS where adult men and women were examined at the Cooper Clinic in Dallas, Texas. The ACLS is a longitudinal observation study in which new and recurring patients visited the clinic for a comprehensive physical examination and for lifestyle counseling, such as exercise, nutrition and stress management, since the 1970s. The current study included cancer participants at baseline between 1987 and 2002 as well as complete data to calculate the non-exercise eCRF. They were then followed for mortality after baseline clinical visit. These individuals, at the time of testing, all reported a history of cancer on their medical history questionnaire. Patients came from all 50 states and were volunteers, sent by their physicians and employers or were self-referred. Patients provided written informed consent for enrollment in the follow-up study. The Cooper Institute Institutional Review Board annually reviewed and approved the study procedures.

Non-exercise eCRF at Baseline

Non-exercise eCRF was calculated in metabolic equivalents (METs; 3.5 mL O₂-kg⁻¹-min⁻¹) with the following two sex-specific algorithms [11]:

eCRF in men (METs) = $21.2870 + (0.1654 \times \text{age}) - (0.0023 \times \text{age}^2) - (0.2318 \times \text{BMI}) - (0.0337 \times \text{waist circumference or WC}) - (0.0390 \times \text{RHR}) + (0.6351 \times \text{physically active}) - (0.4263 \times \text{current smoker})$; and eCRF in women (METs) = $14.7873 + (0.1159 \times \text{age}) - (0.0017 \times \text{age}^2) - (0.1534 \times \text{BMI}) - (0.0085 \times \text{WC}) - (0.0364 \times \text{RHR}) + (0.5987 \times \text{physically active}) - (0.2994 \times \text{current smoker})$.

METs was implemented as a continuous variable and higher METs equates to better CRF. Participants were further classified into lower, middle and upper groups on the basis of age- (18-30, 40-49, 50-59 or ≥60 years) and sex-specific thirds of the estimated METs distribution. Table 1 shows the thresholds that define the 3 CRF categories.

Age, BMI, WC and RHR were entered as continuous variables, while being physically active and a current smoker were considered dichotomous variables, with a value of 1 when present and 0 when absent. BMI was calculated from measured height and weight according to standard procedures during patients' visits. WC was measured in line with the umbilicus. Resting heart rate was determined with the participants recumbent after 5-minute rest prior to the test and was retrieved from the resting electrocardiogram. A 5-level index was used to determine PA, based on a prior validated questionnaire [12]. Walking or jogging >10 miles per week was considered physically active and was equal to index levels 3-4. Walking or jogging <10 miles per week, participating in some sport without walking or jogging or not walking or jogging at all was considered inactive and equal to index levels 0-2. Participants self-reported their smoking status as never smoked, former smoker or current smoker.

Potential Confounders

Potential confounders of the study included age, sex, alcohol consumption, hypertension, Diabetes Mellitus (DM) and hypercholesterolemia. This information was obtained during baseline examinations following the Cooper Clinic's standardized manual of operation. Following a minimum of 12 hours fasting overnight, a physical examination and preventative health evaluation were performed. Measures of BP, a chemical analysis of blood, personal medical history and lifestyle habits were included in the examination. Hypertension (Systolic BP/Diastolic BP ≥130/80 mmHg or physician diagnosis), DM (fasting glucose ≥7 mmol/L, insulin use or physician diagnosis), hypercholesterolemia (cholesterol ≥ 6.2 mmol or physician diagnosis), depression and parental history of cancer were determined from medical history.

All-Cause Mortality Determination

Vital status was ascertained using the National Death Index and death certificates from states in which participant deaths occurred. More than 95% of mortality follow-up is complete by these methods. The follow-up interval was computed from the date of a participant's baseline examination until the date of death for decedents or until December 31, 2003, for survivors.

Statistical Analysis

Baseline characteristics of the population of patients in the study were summarized by survival status. Groups were compared using t tests and χ^2 tests. The association between non-exercise eCRF and risk of all-cause mortality was examined using Cox regression models. Hazard Ratios (HRs) and 95% Confidence Intervals (CIs) were implemented as an index of the strength of association. Two separate models were tested: an age- and gender-adjusted model and a multivariable-adjusted model. Covariates included in the multivariable-adjusted model included: age (years), gender, year of baseline examination, heavy alcohol intake (>14 drinks/week in men or >7 drinks/week in women), presence of hypertension, DM or hypercholesterolemia, depression and parental history of cancer. We assessed linear trends in the association of non-exercise eCRF with the risk of all-cause mortality. We also examined non-exercise eCRF as a continuous variable so that each HR represents the risk associated with a 1-MET increase of eCRF. The proportional hazards assumptions were met for eCRF by comparing the log-log survival plots. Analyses were conducted in 2024 using SAS, version 9.4 (SAS, Cary, NC) with alpha set at $P < 0.05$.

ACLS Equation	Age Groups			
	18-30 year	40-49 year	50-59 year	≥60 year
Non-exercise estimated cardiorespiratory fitness in METs in men				
T1 (Lower third)	≤ 12.58	≤12.47	≤11.77	≤10.58
T2 (Middle third)	12.58-13.80	12.47-13.57	11.77-12.93	10.58-11.84
T3 (Upper third)	>13.80	>13.57	>12.93	>11.84
Non-exercise estimated cardiorespiratory fitness in METs in women				
T1 (Lower third)	≤ 10.50	≤10.26	≤9.64	≤8.61
T2 (Middle third)	10.50-11.19	10.26-10.96	9.64-10.33	8.61-9.43
T3 (Upper third)	>11.19	>10.96	>10.33	>9.43

Table 1: The thresholds of the three fitness categories in men and women cancer survivors.

Results

Table 2 shows the baseline characteristics of the study participants, including survivors and decedents. The average age was 53.59 ± 10.01 for the entire population, and 25.86% of the total population were women. Survivors were more likely to be younger, to be women, to have higher RHR and lower systolic BP, and to have higher parental history of cancer, as compared to the decedents. All the other baseline variables were not statistically different between survivors and decedents. Further, Table 2 shows that 96.63% ($n=2,323$) of the 2,404 participants survived, while 3.4% ($n=81$) died. The average age of the survivors was 53.32 ± 9.81 and the average age of the decedents was 61.44 ± 12.43 . Females constituted 26.33% of survivors but only 12.35% of decedents.

Table 3 shows the incremental tertiles of eCRF and associated risk of all-cause mortality for both the age- and gender- adjusted model as well as the multivariable- adjusted model. In Model 1 (adjusted for age and gender), there was an inverse association between incremental tertiles of eCRF and risk of all-cause mortality. Compared with the reference group (lower fitness), the middle fitness group (T2) had a 45% lower risk of death and the upper fitness group (T3) had a 65% lower risk ($P=0.002$). In Model 2, the multivariable- adjusted model, there was also an inverse association between incremental tertiles of eCRF and risk of all-cause mortality. Compared with the reference group (T1), T2 had a 58% lower risk of death and T3 had a 78% lower risk ($P=0.0002$).

	Total (n=2404)	Survivors (n=2323)	Decedents (n=81)	P value*
Age (yr)	53.59 (10.01)	53.32 (9.81)	61.44 (12.43)	<0.0001
Female	25.86	26.33	12.35	0.005
Body Mass Index (kg/m ²)	25.84 (3.93)	25.86 (3.95)	25.34 (3.35)	0.24
Waist circumference (cm)	89.23 (13.07)	89.17 (13.13)	90.79 (10.95)	0.20
Resting heart rate	60 (10)	60 (10)	57 (10)	0.007
Systolic blood pressure (mmHg)	123 (16)	123 (15)	128 (21)	0.07
Diastolic blood pressure (mmHg)	81 (10)	81 (10)	80 (13)	0.11
Fasting glucose (mg/dL)	99.82 (17.32)	99.79 (17.45)	100.77 (13.18)	0.52
Total cholesterol (mg/dL)	204.36 (39.13)	204.34 (38.21)	204.92 (35.92)	0.89
ACLS-estimated CRF (METs)	11.54 (1.75)	11.55 (1.75)	11.37 (1.68)	0.38
Current smoker	8.52	8.61	6.17	0.44
Heavy alcohol intake	13.60	13.43	18.52	0.19
Physically inactive	19.38	19.58	13.58	0.18
Hypertension	67.19	67.34	62.96	0.41
Diabetes mellitus	6.24	6.20	7.41	0.66
Hypercholesterolemia	16.22	16.14	18.52	0.57
Depression	13.85	13.98	9.88	0.29
Parental history of cancer	8.73	9.04	0	0.005
ACLS=Aerobics Center Longitudinal Study; CRF= Cardiorespiratory Fitness; METs = Metabolic Equivalents. Data are means (SD) for continuous variables or percentage for categorical variables. To convert the values for fasting glucose to mmol/L, multiply by 0.0555 and total cholesterol values to mmol/L, multiply by 0.0259. * For comparison of survivors and decedents.				

Table 2: Baseline characteristics of study participants by survival status.

ACLS-estimated CRF	N/deaths	Model 1* HR (95% CI)	Model 2† HR (95% CI)
T1 (Lower)	29/664	1.00	1.00
T2 (Middle)	25/847	0.55 (0.26-1.17)	0.42 (0.19-0.94)
T3 (Upper)	27/893	0.35 (0.17-0.71)	0.22 (0.10-0.50)
P for linear trend		0.002	0.0002
Per 1- MET increase		0.86 (0.77-0.95)	0.83 (0.74-0.93)
*Model 1 adjusted for age and gender; †Model 2 adjusted all variables in model 1 plus year of baseline examination, heavy alcohol intake, presence of hypertensions, diabetes and hypercholesterolemia, depression and parental history of cancer.			

Table 3: Association of estimated cardiorespiratory fitness and all-cause mortality in cancer survivors.

Discussion

In the cohort of cancer patients followed for an average of 7.28 years (SD=4.88), we found an inverse association between eCRF and all-cause mortality. These results are consistent with previous findings that CRF is an independent predictor of mortality from all-causes in both men and women [13,14]. These results are also consistent with that denote inverse relationships between CRF and all-cause or cause-specific mortality in cancer populations. It confirmed the findings from the same cohort but with measured CRF from exercise testing [10]. A recent paper evaluated CRF using an ETT before a cancer diagnosis in a population of 19,134 self-referred adults. It was found that better midlife CRF was associated with greater survival among cancer patients [15]. Further, in the same year, a single-center cohort analysis of 1,632 adult-onset cancer patients determined that CRF is a significant indicator of risk regarding all-cause, CVD and cancer mortality [3]. To the best of our knowledge, no study has been conducted on the association between non-exercise eCRF and all-cause mortality in cancer patients. Future studies are warranted to confirm or reject our findings.

PA is defined broadly as “any bodily movement produced by skeletal muscles that results in energy expenditure,” and exercise

is the planned and organized subset of PA [16]. CRF, on the other hand, is not behavioral, but rather describes the potential to accomplish a certain physical task or performance standard [17]. Although genetics can explain about 25-40% of the variation in CRF, habitual PA is the major determinant of CRF [18-20]. PA or exercise can improve CRF and the CV function [20,21] and therefore, lower the risk of all-cause mortality. Structured exercise training not only increases CRF, but also improves glycemic control, reduces blood pressure, promotes weight loss and can have favorable effects on lipid profile [22]. PA decreases blood glucose and lipids, which therefore may relieve glucolipotoxicity in β -cells and allow restoration of appropriate insulin secretory function [23]. Randomized controlled trials have shown the magnitude of blood pressure reduction ranging from 2 to 5 mmHg for systolic blood pressure and 1 to 4 mmHg for diastolic blood pressure, which may be sufficient to reduce the risk of coronary heart disease and stroke [24]. Exercise training reduces body weight, total body fat and visceral adipose tissue in adults with overweight or obesity [25]. In addition, higher levels of PA can lower circulating proinflammatory cytokines such as C-reactive protein, a major CV risk marker [26]. These potential pathways may underlie the link between CRF and all-cause mortality.

There are multiple limitations to the present study, particularly dealing with the sample population. First, the relative number of women in the population was low, which inhibited deeper analyses of subgroups across gender and the six factors associated with non-exercise eCRF. Second, the study population lacked diversity, as it was conducted among a cohort of primarily non-Hispanic Caucasian people with middle to high socioeconomic status. The lack of racial diversity among the sample impedes the study's external validity. On the contrary, the population was homogenous, which reduced any potential confounders which could have arisen from socioeconomic factors, thus strengthening the internal validity of the findings. Owing to limited information, we were unable to determine the types of cancer. It has been suggested that certain types of cancer may be more sensitive to changes in physical activity/fitness status [27,28]. A limitation also arose from a lack of availability of data on each patient's diet and medications. Regarding medication, unless it was included in the physician's diagnosis, it could not be accounted for in the study. We were unable to adjust for cancer therapies (e.g., chemotherapy, radiation). Dietary information was insufficient to be utilized and familial fitness was not assessed. In addition, we were unable to adjust the pre-diagnosis PA history due to the inability to obtain such data before patients' cancer diagnosis. However, we do have the PA data during patients' clinical visits in the current study. In Table 2, about one fifth of cancer patients were physically inactive and there was no difference between survivors and decedents. In fact, in our previous study among the cancer patients, we found that PA was not associated with a lower risk of all-cause mortality [9]. Finally, the non-exercise equation was taken from our previous publications, so it is unknown whether our results would significantly differ had another equation been used. Future studies with more diverse populations across multiple settings will be warranted.

Conclusion

The current report suggests a strong inverse association for cancer patients between non-exercise eCRF and mortality due to all causes. This result persisted after adjustment for clinical variables. Since eCRF is readily available from routine clinical information and does not require an ETT, this information is potentially very applicable to clinical practice in the management of cancer patients. Nearly 20% of the cancer patients in this study were not physically active. Clinicians should encourage their cancer patients to maintain an active lifestyle and to improve their CRF level for better overall survival. However, due to the observational nature of the study, future studies are needed to confirm or reject our findings reported here.

Conflict of Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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No funding was not involved in the manuscript writing, editing, approval or decision to publish.

Authors Contribution

The concept and design for the paper was by XS; XS analyzed the data; JH drafted the first draft; all authors provided critical input to the manuscript draft for intellectual content and approved the final document.

Data Availability

The data underlying this article cannot be shared publicly due to an agreement with the Cooper Institute. However, a limited working dataset might be shared on reasonable request to the corresponding author.

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