SPORTS & EXERCISE | RESEARCH ARTICLE

Cardiopulmonary exercise performance of cancer survivors and patients with stable coronary artery disease with preserved ejection fraction compared to healthy controls

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Abstract: Purpose: Cardiorespiratory fitness (CRF) is a predictor of lower mortality in patients with coronary artery disease (CAD) and cancer patients. Whether cancer survivors with preserved ejection fraction (EF) have a higher fitness level than patients with stable CAD and heart failure with preserved EF (HFpEF) is unknown. Methods: We enrolled 61 cancer survivors with an EF >50% (mean age 56.9 years ± 12.4), 60 patients with HFpEF and stable CAD (mean age 58.9 years ±8.1) and 60 healthy control subjects (mean age 61.2 years±9.9) to perform cardiopulmonary exercise testing (CPET) in our outpatient sports medical centre. Results: Maximal power [W] was inferior in cancer survivors (mean: 141.52W ± 67.43; CI: 124.26–158.79 W) than in HFpEF patients (mean: 157.90W ± 58.31; CI: 142.84W-172.96W) and healthy controls (mean: 196.58 W ± 79.37; CI: 176.08–217.09W). Performance at the individual anaerobic threshold (IAT; p = .033) and ventilatory compensation point (VCP, p = .003) were worse in the cancer and HFpEF groups than in the controls. Conclusion: CRF is significantly inferior in stable CAD patients with preserved EF and in cancer patients than in matched controls. There is a trend that cancer survivors even perform worse than HFpEF patients. Regular follow-up of CRF in...
these two groups is crucial for early detection of health deterioration in these seemingly stable patients.

**Subjects:** Sport and Exercise Science; Exercise Physiology; Heart Failure

**Keywords:** cardiopulmonary exercise testing; cancer survivors; stable cardiovascular disease; exercise response; VO$_{2peak}$

1. Introduction

Coronary artery disease (CAD) and cancer are two of the most prominent reasons for death, influenced by both genetic and environmental factors. Modifiable risk factors, such as smoking, obesity and physical inactivity can promote disease occurrence and progression and have become a major economic burden. (Adams et al., 2006; Berrington de Gonzalez et al., 2010; Hu et al., 2004) Over the last decades awareness of the positive effect of physical activity on primary and secondary cardiovascular disease prevention (Khera et al., 2016) as well as on cancer survival (Kerr, Anderson, & Lippman, 2017; Lemes et al., 2019) and on improvement of life quality through fatigue reduction have been documented. (Hutchison et al., 2019) Exercise can delay cardiac dysfunction in cancer patients (Howden et al., 2019) and cardiorespiratory fitness (CRF) itself can reduce mortality. (Imboden et al., 2019; Steell et al., 2019) Moreover, the growing co-morbidity of cardiovascular disease and cancer has led to the introduction of cardio-oncological rehabilitation programs (Gilchrist et al., 2019) and the inauguration of guidelines for exercise intensity and duration. (Kemps et al., 2019)

Cardiopulmonary exercise testing (CPET) is an established tool to assess cardiopulmonary fitness and certain parameters even seem to be prognostic factors for morbidity and mortality. (Francis et al., 2000; Guazzi et al., 2016, 2008; Letnes, Dalen, Vesterbekkmo, Wisloff, & Nes, 2018) Ventilatory threshold (VT) and ventilator compensation point (VCP) have recently been suggested for prognostic stratification in heart failure patients with reduced ejection fraction. (Carriere et al., 2019)

Patients with stable coronary artery disease (CAD) and cancer survivors are at an increased risk of adverse cardiovascular and thrombotic events and their cardiorespiratory fitness is believed to be lower than in age-matched controls. However, little is known whether these two seemingly recovered groups differ in terms of their fitness level.

We aimed to investigate whether cancer survivors and CAD patients with preserved ejection fraction (>50%; in the following termed as HFpEF patients) have a comparable CRF measured through oxygen uptake at peak performance (VO$_{2peak}$), peak power ($P_{max}$) and oxygen uptake efficiency slope (OUES) and compare them to healthy controls. We also wanted to analyze the correlation between weekly endurance training and performance level in these three groups. Apart from that, we aimed to elucidate if there are group-specific response patterns of the cardiovascular system during cardiopulmonary exercise testing (CPET), such as differences in blood pressure and heart rate amplitude.

2. Methods

2.1. Subjects and design

We screened 980 patients who consulted our sports medical outpatient clinic for a regular cardiopulmonary exercise test during a period of one year. 966 patients provided written consent, institutional review board appraisal was obtained (Figure 1). Subjects had to be between 40 and 75 years of age and had to be physically and mentally able to understand the purpose of the study. The study design was a cross-sectional comparison of the three groups with the dependent variable VO$_{2peak}$ and $P_{max}$.

In group 1 we included stable cancer patients with at least one year freedom from tumor progression or recurrence and no documented cardiovascular disease (CAD) and an ejection
fraction (EF) of at least 50% measured in routine transthoracic echocardiography (n = 61; 45 females and 16 males). 16 patients from this group were currently under oral maintenance chemotherapy, while 45 did not take any oncological medication (for the distribution of cancer types see supplemental material).

Group 2 consisted of patients with stable coronary artery disease with an EF of at least 50%, exertional dyspnea had to be lower or equal to NYHA II. Coronary artery disease was diagnosed via invasive catheterization and a luminal obstruction of at least 50% in at least one vessel (n = 60; 40 females and 20 males). 39 patients in this group had not suffered from a major cardiovascular event in the past, the other 21 patients had had acute coronary syndrome (ACS; 6 STEMI and 15 NSTEMI) in the past. Of the 21 ACS patients three had been treated conservatively, 16 received primary PCI and two had been referred for CABG. The last myocardial infarction had to be longer than 12 months in the past in order to get enrolled into the study.

Group 3 was formed out of 60 age-matched control subjects without a history of cancer or cardiovascular disease. Due to the high number of females, both in the cancer and cardiovascular group, inclusion was matched to the other groups (40 females and 20 males).

Exclusion criteria were clinically relevant diseases, which could limit patients’ performances, such as chronic obstructive lung disease, uncontrolled asthma and previously diagnosed pulmonary fibrosis. Other exclusion criteria were acute chest pain, dyspnea > NYHA II reported by the patient, new ECG findings suggestive of acute myocardial ischemia according to current guidelines (Thygesen et al., 2019) as well as a resting systolic blood pressure >160 mmHg.

A physical exam by a certified physician and a 12-lead ECG were conducted prior to CPET to assess health status and eligibility for maximal exercise testing. Standard transthoracic echocardiography was performed if the last available echo was longer than three months in the past. Exclusion criteria were an EF <50%, diminished right heart function (tricuspid annular plane systolic excursion, TAPSE <15mm) and significant valvular disease (grade two or higher).
Patients’ mean weekly endurance activity during the last six months was assessed via questionnaire and an extensive medical history regarding cardiovascular risk factors and drugs was taken. Participants were briefed about the importance of maximal exertion and were asked to report thoracic pain, disproportionate dyspnea and dizziness during the exam.

2.2. Methodology

Standard respiratory data were acquired with continuous breath-to-breath gas measurements. Gas analyzers were autocalibrated before each test. We used our most common exercise protocol for all patients, starting at 25W, with a 25W increase every 3 minutes. Shortly before the next increase blood lactate levels were taken.

Blood pressure was measured every three minutes and heart rate was monitored continuously. Criteria for exercise termination were relevant ECG alterations (new left bundle branch block, significant ST-segment alterations, increasing number of polymorphic, premature ventricular beats and sustained ventricular tachycardia), typical angina, dizziness, a systolic blood pressure drop > 20 mmHg or a systolic blood pressure above 250 mmHg. Data acquisition was performed according to current guidelines. (Guazzi et al., 2018)

Maximal oxygen uptake at peak performance (VO$_{2peak}$), at the ventilatory threshold (VO$_2$ at VT) and the ventilatory compensation point (VO$_2$ at VCP) as well as attained peak power (P$_{max}$), power at VT (P at VT) and power at VCP (P at VCP) were measured.

The VT was defined as the first non-linear rise in ventilation (disproportional rise of VCO$_2$/VO$_2$; V-slope>1), while the VCP was defined as the second change of slope in the VCO$_2$/VO$_2$-curve. The VCP was double-checked in the VE/VCO$_2$-curve as the first disproportional rise (between VT and VCP isocapnic buffering takes place).

In the lactate curve, lactate threshold (LT) was defined as the first rise of lactate levels above the resting state. The individual anaerobic threshold (IAT) was set at the second rise of lactate of at least 0.5mmol/l above the previous value (threshold concept of Baldari & Guidetti, 2000).

OUES, as a valid measure of cardiorespiratory reserve at submaximal exertion, was calculated. (Hollenberg & Tager, 2000)

Established respiratory equivalents and heart rate recovery 1 minute after exercise termination (HRR1) were documented according to current guidelines. (Guazzi et al., 2018)

2.3. Statistical analysis

Analysis and graphical layout was performed with SPSS 23 and Microsoft Excel 2007. Normality was tested using the Kolmogorow-Smirnow test. Normally distributed, independent variables in the three groups were analyzed with ANOVA, Bonferroni corrections were made for multiple testing. Non-parametric data for two independent groups were analyzed with the Mann-Whitney U-test, while we used the H-test of Kruskal-Wallis for three-group analyses. Between-group correlations were calculated using Spearman’s rho and linear regression was modeled to analyze the influence of significant independent parameters on the dependent variable VO$_{2peak}$.

3. Results

3.1. Anthropometric results

The three groups did not differ significantly in terms of age (p = .07), sex (p = .62) and endurance sport per week (p = .56). The majority of participants performed less than five hours/week (HFnEF n = 46; cancer n = 43; controls n = 39). Around three quarters of all groups were current non-smokers. However, 15% of former smokers in the HpEF group had more than 20 pack years (py) compared to 5% in the cancer and 2% in the control groups.
In the HFpEF group 95% were treated with statins (vs. 2% in the controls and 8% in the cancer group). Only 8% of the treated HFpEF patients had an LDL-cholesterol level of <70mg/dl as opposed to 44% in the cancer and 22% in the control group. The majority of HFpEF patients (47%) were in the range between 100-150mg/dl (vs 23% in the cancer and 28% in the control groups).

Around a quarter of all patients had BMIs >30 kg/m2 (HFpEF 20%, cancer 20% and controls 15%), while more patients in the cancer group had BMIs <20 kg/m2 (18% vs 5% in the HFpEF and 3% in the control groups). Table 1 provides an overview of the distribution of cardiovascular risk factors.

### 3.2. VO$_{2\text{peak}}$ and $P_{\text{max}}$

The three groups differed significantly in terms of maximal power ($p < .001$), with the control group (mean: 196.58 W ± 79.37; CI: 176.08–217.09 W) performing best. Additionally, HFpEF patients (mean: 157.90 W ± 58.31; CI: 142.84–172.96 W) performed significantly better in terms of $P_{\text{max}}$ ($p = .023$) than cancer patients (mean: 141.52 W ± 67.43; CI: 124.26–158.79 W; Figure 2(a)).

Analogously, the three groups also differed in VO$_{2\text{peak}}$ ($p < .001$). The control group performed best (mean: 2.24 l/min±0.8; CI: 2.03–2.45 l/min), while VO$_{2\text{peak}}$ was also significantly better in the HFpEF group (mean:1.91 l/min±0.63; CI: 1.75–2.07 l/min) than in the cancer survivors (mean: 1.71 l/min±0.67; CI: 1.54–1.88 l/min; $p = .030$). Adjusted to body weight expressed as relative VO$_{2\text{peak}}$, the controls (mean: 30.80 ml/kg/min ± 9.83; CI: 28.24–33.36 ml/kg/min) were significantly better than HFpEF patients (mean: 23.70 ml/kg/min±6.48; CI: 22.03–25.37 ml/kg/min) and cancer survivors (mean: 23.36 ml/kg/min ±6.64; CI: 21.66–25.06 ml/kg/min); the latter two did not differ significantly ($p = .950$, Figure 2(b)).

### 3.3. Heart rate response

O$_2$ pulse (ml O$_2$/heart beat) was significantly better in HFpEF (mean: 14.53 ml/beat±4.55; CI: 13.36–15.71 ml/beat) and controls (mean 14.12 ml/beat±4.68; CI: 12.91–15.32 ml/beat) than in cancer patients (mean 11.54 ml/beat±3.70; CI: 10.59–12.49ml/beat; $p < .001$). This is a result of the higher VO$_{2\text{peak}}$ in the HFpEF and control groups as mentioned above and the

| Table 1. Cardiovascular risk factors across the three groups. Significance (<.05) was marked with an asterisk. |
|---------------------------------------------------------------|
| **Hypertension**                                              |
| Medically controlled hypertension                             | 63% | 18% | 13% |
| **Diabetes**                                                 |
| Medically controlled diabetes                                 | 17% | 2%  | 2%  |
| **LDL cholesterol [mg/dl]**                                   |
| <70                                                           | 8%  | 44% | 22% |
| 100–150                                                      | 47% | 23% | 28% |
| **Smoking**                                                   |
| Non-Smokers                                                  | 72% | 74% | 78% |
| >20 pack years                                               | 15% | 5%  | 2%  |
| **BMI [kg/m2]**                                               |
| BMI<20                                                       | 5%  | 18% | 3%  |
| BMI >30                                                      | 20% | 20% | 15% |
| **Weekly endurance traning hours**                           |
| <5 h/week                                                    | 77% | 70% | 65% |
| >5 h/week                                                    | 23% | 30% | 35% |
significantly lower peak heart rate in HFpEF (mean: 139.28/min±25.35; CI: 132.73–145.83/min) than cancer (p = .013; mean: 151.18/min±20.38; CI: 145.92–156.45/min) and controls (p < .001; mean: 160.30/min±21.04; CI: 154.86–165.74/min).

ΔHR (difference between resting and peak heart rate) differed significantly between the three groups (p < .001). The HFpEF (p < .001; mean: 67.35/min±22.09; CI: 61.64–73.06/min) and cancer groups (p = .006; mean: 71.67/min±21.26; CI: 66.23–77.12/min) displayed lower values than the controls (mean: 84.15/min±19.61; CI: 79.08–89.22/min), while HFpEF and cancer patients did not differ significantly (p = .085).
Heart rate recovery 1 minute after exercise termination (HRR1) was significantly worse in cancer patients ($p = .006$; mean: 19.60 beats±7.2; CI: 17.76–21.46 beats) and HfP EF patients ($p = .01$; mean: 19.92 beats±9.02; CI: 17.59–22.25 beats) than in healthy controls (mean: 24.3 beats±9.21; CI: 21.92–26.68 beats).

### 3.4. Blood pressure response

Resting systolic ($p = .224$) and diastolic ($p = .874$) pressures did not differ between the groups, while peak systolic pressures ($p = .005$) and the difference between systolic resting and peak pressures ($ΔRRsys$; $p = .018$) varied. Peak systolic pressure was significantly higher in the controls than in the cancer patients ($p = .004$), but controls and HfP EF patients did not differ ($p = .818$). $ΔRRsys$ differed significantly between cancer and controls ($p = .017$) but not between HfP EF and cancer ($p = .181$) and HfP EF and the controls ($p = .99$). There was no difference in diastolic peak ($p = .871$) and $ΔRRdia$ ($p = .873$; Table 2).

### 3.5. Thresholds

At the LT no overall group differences were found ($p = .052$), while they did differ at the IAT ($p = .033$), with a significant difference between the cancer and control groups ($p = .027$). At the VT performance differed significantly among the three groups ($p = .001$), driven by the difference between cancer and controls ($p = .001$; HfP EF vs. controls $p = .258$; cancer vs. HfP EF $p = .153$). Power at VCP also differed ($p = .003$) driven by the difference of cancer and controls ($p = .002$; HfP EF vs. cancer $p = .317$; controls vs. HfP EF $p = .289$). Analogously, VO2 at VT and VCP differed significantly only between the cancer and control groups ($p < .001$ and $p = .007$; Figure 3).

### 3.6. CPET parameters

HfP EF patients tended to have higher VE/VCO2 slopes (mean: 35.94 ± 8.67; CI: 33.71–38.18) than cancer survivors (mean: 33.72 ± 5.74; CI: 32.22–35.22) and controls (mean: 31.28 ± 5.29; CI: 29.91–32.65). Statistically, the difference between the controls and the HfP EF groups was significant ($p = .002$), but not between controls and cancer ($p = .059$) and HfP EF and cancer ($p = .770$).

We further analyzed the correlation of weekly endurance hours with $P_{max}$, VO2peak and OUES. In the HfP EF and the cancer group all three parameters correlated significantly (Table 3).

Additionally, we performed a sub-analysis of performance expressed through $P_{max}$, VO2peak and OUES in the HfP EF group for patients with and without MACE (major adverse cardiovascular event).

### Table 2. Blood pressure at rest and peak exercise across the three groups

|                | HfP EF | Cancer | Controls | p-values |
|----------------|--------|--------|----------|----------|
| RRsysRest [mmHg] | 128.17 ± 14.87 | 123.31 ± 14.93 | 128.25 ± 14.67 | .224 |
| CI: 124.32–132.01 | CI: 119.41–127.20 | CI: 124.46–132.04 |
| RRdiaRest [mmHg] | 80.25 ± 8.66 | 80.25 ± 7.85 | 80.45 ± 8.3 | .704 |
| CI: 78.01–82.49 | CI: 78.21–82.30 | CI: 79.22–81.67 |
| RRsysPeak [mmHg] | 193.75 ± 29.32 | 182.88 ± 28.48 | 200.17 ± 24.97 | .005* |
| CI: 186.18–201.32 | CI: 175.46–190.30 | CI: 193.72–206.62 |
| RRdiaPeak [mmHg] | 86.05 ± 14.41 | 84.75 ± 10.92 | 84.83 ± 9.52 | .871 |
| CI: 82.33–89.77 | CI: 81.10–87.89 | CI: 82.37–87.29 |
| ΔRRsys [mmHg] | 67.58 ± 24.78 | 60.08 ± 21.41 | 71.25 ± 20.58 | .018* |
| CI: 61.18–73.98 | CI: 54.51–65.66 | CI: 65.93–76.57 |
| ΔRRdia [mmHg] | 5.17 ± 11.39 | 5.34 ± 9.69 | 4.00 ± 8.70 | .873 |
| CI: 2.23–8.11 | CI: 2.81–7.86 | CI: 1.75–6.25 |

Table 2: Mean values of resting and peak systolic and diastolic blood pressures with standard deviations in the three groups. A 95% confidence interval (CI) is depicted as well as p-values. Significance (alpha<.05) is marked with an asterisk. RRsysRest: systolic pressure at rest; RRdiaRest: diastolic pressure at rest; RRsysPeak: systolic pressure at peak performance; RRdiaPeak: diastolic pressure at peak performance; ΔRRsys: Difference between systolic resting and peak pressure; ΔRRdia: difference between diastolic resting and peak pressure.
Neither \( P_{\text{max}} \) (\( p = .153 \)) nor \( VO_2\text{peak} \) (\( p = .123 \)) and OUES (\( p = .424 \)) achieved the level of significance. Furthermore no differences were found in the cancer patients with and without oral maintenance chemotherapy (\( p = .636 \) for \( P_{\text{max}} \); \( p = .496 \) for \( VO_2\text{peak} \) and \( p = .421 \) for OUES).

A linear regression model calculated for the dependent variable \( VO_2\text{peak} \) demonstrated age (beta = \(-.258\)), group (beta = \(.192\)), sex (beta = \(-.450\)) and weekly endurance training hours (beta = \(.364\)) to be independent predictors of \( VO_2\text{peak} \) (all parameters with \( p < .001 \)).

### 4. Discussion

We aimed to analyze CPET performance in cancer survivors and HFpEF patients as opposed to matched controls. To our knowledge, this is the first study to directly compare performance of cancer survivors and HFpEF patients with stable CAD. Our study consisted of 2/3 females, which adds data to a recently published pilot study, which has shown that greater CRF is associated with a lower mortality risk in women with cancer. (Vainshelboim, Lima, & Myers, 2019)

We found that seemingly healthy cancer survivors, consisting mainly of breast cancer patients, were inferior in terms of \( VO_2\text{peak} \) and peak power achieved in CPET compared to a group of HFpEF patients with stable CAD and the matched controls. However, relative \( VO_2\text{peak} \) did not differ between cancer and HFpEF patients, but was significantly inferior to healthy controls. From our study we learn that the group of cancer survivors is limited in their exercise performance and is thus exposed to a higher cardiovascular risk than healthy individuals of the same age. For heart failure patients regular check-ups are suggested for primary and secondary prevention. According to our data, this should also be encouraged in cancer survivors.

Despite an EF >50%, cancer survivors were inferior in CPET performance than healthy controls. However, over the last couple of years we have learnt that global longitudinal strain (GLS) is a more
subtle parameter to detect early decline in cardiac function and has already been implemented into guidelines of cardio-oncology. We did not have the opportunity to measure GLS in our study and thus, cannot exclude pre-existing subtle differences in cardiac function between HfPEF and cancer survivors. A large percentage of our cancer patients had breast cancer, some of which received Tamoxifen, which is known to negatively affect myocardial function. (Khosrow-Khavar et al., 2017) Our study highlights that regular cardiovascular check-ups are warranted in cancer survivors.

The majority of patients were non-smokers at the time of the study, but the HfPEF group had accumulated a significantly higher amount of pack years. The high percentage of non-smokers in all groups shows that there is a selection bias towards motivated participants who try to reduce their risk profiles ("positive" selection). HfPEF patients had significantly more cardiovascular risk factors than cancer survivors, such as diabetes and hypertension.

The heart rate response to exercise differed between the three groups. Not surprisingly, the greatest range of ΔHR was found in the healthy controls, while the lowest was seen in the HfPEF patients. Additionally, O₂ pulse was the lowest in this group as a result of a lower peak heart rate and higher VO₂peak values in the HfPEF group compared to the cancer survivors. The dampered heart rate response in the HfPEF group may be explained by the higher number of beta-blockers as part of CAD and heart failure medication (75% in HfPEF vs 4% in the controls and 6% in the cancer patients). Interestingly, cancer patients had significantly lower ΔHR than controls, which cannot be explained by beta-blocker influence. On the other hand there was no significant difference in ΔHR between HfPEF patients and cancer survivors. Thus, cancer survivors without any known cardiac disease may already show cardiac limitations during exercise expressed through a lower range of heart rate during strenuous work. Furthermore, HRR1 was worse in cancer and HfPEF patients than in controls, presumably as a result of worse physical fitness.

As for the blood pressure response, diastolic values underlie little changes and may be harder to measure during exercise. They do not seem to differentiate very well between the groups. However, systolic peak pressure as well as ΔRRsys differed significantly. Notably, cancer patients display lower values than both controls and HfPEF patients.

We can only speculate on the different responses of heart rate and systolic blood pressure among the three groups. Since it is has been shown that cancer patients display a decrease of longitudinal strain while maintaining normal ejection fraction as an early sign of cardiac limitation (Narayan et al., 2016), the different heart rate and blood pressure response of (seemingly healthy) cancer survivors may reflect cardiac limitation. This hypothesis is backed up by the obvious difference in relative VO₂peak between age-matched cancer survivors and healthy individuals, the former performing much worse. Peak power seems to be an inferior parameter compared to relVO₂peak in cancer survivors, since a considerable amount of cancer patients had a BMI <20 kg/m². Peak power, as an absolute value, is more influenced by muscle mass and body weight than relVO₂peak.

Looking at lactate and ventilatory thresholds, cancer patients performed significantly worse than the controls and there was also a trend that they performed worse than HfPEF patients (see Figure 3). Not surprisingly, the main difference occurred between the IAT and the VCP with increasing workload (however, the rather large standard deviations have to be taken into account). The tendency of higher VE/VCO₂ slopes in the HfPEF group does not seem to be clinically relevant (mean values mainly below 40).

Furthermore, we found modest but significant correlations between weekly endurance training hours and Pmax, VO₂peak and QUES for HfPEF and cancer patients. In a linear regression model we found the parameters age, sex, group and weekly training hours to be independent determinants for VO₂peak. This also highlights the observation that group affiliation (HfPEF vs. cancer survivors vs.
controls) has a major impact on performance in CPET. Consequently, encouraging physical training in HFP EF as well as cancer survivors should improve physical fitness and reduces morbidity in these patients.

5. Practical application and limitations
It is widely acknowledged that cancer survivors have limited physical fitness compared to healthy age-matched controls. On the other hand heart failure patient with preserved ejection fraction also have limited aerobic capacity due to enhanced ventricular filling pressures and reduced compliance. In both groups physical activity is recommended to prevent disease recurrence or progression. To our knowledge no study has ever compared these two groups to healthy controls in terms of exercise capacity. In our study we were able to show that seemingly stable cancer survivors are inferior to healthy age-matched controls in cardiopulmonary exercise testing. Secondary prevention in heart failure patients is widely accepted and physicians are aware of the necessity of regular check-ups. However, we show that cancer survivors perform similarly in CPET than HFP EF patients and therefore also warrant regular surveillance, which may not always be the case in seemingly recovered cancer survivors. Our study therefore adds information to the literature that physicians and coaches have to be aware of the limited cardiorespiratory fitness of cancer survivors, in an extent similar to HFP EF patients.

The majority of subjects in our three groups performed less than 5 hours per week, which is below the recommended “weekly dose” of established prevention guidelines. Therefore, our results may not be transferred to more physically active subjects with the same diseases.

Our study is limited to a cross-sectional design and does not contain long-term data. We are also aware of the fact that cardiovascular risk and mortality factors differed between the groups and may have influenced the results. The health status of the control group was assessed by taking a medical history, a physical exam, routine lab works as well as lung function testing and transthoracic echocardiography. Therefore, covert diseases, although unlikely, may have been missed during the process of study inclusion.

6. Conclusion
Two observations of our study are of clinical importance: (1): Both HFP EF and cancer patients were clearly inferior to healthy controls and therefore have a higher risk of morbidity and mortality. (2) Supposedly cured cancer patients do not perform similarly to healthy controls. There is even a trend that they perform worse than HFP EF patients (despite a significantly lower percentage of arterial hypertension and diabetes), which also exposes them to a considerable cardiovascular risk and should prompt meticulous health check-ups.

Supplementary material
Supplemental data for this article can be accessed here.

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Authors’ contributions
SW was responsible for the draft and outline of the manuscript, MH reviewed the design of the study and supervised the interpretation of statistical data. All authors have read and agree to the final version of the manuscript and also agree to the order of presentation of authors.

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