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Cardiorespiratory fitness in survivors of cervical, endometrial, and ovarian cancers: The Cooper Center Longitudinal Study

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HIGHLIGHTS

- Cardiorespiratory fitness is impaired among women with gynecologic cancer.
- Cardiorespiratory fitness levels differ among women with endometrial, ovarian, and cervical cancers.
- Confirmation of the results in larger studies is needed to inform exercise training programs.

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ABSTRACT

Background. Cardiorespiratory fitness (CRF), a strong predictor of mortality, is impaired among cancer patients. There is limited data, however, regarding CRF levels in women diagnosed with gynecologic cancers.

Methods. We compared CRF among ovarian, endometrial, and cervical cancer cases (n = 89) to age-matched controls (n = 89) in the Cooper Center Longitudinal Study (CCLS). CRF was evaluated by a maximal treadmill exercise tolerance test using a modified-Balke protocol. Conditional logistic regression was used to test for case–control differences in cardiorespiratory fitness, after controlling for age and body mass index, and adhering to the matched pairs design.

Results. The mean ages of cancer cases and controls were 50.9 years and 51.1 years, respectively (p = 0.81). Peak METs (1 MET = 3.5 mL kg^{-1} min^{-1}) were 9.2 ± 2.0 in cancer cases compared to 10.0 ± 2.2 in controls (p = 0.03). When stratifying by type of cancer, peak METs were 8.9 ± 2.2, 8.4 ± 1.9, 9.5 ± 2.0 for patients with ovarian, endometrial, and cervical cancer, respectively. A gynecological cancer diagnosis was associated with greater odds of having 1-MET lower CRF compared to controls (OR 1.31, 95% CI: 1.05–1.64, p = 0.018), after controlling for age and BMI.

Conclusion. Gynecologic cancer survivors were more likely to have a 1-MET lower CRF than controls. Given a 1-MET change in CRF is associated with a significant, we advocate for more robust research regarding CRF in gynecologic cancer patients.

1. Introduction

Cardiorespiratory fitness (CRF), measured via incremental exercise testing, is an accurate assessment of global cardiovascular function and the efficiency of oxygen transport and utilization [1,2]. CRF is a powerful predictor of all-cause mortality [3], and more recently, has been found to be prognostic of survival among cancer patients [4,5]. Two studies, both by our group, have shown that CRF is a strong independent predictor of all-cause mortality in cancer patients [4,5]. In the breast cancer literature, we have shown that CRF is lower among women with all stages of breast cancer compared to healthy, sedentary women, possibly attributed to the direct as well as indirect negative effects of adjuvant therapy in addition to unfavorable lifestyle changes [6].

Despite the known prognostic significance of CRF in cancer patients, there is currently a paucity of data regarding CRF levels in women diagnosed with gynecologic cancers. Importantly, these patients are subject to many of the same contributors to CRF impairment as breast cancer patients, including sedentary behavior [7,8], weight gain [7,8], and cytotoxic therapy. In support of this notion, Modesitt et al. [9] found CRF to be significantly lower in morbidly obese endometrial cancer patients (n = 17) compared to obese controls (n = 14) (15.0 vs. 17.9 mL kg^{-1} min^{-1}, respectively, p = 0.03). However, further study

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is needed to expand knowledge of CRF in gynecologic cancers as well as differences in CRF by gynecologic cancer type.

As such, we utilized the Cooper Center Longitudinal Study (CCLS) (1971–2007) [10] database to assess mean levels of CRF among prevalent ovarian, endometrial, and cervical cancer cases compared to age-matched controls. We hypothesized that cancer survivors would have significant impairments in CRF compared to women without a history of cancer.

2. Methods

2.1. Participants and procedures

The CCLS is a prospective observational cohort study of participants undergoing a preventative health examination including exercise tolerance testing to symptom limitation or volitional exhaustion at the Cooper Clinic in Dallas, TX. Patients enrolled in the CCLS signed an informed consent, and the Cooper Institute's Institutional Review Board approved this study.

An overview of the methods and procedures of the CCLS has been previously described [10–12]. In the present study, the CCLS database ($n = 24{,}631$) was queried for individuals reporting a history of non-skin-related cancer. A detailed medical chart review was then conducted to confirm a history of ovarian cancer, endometrial cancer, or cervical cancer as well as to ascertain date of diagnosis and type of local and/or systemic therapy. A total of 89 participants with a history of cancer were included in the study: 11 with ovarian cancer, 26 with endometrial cancer, and 55 with cervical cancer ($n = 89$, given 3 patients had a cancer diagnosis at 2 different sites). They were examined between 1986 and 2011. A non-cancer control group ($n = 89$) individually matched to cancer patients by sex, age, and date of the CCLS preventative medical exam was included for comparison purposes.

2.2. Cardiorespiratory fitness

CRF was evaluated by a maximal treadmill exercise tolerance test using a modified Balke protocol. Treadmill speed was initially set at 3.3 mph. In the first minute, the grade was set at 0% followed by a 2% increase in the second minute and a 1% increase every minute thereafter. After 25 min, the grade remained unchanged but the speed was increased 0.3 mph (5.4 m/min) for each additional minute until test termination. The test was terminated by volitional exhaustion reported by the participant or by the physician for medical reasons. Time to exhaustion (stress time) utilizing this protocol correlates with direct measurement of VO_{2peak} ($r = 0.92$) [13]. Furthermore, using well-characterized regression equations, CRF was estimated in peak metabolic equivalents (METs) (1 MET = 3.5 mL kg^{-1} min^{-1}) [14]. Continuous electrocardiography (ECG) and heart rate monitoring were performed during exercise and into recovery. Abnormal resting and exercise ECG findings were broadly categorized as rhythm and conduction disturbances and ischemic ST–T wave abnormalities described elsewhere [15].

2.3. Other CVD risk factors

Information about age, gender, and health habits was obtained by questionnaire and verified by a physician. Body mass index (BMI) was calculated from measured height and weight. Blood pressure was measured with standard auscultatory methods after the participant had been seated for 5 min. Systolic and diastolic pressures were recorded as the first and fifth Korotkoff sounds, respectively. Physical activity was assessed by self-report and was used to calculate MET·min/week [16]. A 12-h fasting antecubital venous blood sample was obtained and plasma concentrations of glucose and lipids were determined with standard, automated bioassays in the Cooper Clinic Laboratory.

2.4. Statistical methods

The study uses a case–control design using matched pairs. Each case is matched to a particular control by sex, age and year of the CCLS preventive medical exam. Summary statistics were calculated in aggregate over cancer sites and within case–control groups, consistent with the design. Summary statistics were compared using rank-sum tests for case–control groups and Kruskal–Wallis tests for cancer sites. Adhering to the matched pairs design, conditional logistic regression was used to test for a case–control difference in cardiorespiratory fitness as a continuous exposure, controlling for age and body mass index. All analyses were programmed in SAS/STAT®, version 9.4 (SAS Institute Inc., Cary NC, USA).

3. Results

3.1. Participant characteristics

Patient characteristics and treatment are summarized in Table 1 and Table 2. The mean time from cancer diagnosis to CRF assessment was 13.5 ± 8.7 years for all cancer patients combined; the time from diagnosis to CRF assessment was 11.7 ± 7.4 years, 10.8 ± 8.3 years, and 15.2 ± 8.8 years for ovarian, endometrial, and cervical cancer patients, respectively. The mean age was 51 ± 11 and 50.9 ± 11.2 years for cancer cases and controls, respectively ($p = 0.81$). The endometrial cancer patients (60 ± 13 years) were older compared to ovarian (49 ± 10 years) and cervical cancer cases (48 ± 8 years) ($p < 0.01$). The mean BMI was 24.7 ± 5.9 kg/m^2 for cancer cases and 23.9 ± 4.9 kg/m^2 for controls ($p = 0.39$). The corresponding BMIs for women with ovarian, endometrial, and cervical cancers were 28.1 ± 5.8 kg/m^2, 25.5 ± 7.9 kg/m^2, and 23.9 ± 4.9 kg/m^2, respectively. High blood pressure was more likely in cases (23%) compared to controls (10%), $p = 0.02$. Elevated blood glucose levels (≥126 mg/dL) were present in only 1% of the women overall. For CRF, peak METs were 9.2 ± 2.0 in cancer cases compared to 10.0 ± 2.2 in controls ($p = 0.03$). Peak METs were 8.9 ± 2.2 in ovarian cancer cases, 8.4 ± 1.9 in endometrial cancer cases, and 9.5 ± 2.0 in cervical cancer cases (Fig. 1).

3.2. Differences in CRF between cancer survivors and non-cancer controls

Conditional logistical regression was used to determine the likelihood that a 1-MET difference in CRF was associated with being a cancer case compared to control. A gynecologic cancer diagnosis was associated with greater odds of having 1-MET lower CRF compared to controls (OR 1.31, 95% CI: 1.05–1.64, $p = 0.02$) after controlling for age and BMI. This association was similar when comparing cervical cancer cases and controls (OR 1.31, 95% CI: 1.00–1.72, $p = 0.05$). Both endometrial (OR 1.22, 95% CI: 0.74–2.00, $p = 0.43$) and ovarian cancer cases (OR 6.02, 95% CI: 0.37–100, $p = 0.206$) had greater odds of having 1-MET lower CRF compared to controls, though these analyses were limited by small sample sizes and were not statistically significant.

4. Discussion

The current study suggests that CRF is impaired in gynecologic cancer survivors. Specifically, 1-MET lower CRF is more likely among gynecologic cancer cases compared to controls. This is the first data directly comparing levels of CRF among ovarian, endometrial, and cervical cancer survivors to women without known cancer. Given a 1-MET increase in CRF is associated with a significant overall mortality advantage in other studied groups [17,18], we now advocate for more robust research regarding CRF and cancer-related outcomes in gynecologic cancer patients.

Emerging evidence shows adjuvant therapy adversely affects CRF in cancer patients [3,19]. Gynecologic cancers, depending on stage and grade of tumor, are treated with surgery alone or in combination with