MINI-FOCUS ISSUE: PHYSICAL ACTIVITY AND LIFESTYLE INTERVENTIONS IN CANCER

ORIGINAL RESEARCH

Validity of Estimated Cardiorespiratory Fitness in Patients With Primary Breast Cancer

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ABSTRACT

BACKGROUND Estimated peak oxygen consumption (VO_2peak) is widely used in oncology; however, estimated VO_2peak equations were developed in noncancer settings.

OBJECTIVES The aim of this study was to evaluate the validity of estimated VO_2peak in women with primary breast cancer and to develop oncology-specific estimated VO_2peak equations.

METHODS VO_2peak was directly measured (TrueOne 2400, Parvo Medics) during 380 cardiopulmonary exercise tests in women previously treated for breast cancer (mean age: 59 ± 10 years; 3.1 ± 1.2 years post-therapy). The American College of Sports Medicine (ACSM), the Fitness Registry and the Importance of Exercise National Database (FRIEND), and heart failure (HF)-FRIEND equations were used to estimate VO_2peak. New equations were developed using patient and peak (Onc_{peak}) or submaximal (Onc_{sub}) exercise test characteristics.

RESULTS The median differences between measured and estimated VO_2peak were 7.0 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$, 3.9 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$, and -0.2 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$ for ACSM, FRIEND, and HF-FRIEND, respectively. The number of estimated VO_2peak values within ± 3.5 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$ of the measured values was 70 (18%), 164 (43%), and 306 (81%) for ACSM, FRIEND, and HF-FRIEND, respectively. The Onc_{peak} and Onc_{sub} models included body mass index, age, a history of chemotherapy or radiation, the peak measured heart rate, and the treadmill grade and/or speed. The median differences between measured and estimated VO_2peak were 0.02 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$ (Onc_{peak}) and -0.2 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$ (Onc_{sub}). Eighty-six percent (n = 325) and 76% (n = 283) estimated VO_2peak values were within ± 3.5 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$ of the measured VO_2peak values for Onc_{peak} and Onc_{sub}, respectively.

CONCLUSIONS HF-FRIEND or oncology-specific equations could be applied to estimate VO_2peak in patients previously treated for breast cancer in settings where cardiopulmonary exercise tests are not available. (Trial Comparing the Effects of Linear Versus Nonlinear Aerobic Training in Women With Operable Breast Cancer [EXCITE]; NCT01186367
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Cardiorespiratory fitness (CRF) provides an integrative measure of the capacity of the pulmonary, cardiovascular, hematologic, and musculoskeletal systems to transport and use oxygen.[1] For this reason, CRF is considered a "clinical vital sign," and assessment is recommended for clinical decision making in many chronic diseases.[2-4] In breast cancer, impaired CRF is a consequence of direct and indirect (ie, lifestyle perturbations) adverse effects of therapy on all organ components of the cardiopulmonary system.[5] Poor CRF is associated with increased symptom burden[6,7] and an increased risk of morbidity and mortality from cancer and noncancer conditions.[8-11] Therefore, accurate assessment of CRF in the large and rapidly growing population of patients with primary breast cancer is of high importance for risk stratification, toxicity monitoring, and evaluation of the efficacy of exercise interventions.[12]

A cardiopulmonary exercise test (CPET) coupled with automated gas exchange to directly measure peak oxygen consumption (Vo₂peak) is the gold standard assessment of CRF.[3] Nevertheless, the widespread applicability of the CPET is limited by requirements for specialized equipment and trained personnel.[13,14] Accordingly, the American College of Sports Medicine (ACSM)[15] and the Fitness Registry and the Importance of Exercise National Database (FRIEND)[16] developed equations derived from patient and exercise test characteristics to estimate Vo₂peak. Three commonly used estimated Vo₂peak equations were developed based on exercise test characteristics from young adults (ie, 19-26 years old),[15] older healthy adults (ie, no comorbidities),[16] and patients with heart failure (ie, reduced or preserved ejection fraction).[17] Estimated Vo₂peak is widely used in oncology research and clinical practice settings[18,19]; therefore, there is a need to evaluate the validity of estimated Vo₂peak equations in patients with a history of cancer.

We evaluated the validity of estimated Vo₂peak equations in comparison with directly measured Vo₂peak from CPETs in women with post-treatment primary breast cancer and developed oncology-specific equations derived from patient and peak (Onc_peak) or submaximal (Onc_sub) exercise test characteristics. We hypothesized that oncology-specific equations would have improved accuracy relative to nononcology estimated Vo₂peak equations.

METHODS

PATIENTS AND ELIGIBILITY. Full details regarding the study sample, recruitment, and procedures have been reported previously[20] and are outlined in the Supplemental Methods. Eligible patients were ≥1 year to <5 years after the completion of primary adjuvant therapy and had Vo₂peak below age- and sex-matched active levels.[3,21] Patients enrolled in the 16-week randomized controlled exercise trial (NCT01186367) completed CPETs at baseline (prerandomization) and postintervention (week 17); a subset of patients completed a CPET at midpoint (week 8). All study procedures were reviewed and approved by Duke University Medical Center and Memorial Sloan Kettering Cancer Center Institutional Review Boards. All patients provided written informed consent.

CPET Vo₂PEAK. Vo₂peak (mL O₂·kg⁻¹·min⁻¹) was assessed by an incremental walking CPET on an electronic motorized treadmill with 12-lead electrocardiographic monitoring (Mac 5000, GE Healthcare) according to standard procedures.[3,22] Breath-by-breath (averaged every 30 seconds) expired gases were collected using a mouthpiece and analyzed continuously by a calibrated metabolic measurement system (TrueOne 2400, Parvo Medics). Before starting the test, a warm-up was completed to familiarize the patient with the treadmill and identify a comfortable walking speed between 1.5 and 4.0 mph. During warm-up, the heart rate response (∼20 beats/min above resting, varied with age), gait, and perceived level of exertion (rating of perceived exertion ∼8-10) were assessed to determine the CPET starting walking speed. After 3 minutes of rest, the test began using a personalized modified Balke protocol. Specifically, the test began at the individually identified warm-up speed and 0% grade for 2 minutes. During the first stage, metabolic metrics including minute ventilation, respiration rate, respiratory exchange ratio, fraction of expired oxygen content, and heart rate response compared with rest were assessed to select the increment of grade (2% or 3%) increase for subsequent stages. A 3% increase per stage was standard; if a patient demonstrated a large increase in minute ventilation and/or the respiratory exchange ratio stayed elevated, a 2% increase in grade was selected. The grade was subsequently increased every 2 minutes until a clear decrease in the fraction of expired carbon dioxide oxygen content from its highest value occurred; after this stage, the grade remained constant, and the speed was increased every minute until exhaustion. Speed increases were 0.2 or 0.3 depending on the patient's gait and the perceived amount of effort left before self-terminating the test. Acceptable

peak CPET criteria for this analysis included any 2 of the following[3]: 1) a plateau in VO_2, concurrent with an increase in treadmill grade or speed; 2) a respiratory exchange ratio ≥1.10; 3) the attainment (±10 beats/min) of an age-predicted heart rate; and 4) volitional exhaustion as measured by a rating of perceived exertion ≥18 on the Borg scale. Upon CPET completion, a trained exercise physiologist identified the ventilatory threshold (ie, submaximal) as defined by the following criteria: 1) a drop in the fraction of expired carbon dioxide oxygen content after a peak or plateau; 2) a nonlinear increase in the minute ventilation; and 3) a respiratory exchange ratio between 0.98 and 1.02.

ESTIMATED Vo₂PEAK. Exercise test characteristics from the CPET were used to estimate Vo_2peak using the following: ACSM[15] (Vo_2peak = [speed (m/min) × 0.1] + [speed (m/min) × fractional grade × 1.8] + 3.5), FRIEND[16] (Vo_2peak = [speed (m/min) × (0.17 + fractional grade × 0.79) + 3.5]), and HF-FRIEND[17] (Vo_2peak = [speed (m/min) × (0.17 + fractional grade × 0.32) + 3.5]) equations.

STATISTICAL ANALYSIS. Data from all arms of the trial were combined for these analyses. Vo_2peak as measured by CPETs and estimated models were summarized using descriptive statistics with the median (quartiles [Q1-Q3]) or mean ± SD for continuous variables and the number and percentage for categoric variables. Patient (eg, treatment history) and exercise test characteristics (eg, treadmill speed and grade) at Vo_2peak and the ventilatory threshold were used to develop Onc_{peak} and Onc_{sub}. Five-fold cross-validation was used to develop the oncology-specific estimated Vo_2peak equations. The cross-validation was based on a linear model with an outcome of measured Vo_2peak and a random intercept to account for repeated CPET measurements for the same patient at up to 3 time points. Variables were considered for inclusion on the basis of previous literature and the potential to impact Vo_2peak[16] (Supplemental Table 1). Variables retained by stepwise selection ($P ≤ 0.20$) in at least 50% of the models were included in the final models (Supplemental Table 2). As a sensitivity analysis, we also examined how results would differ if variables selected in at least 80% of the models were retained. Two variables introduced collinearity issues: the measured versus estimated heart rate and heart reserve. These variables were removed before fitting the stepwise selection model. The average root mean-squared error across the cross-validation models was evaluated to indicate model accuracy based on the difference between estimated and measured Vo_2peak values.[23] The

average fixed effects from the random intercept model were used to generate estimated values for the oncology-specific equations.

Bland-Altman plots were used to display the difference between measured and all estimated Vo_2peak measures along the y-axis and the average of measured and estimated observations along the x-axis, along with the average bias and 95% limits of agreement.[24] The data were visually inspected and log transformed before computing the limits of agreement in order to meet the assumptions of the method; Vo_2peak values were transformed back to the original scale for interpretation of the results. Estimates of the SD of the difference in Vo_2peak between methods reflect the within- and between-participant variation to account for repeated Vo_2peak measurements.[24,25] The concordance between the estimated and measured Vo_2peak values was evaluated by Lin's concordance correlation coefficient (CCC)[26] and SD, which accounts for the longitudinal experimental design.[24] A CCC value of 1 indicates perfect agreement; values <0.6 were considered to be poor agreement.[27] Sensitivity analyses of the CCC and Bland-Altman limits of agreement were performed among baseline CPET measurements only to assess whether the removal of repeated measurements changed the results. Based on previous work demonstrating that a 3.5 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$ (ie, 1 metabolic equivalent) higher Vo_2peak is associated with a ~20% reduced risk of all-cause mortality,[28] we used this value to serve as an acceptable difference threshold for estimated Vo_2peak values (ie, a difference between the estimated and CPET Vo_2peak of ≤3.5 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$ considered an acceptable value). Analyses were performed in R version 4.0.0 (R Foundation for Statistical Computing).

RESULTS

A total of 170 patients with primary breast cancer (mean post-primary adjuvant therapy: 3.1 ± 1.2 years; age: 59 ± 10 years; body mass index [BMI]: 29.8 ± 5.5 kg/m²) were included (Table 1).[20]

MEASURED Vo₂PEAK AND VENTILATORY THRESHOLD. At baseline, midpoint, and post-intervention, 174, 77, and 156 CPETs were conducted, respectively. Of the 407 CPETs conducted, 27 did not meet criteria and were excluded, resulting in 380 included CPETs (Table 2). Across all time points, the median (Q1-Q3) peak treadmill grade and peak treadmill speed were 0.10 (Q1-Q3: 0.09-0.12) and 89 m/min (Q1-Q3: 80-99 m/min), respectively. The median treadmill grade and treadmill speed at the ventilatory threshold were 0.09 (Q1-Q3: 0.06-0.12)

TABLE 1 Characteristics of the Participants (N = 170)	
Time from surgery to enrollment, y	
Median (Q1-Q3)	3.0 (2.1-3.9)
Mean ± SD	3.1 ± 1.2
Age, y	
Median (Q1-Q3)	59 (51-65)
Mean ± SD	59 ± 10
BMI, kg/m²	
Median (Q1-Q3)	29.0 (25.5-33.5)
Mean ± SD	29.8 ± 5.5
Left ventricular ejection fraction, %	
Median (Q1-Q3)	62.8 (59.4-65.1)
Mean ± SD	62.1 ± 4.5
Not available	21
Race	
Non-Hispanic White	105 (62)
Other group	65 (38)
Smoking	
Never	106 (63)
Former	55 (33)
Current	7 (4.2)
Unknown	2 (1.2)
Disease stage	
I	96 (57)
II	59 (35)
III	14 (8)
Unknown	1 (<1)
Clinical subtype	
ER⁺/PR⁺/HER2⁻	101 (60)
HER2⁺	34 (20)
ER⁻/PR⁻/HER2⁻	28 (17)
Other	6 (3)
Unknown	1 (<1)
Surgery	
Lumpectomy	86 (51)
Mastectomy	84 (49)
Previous chemotherapy	99 (58)
Previous radiotherapy	121 (71)
Current endocrine therapy	123 (72)
Current medications	
Beta-blockers	24 (14)
ACE inhibitors	30 (18)
Angiotensin receptor blockers	12 (7.1)
Diuretic	33 (19)
Aspirin/antiplatelet	34 (20)
Statins	39 (23)
Calcium-channel blocker	14 (8.2)
Pre-existing (controlled) cardiovascular conditions	
Coronary artery disease	3 (1.8)
Osteoporosis	13 (7.6)
Arthritis	22 (13)
Type II diabetes	18 (11)
Hyperlipidemia	41 (24)
Hypertension	68 (40)
Any	93 (55)

Values are n or n (%) unless otherwise indicated.

ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; BMI = body mass index; ER = estrogen receptor; HER2 = human epidermal growth factor; PR = progesterone receptor.

TABLE 2 Cardiopulmonary Exercise Test Characteristics (N = 380)[a]	
Rest	74 (68-83)
Heart rate, beats/min	74 (68-83)
Ventilatory threshold	
Treadmill speed, mph	3.00 (2.60-3.30)
Treadmill speed, m/min	80 (70-89)
Treadmill grade, %	9.0 (6.0-12.0)
Treadmill grade, decimal	0.09 (0.06-0.12)
Treadmill speed x grade	6.76 (5.19-8.37)
Measured heart rate, beats/min	146 (136-156)
Heart rate reserve, beats/min	70 (60-81)
Age-predicted heart rate at 80%, beats/min	145 (139-150)
Difference between measured and age-predicted heart rate at 80%, beats/min	2 (−7 to −10)
Peak	
Treadmill speed, mph	3.30 (3.00-3.70)
Treadmill speed, m/min	89 (80-99)
Treadmill grade, %	10.0 (9.0-12.0)
Treadmill grade, decimal	0.10 (0.09-0.12)
Treadmill speed × grade	9.3 (7.5-11.3)
Measured heart rate, beats/min	163 (151-176)
Heart rate reserve, beats/min	89 (76-99)
Age-predicted peak heart, beats/min	161 (155-168)
Difference between measured and age-predicted peak heart rate, beats/min	2 (−7 to −9)

Values are median (Q1-Q3). [a]7 patients were missing data on resting heart rate; 10 patients were missing data on ventilatory threshold treadmill speed (mph and m/min), grade, heart rate, heart rate reserve, and age-predicted heart rate at 80% beats/min.

Q = quartile.

and 80 m/min (Q1-Q3: 70-89 m/min), respectively. The median difference between the measured and 80% of the age-predicted peak heart rate at the ventilatory threshold was −2 beats/min (Q1-Q3: −7 to −10 beats/min).

ONC$_{PEAK}$ AND ONC$_{SUB}$ ESTIMATED Vo₂PEAK EQUATIONS. Variables retained by stepwise selection ($P \leq 0.20$) in at least 50% of the Onc$_{peak}$ and Onc$_{sub}$ models included the peak measured heart rate (beats/min), BMI (kg/m²), age (years), a history of chemotherapy (yes/no) or radiation (yes/no), and treadmill grade (decimal) and/or speed (mph). The resultant estimated Vo₂peak equations were as follows: Onc$_{peak}$ ([−0.08 × age (years)] + [−0.24 × BMI] + [0.06 × peak measured heart rate (beats/min)] + [25.34 × peak fractional grade] + [2.64 × peak treadmill speed (mph)] + [−0.64 if previous chemotherapy] + 13.8) and Onc$_{sub}$ ([−0.30 × BMI] + [−0.14 × age (years)] + [0.16 if previous radiation therapy] + [0.08 × submaximal speed (mph)] + 32.99). The average root mean-squared error across the cross-validation models was 2.53 (range: 2.43-2.65) for Onc$_{peak}$ and 3.06 (range: 2.81-3.48) for Onc$_{sub}$.

VALIDITY OF ACSM, FRIEND, HF-FRIEND, AND ONC_PEAK AND ONC_SUB ESTIMATED Vo₂PEAK. Measured and estimated Vo₂peak values ar presented in the **Central Illustration and Table 3**. The median difference between measured and estimated Vo₂peak was 7.0 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$ and 3.9 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$ in ACSM and FRIEND compared with -0.21 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$, 0.02 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$, and -0.23 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$ in HF-FRIEND, Onc_peak, and Onc_sub, respectively. The number of estimated Vo₂peak values within ± 3.5 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$ of the measured values was below 50% for ACSM and FRIEND and above 75% for HF-FRIEND, Onc_peak, and Onc_sub. ACSM and FRIEND overestimated Vo₂peak with 95% limits of agreement ranging from -2% to 84% and -6% to 51%, respectively, whereas the limits of agreement were similar for HF-FRIEND (-22% to 25%), Onc_peak (-19% to 24%), and Onc_sub (-23% to $+30\%$) (**Figures 1A-1E**). There was a low CCC between measured and ACSM (CCC = 0.31; 95% CI: 0.27- 0.36) and FRIEND (CCC = 0.53; 95% CI: 0.48-0.58) estimated Vo₂peak and a high CCC between measured and HF-FRIEND (CCC = 0.75; 95% CI: 0.71-0.79), Onc_peak (CCC = 0.81; 95% CI: 0.77-0.84), and Onc_sub (CCC = 0.68; 95% CI: 0.63-0.72; **Figures 2A-2E**). In sensitivity analyses restricted to variables retained in at least 80% of the models, the number of estimated Vo₂peak values within ± 3.5 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$ of the measured values was 80% and 71% for Onc_peak and Onc_sub, respectively (Supplemental Table 3). Sensitivity analyses restricted to the baseline assessment did not vary from the primary results (Supplemental Table 4).

DISCUSSION

Poor Vo₂peak is prevalent across the breast cancer continuum (ie, from diagnosis to survivorship)[10,29,30] and correlates with heightened symptom burden.[31] Vo₂peak is also a significant predictor of all-cause[10,32] and cause-specific mortality,[33] even after adjustment for important clinical covariates. Despite the importance of accurate assessment of Vo₂peak in the large and rapidly growing population of patients with cancer,[34] prediction equations are commonly used in oncology clinical and research settings.[13] For instance, in a systematic review evaluating exercise testing in cancer patients, Jones et al[19] reported that among 90 studies, 49 (54%) used exercise tests other than the CPET. In a meta-analysis evaluating the effects of exercise therapy on Vo₂peak in patients with adult-onset cancers,[18] 18 of 48 (38%) studies used prediction equations to estimate Vo₂peak. Collectively, given that in noncancer clinical populations

Vo₂peak is considered a "clinical vital sign"[2] and that an exercise-induced improvement in Vo₂peak of 3.5 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$ is associated with an adjusted 30%[35] to 38%[36] risk reduction in all-cause mortality, accurate estimation of Vo₂peak is of high importance in research and clinical practice settings for risk stratification, toxicity monitoring, and evaluation of exercise intervention efficacy.

Our findings are consistent with results from prior studies demonstrating that estimated Vo₂peak equations developed in individuals without comorbidities have low validity in noncancer clinical populations.[37,38] In obese patients with metabolic syndrome, Debeaumont et al[37] reported that estimated Vo₂peak ranged from -5% to 31% of measured Vo₂peak. Similarly, Moneghetti et al[38] reported that FRIEND estimated Vo₂peak was significantly different than CPET Vo₂peak in 1,094 patients referred for CPET evaluation for HF symptoms. ACSM and FRIEND equations were developed in young (ie, 19-26 years old)[15] and older healthy (ie, >40 years, free from cardiovascular disease)[16] participants. The discrepancy between estimated and measured Vo₂peak in clinical settings may be caused by the omission of potentially important clinical factors contributing to impaired Vo₂peak. As such, our findings demonstrating that ACSM and FRIEND equations have poor validity in patients previously treated for primary breast cancer support the application of alternative equations to estimate Vo₂peak.

Intriguingly, there was high validity between measured Vo₂peak and estimated Vo₂peak using the equation developed in patients with HF. The HF-FRIEND equation was developed from a cohort that included HF patients with both reduced and preserved ejection fraction.[17] Although patients with primary breast cancer in the present trial had intact resting systolic function, whether the strong correlation between HF-FRIEND estimated and measured Vo₂peak was caused by a preserved ejection fraction phenotype is not known. Patients with breast cancer reach Vo₂peak for a particular age group approximately 20 to 30 years earlier than apparently healthy women without a history of breast cancer[10]; therefore, applying equations with treadmill grade and speed derived from patients with HF with similar Vo₂peak is likely more accurate than those derived from nonclinical populations. Impaired Vo₂peak in patients with breast cancer is also attributed, in part, to a blunted inotropic response.[39,40] Thus, given that breast cancer patients have an intact chronotropic reserve,[39,40] prediction equations derived from patients with similar exercise limitations such as HF

CENTRAL ILLUSTRATION Measured Versus Estimated Peak Oxygen Consumption in Post-Treatment Primary Breast Cancer
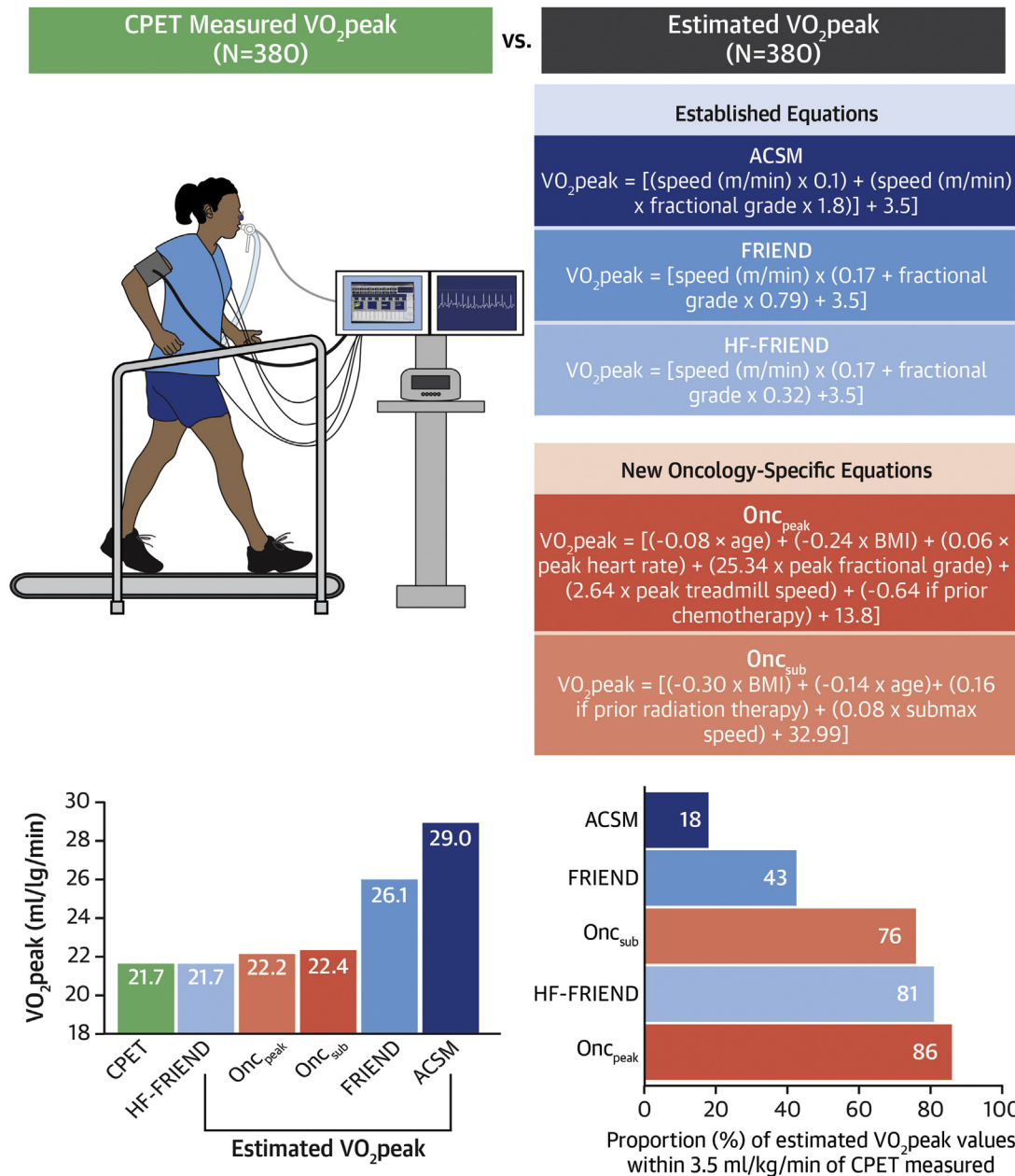
Michalski M, et al. J Am Coll Cardiol CardioOnc. 2022;4(2):210–219.

(Top) Directly measured peak oxygen consumption (Vo₂peak) using a CPET (n = 380) and estimated Vo₂peak using established equations (American College of Sports Medicine [ACSM], Fitness Registry and the Importance of Exercise National Database [FRIEND], and heart failure [HF]-FRIEND) and oncology-specific equations developed from patient and exercise test characteristics were compared in women previously treated for breast cancer. **(Bottom)** ACSM and FRIEND equations overestimated Vo₂peak and had poor accuracy compared with cardiopulmonary exercise test (CPET)-measured Vo₂peak. HF-FRIEND and oncology-specific equations could be applied to estimate Vo₂peak in settings where the CPET is not available. Onc$_{peak}$ = oncology peak; Onc$_{sub}$ = oncology submaximal.

TABLE 3 Measured and Estimated Vo$_2$peak Using ACSM, FRIEND, HF-FRIEND, Onc$_{peak}$, and Onc$_{sub}$

	CPET Measured	ACSM	FRIEND	HF-FRIEND	Onc$_{peak}$	Onc$_{sub}$
Vo$_2$peak, mL O$_2 \cdot$ kg$^{-1} \cdot$ min^{-1}	21.7 (19.1-25.4)	29.0 (25.3-33.4)	26.1 (23.5-29.1)	21.7 (19.9-23.6)	22.2 (20.1-24.4)	22.4 (20.3-24.3)
Difference between measured and estimated Vo$_2$peak, mL O$_2 \cdot$ kg$^{-1} \cdot$ min^{-1}		7.0 (4.2-9.9)	3.9 (2.3-5.9)	−0.2 (−2.1 to 1.5)	0.02 (−1.7 to 1.5)	−0.2 (−2.3 to 1.9)
Values within 3.5 mL O$_2 \cdot$ kg$^{-1} \cdot$ min^{-1}		70 (18)	164 (43)	306 (81)	325 (86)	283 (76)

Values are median (Q1-Q3) or n (%).

ACSM = American College of Sports Medicine; CPET = cardiopulmonary exercise test; FRIEND = Fitness Registry and the Importance of Exercise National Database; HF = heart failure; Onc$_{peak}$ = oncology peak; Onc$_{sub}$ = oncology submaximal; Q = quartile; Vo$_2$peak = peak oxygen consumption.

with a reduced or preserved ejection fraction will likely improve the accuracy of Vo$_2$peak estimations.[41]
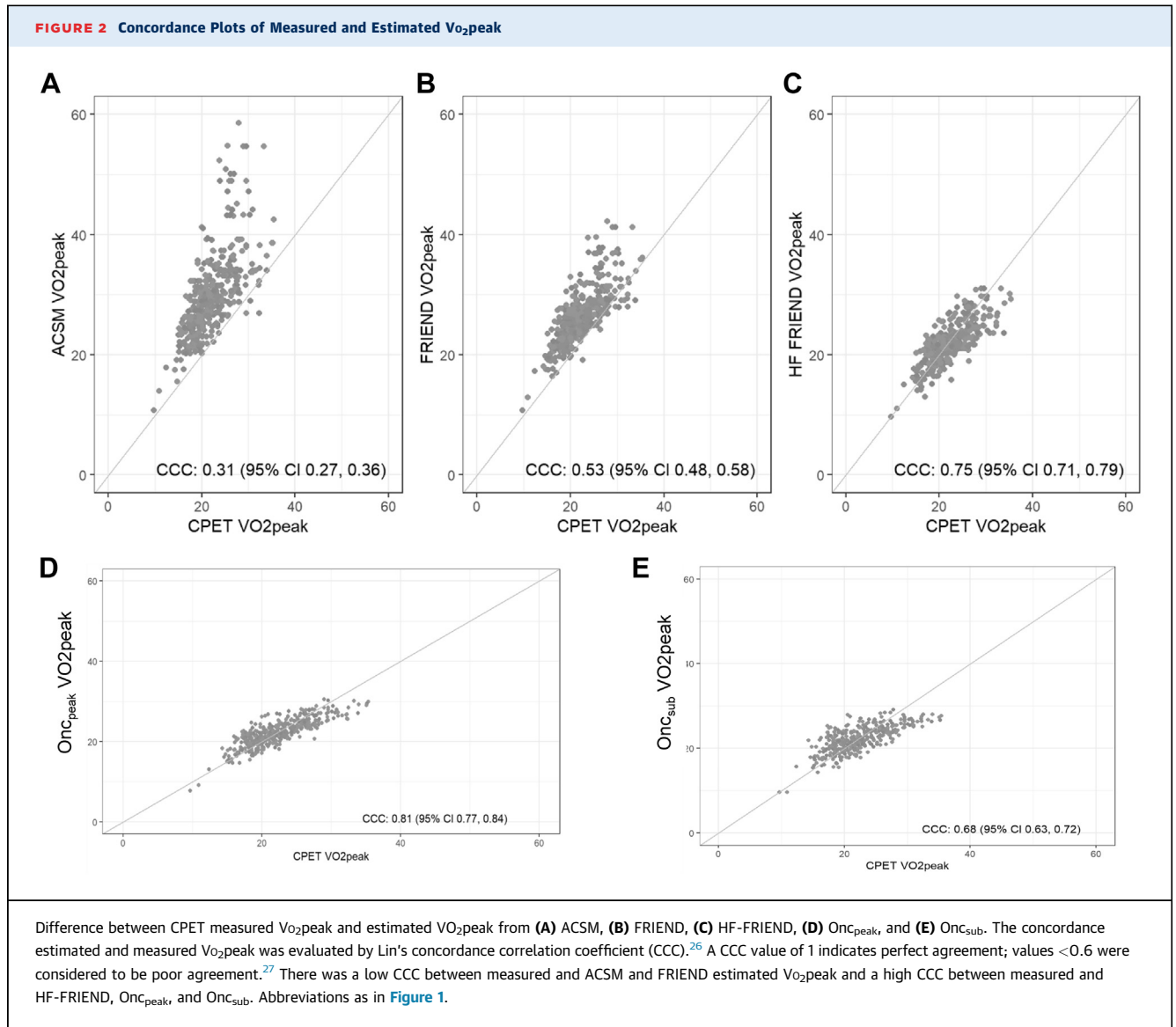
Although there was high validity between measured and HF-FRIEND estimated Vo$_2$peak, the inclusion of cancer treatment history in Vo$_2$peak estimation formulas may be important given the potential of anticancer treatment regimens to impact all components of O$_2$ transport and uptake.[42] In addition to adverse cardiac effects, radiation and chemotherapy can result in pulmonary dysfunction, anemia, and vascular and skeletal muscle dysfunction.[12] To this end, cancer treatment history was a key factor that distinguished oncology-specific from other estimated Vo$_2$peak equations where Onc$_{peak}$ includes previous chemotherapy and Onc$_{sub}$ includes previous radiation. The reason for the inclusion of disparate treatment modalities between Onc$_{peak}$ and Onc$_{sub}$ is not known. However, chemotherapy and radiation were retained in 80% and 40% peak models, respectively, whereas in submaximal models, radiation was retained in 100% and chemotherapy in just 40% of the models. These findings

FIGURE 1 Bland-Altman Plots of Measured and Estimated Vo$_2$peak
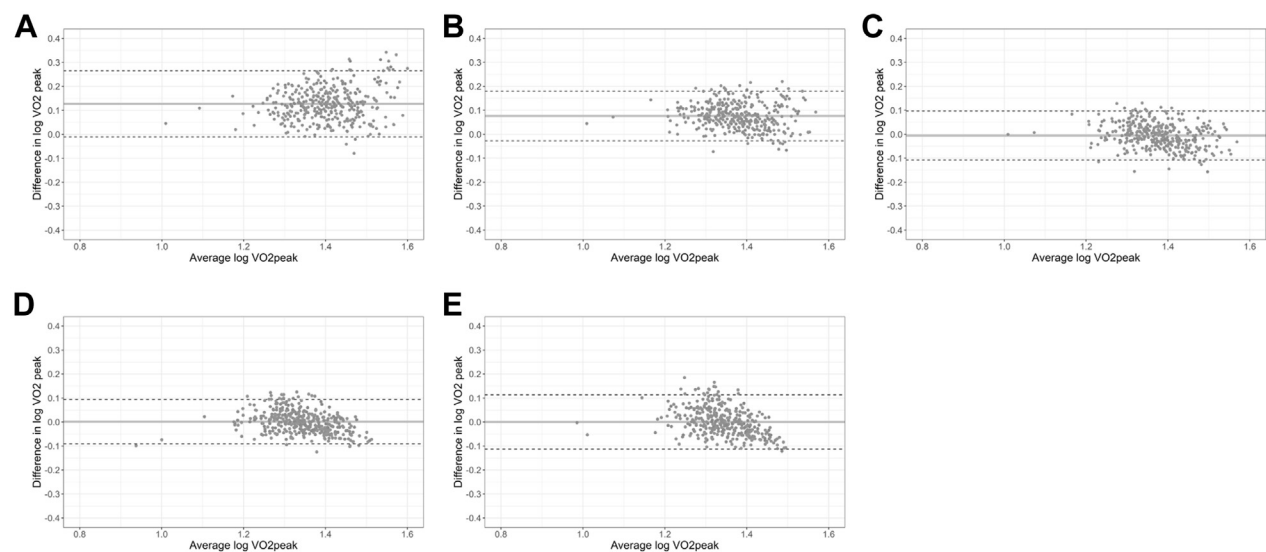
Estimated Vo$_2$peak from **(A)** ACSM, **(B)** FRIEND, **(C)** HF-FRIEND, **(D)** Onc$_{peak}$, and **(E)** Onc$_{sub}$. The difference between CPET measured Vo$_2$peak and all estimated Vo$_2$peak measures along the y-axis and the average of the measured and estimated observations along the x-axis, along with the average bias and 95% limits of agreement.[24] ACSM and FRIEND overestimated Vo$_2$peak with 95% limits of agreement ranging from −2% to 84% and −6% to 51%, respectively, whereas the limits of agreement were evenly distributed for HF-FRIEND (−20% to 25%), Onc$_{peak}$ (−20% to 27%), and Onc$_{sub}$ (−23% to 30%). CPET = cardiopulmonary exercise test; Vo$_2$peak = peak oxygen consumption; ACSM = American College of Sports Medicine; FRIEND = Fitness Registry and the Importance of Exercise National Database; HF = heart failure; Onc$_{peak}$ = oncology peak; Onc$_{sub}$ = oncology submaximal.

FIGURE 2 Concordance Plots of Measured and Estimated Vo₂peak

Difference between CPET measured Vo₂peak and estimated VO₂peak from **(A)** ACSM, **(B)** FRIEND, **(C)** HF-FRIEND, **(D)** Onc$_{peak}$, and **(E)** Onc$_{sub}$. The concordance estimated and measured Vo₂peak was evaluated by Lin's concordance correlation coefficient (CCC).[26] A CCC value of 1 indicates perfect agreement; values <0.6 were considered to be poor agreement.[27] There was a low CCC between measured and ACSM and FRIEND estimated Vo₂peak and a high CCC between measured and HF-FRIEND, Onc$_{peak}$, and Onc$_{sub}$. Abbreviations as in **Figure 1**.

suggest the differences are likely caused by specific treatment-related effects on maximal and submaximal exercise responses. For instance, the direct cardiac effects of chemotherapy are likely a primary factor contributing to impaired inotropic response at peak exercise,[39,40] whereas the effects of radiation on skeletal muscle may contribute to altered anaerobic glycolysis at submaximal exercise.[43] Additional research evaluating the effects of chemotherapy and/or radiation on the contributions of heart rate, stroke volume, and peripheral oxygen extraction at submaximal and peak exercise are needed.

Confirmatory studies in larger cohorts are required; however, our findings support the recommendation of Onc$_{peak}$ or HF-FRIEND in settings where treatment history is not available to estimate Vo₂peak in patients with primary breast cancer. In settings where peak exercise tests cannot be performed, Onc$_{sub}$ is an acceptable alternative.

STUDY LIMITATIONS. Our results are limited by a relatively small number of breast cancer patients; external validation of oncology-specific estimated Vo₂peak equations in a larger cohort is warranted, as well as validation in other patient populations with

cancer exposed to chemotherapy and/or radiation. External validation should be performed for the prediction models built using the 2 stepwise selection thresholds considered based on variables retained in 50% (primary results) and 80% (supplement) of models. Second, to develop oncology-specific equations, we used binary indicators of treatment exposure. Future studies should evaluate whether the inclusion of specific doses and agents improves estimated Vo$_2$peak accuracy. Finally, most CPETs in the United States are performed on a treadmill; our findings will not extend to nonincremental and cycle ergometry CPETs.

CONCLUSIONS

In summary, equations developed in healthy noncancer populations to estimate Vo$_2$peak are suboptimal in patients previously treated for breast cancer. HF-FRIEND or oncology-specific equations could be applied to estimate Vo$_2$peak in settings where CPETs are not available.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Accurate assessment of CRF in the large and rapidly growing population of patients with primary breast cancer is of high importance for risk stratification, toxicity monitoring, and evaluation of the efficacy of exercise interventions. However, the widespread applicability of directly measured is limited by requirements for specialized equipment and trained personnel. We found that in post-treatment patients with primary breast cancer, equations developed in healthy noncancer populations to estimate CRF are suboptimal. Heart failure and oncology-specific estimated CRF equations had high validity and could be used to estimate CRF in breast cancer settings where CPETs are not available.

TRANSLATIONAL OUTLOOK: Further research evaluating the validity of heart failure and oncology-specific estimated CRF equations in other cancer settings is needed.

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APPENDIX For an expanded Methods section and supplemental tables, please see the online version of this paper.