Increased Duration of Exercise Decreases Rate of Nonresponse to Exercise but May Not Decrease Risk for Cancer Mortality

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ABSTRACT

LIN, D., M. POTIAUMPAI, K. SCHMITZ, and K. STURGEON. Increased Duration of Exercise Decreases Rate of Nonresponse to Exercise but May Not Decrease Risk for Cancer Mortality. *Med. Sci. Sports Exerc.*, Vol. 53, No. 5, pp. 928–935, 2021. **Introduction:** Previous studies have observed an inverse relationship between exercise and breast cancer risk. However, there is interindividual variability in response to exercise training interventions. We investigated whether increasing the dose of aerobic exercise (150 or 300 min·wk^{-1}), while keeping intensity of exercise constant (70%–80% HR_{max}), decreases the number of exercise nonresponders and further decreases associated risk for cancer mortality in our study population of women genetically predisposed for breast cancer. **Methods:** Healthy premenopausal women at elevated risk of breast cancer were randomized into control (<75 min·wk^{-1}, n = 47), low-dose exercise (150 min·wk^{-1}, n = 39), and high-dose exercise groups (300 min·wk^{-1}, n = 39) for approximately 6 months. We assessed 1) clinical effectiveness (CE), defined as an improvement in predicted $\dot{V}O_{2max}$ of ≥1 mL·kg^{-1}·min^{-1}, and twice the typical error (2× TE) of $\dot{V}O_{2max}$ as thresholds to classify exercise "nonresponders"; 2) CE and 2× TE relative to exercise adherence levels; and 3) related changes in $\dot{V}O_{2max}$ to predicted cancer mortality risk. **Results:** After our 6-month intervention, we observed that 23.5% of women in the low-dose group and 5.6% of women in the high-dose group were clinical nonresponders (P = 0.04). Clinical nonresponder status was independent of adherence level. Associated reduction in risk for cancer mortality was observed among 87.2% of women in the low-dose group and 94.9% in the high-dose group (P = 0.43). **Conclusion:** Increasing volume (not intensity) of exercise via time spent exercising significantly decreases the number of "nonresponders." True nonresponders were observed as some women did not improve their fitness capacity despite high exercise adherence levels. Lastly, it appears 150 min·wk^{-1} is sufficient to decrease the predicted risk of cancer mortality. **Key Words:** EXERCISE, NONRESPONDER, PREVENTION, NEOPLASM, MORTALITY

APPLIED SCIENCES

Breast cancer in women, measured by incidence, mortality, and financial costs, is a serious global health crisis (1–3). It is estimated that more than 1 million women are diagnosed with breast cancer every year around the world, and 41% of them die from the disease (1). In addition, breast cancer is the most common occurring neoplasm in women, accounting for nearly one-quarter of the estimated annual 8.6 million cancer diagnoses in females (4). The mortality rate in low-income countries is even higher (48%) because of late diagnosis and insufficient medical infrastructure (1,5). Among U.S. women, breast cancer is the most common cancer diagnosed and is the second leading cause of cancer death after lung cancer (6).

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Exercise training increases fitness capacity, commonly determined by maximal oxygen uptake ($\dot{V}O_{2max}$) (7–10). In previous studies, it has been observed that increased levels of physical activity are associated with reduced risk of cancer-specific mortality (11–13). A longitudinal U.S. study conducted two cardiopulmonary exercise tests, 1 yr apart, in 833 participants who were then followed up to 17.7 yr (10). They observed 172 deaths and reported that change in $\dot{V}O_{2max}$ over 1 yr is inversely related to cancer mortality, each 1 mL·kg^{-1}·min^{-1} increase in $\dot{V}O_{2max}$ was associated with a 16% reduction in cancer mortality (10). However, there are strong interindividual variations to exercise interventions (14). Many researchers have observed "nonresponders" to exercise: individuals who show no improvement in $\dot{V}O_{2max}$ after exercise interventions (15–19). Yet, others question the concept of "nonresponders," arguing that it may be a matter of exercise prescription (e.g., time, intensity, and frequency) (20). Some people may require a modified dose of exercise or an adjusted exercise prescription to show exercise-induced benefits rather than being identified as exercise "nonresponders" (21).

We hypothesized that increasing the dose of aerobic exercise through total time spent exercising per week (150 or 300 min·wk^{-1}) would decrease the number of exercise nonresponders. We conducted a secondary analysis of the Women in Steady Exercise Research (WISER) Sister study, a randomized

controlled trial testing dose–response effects of aerobic exercise (22). In addition, we assessed if the doses of exercise would alter the magnitude of change in $\dot{V}O_{2max}$ enough to reflect predicted risk reduction in cancer mortality in our study population of women at high risk for breast cancer.

METHODS

Study recruitment and intervention. The WISER Sister study was a randomized controlled three group parallel-arm trial designed to compare the effect of two doses of aerobic exercise training to a control group in healthy premenopausal women at elevated risk of breast cancer over 5 menstrual cycles (22). Women recruited into the WISER Sister study 1) were ≥18 yr, 2) were eumenorrheic, 3) were nonsmokers, 4) had a body mass index (BMI) ranging from 18 to 50 $kg \cdot m^{-2}$, 5) had a >18% lifetime risk of developing breast cancer according to the Gail or Claus prediction models (23,24), 6) had a known deleterious mutation (e.g., *BRCA1* or *BRCA2*) or documentation of a family member with the mutation, and 7) were not currently doing more than 75 min of aerobic exercise per week (22). Further details of recruitment and screening are provided in previous papers (22–25).

One hundred and thirty-nine women were randomly assigned to one of the following groups: control (CONT, $n = 46$), low-dose exercise (LOW, $n = 45$), or high-dose exercise (HIGH, $n = 48$). To account for potential confounders, participants were stratified by baseline BMI (BMI < 30 vs ≥30 $kg \cdot m^{-2}$) and gynecological age at start of menses (<10 vs ≥10). In-home treadmills (model 5.65; Smooth Fitness, King of Prussia, PA) were provided to study participants to complete the exercise training sessions. Before randomization, all participants were provided an in-person orientation on the exercise intervention from a certified personal trainer. The trainer also provided ongoing support and monitoring of participants' adherence to the protocol. Participants randomized to treatment groups were asked to wear a downloadable Polar Heart Rate monitor (U.S. model RS400; Polar Electro Inc., Lake Success, NY) and fill out an exercise log for the purpose of objectively monitoring their exercise adherence. Heart rate data were downloaded by research staff and analyzed to document objective monitoring of exercise adherence.

Exercise intensity was set at 65%–70% of age-predicted maximum heart rate (MHR) for the first 4 wk of exercise (where age-predicted MHR = 220 − age), which progressed to 70%–80% of MHR for the remainder of the study. Exercise intensity did not differ between the low- and the high-dose groups. Only those minutes of exercise completed within the target heart rate zone counted toward total minutes for the week. Exercise adherence was defined as the proportion of total prescribed minutes completed for the full study.

Women in the low-dose group completed 150 $min \cdot wk^{-1}$ of aerobic exercise, whereas women in the high-dose group were asked to increase exercise duration by 20–25 min every 2 wk until they reached 300 min of aerobic exercise per week. Participants randomized into the CONT group were asked to maintain their usual level of physical activity and to not engage in any new exercise program during study participation. Strength and flexibility training were not included within this study. During the study period, 14 participants were lost to follow-up (did not return for follow-up exercise test), leaving 125 participants available for analysis (CONT, $n = 47$; LOW, $n = 39$; HIGH, $n = 39$). The study was approved by the University of Pennsylvania Institutional Review Board, and no study activities occurred before written informed participant consent.

Categorization of responders and nonresponders. Participants' aerobic fitness level was assessed at baseline and follow-up using a maximal treadmill test, the Bruce protocol. Exercise testing was conducted 6–10 d after start of menstrual cycle. Exercise testing technicians were blinded to the intervention group allocation. $\dot{V}O_{2max}$ was estimated using the method by Pollock et al. for maximal exercise testing with the Bruce protocol ($\dot{V}O_{2max} = 0.073$ (time in seconds on the Bruce protocol) − 3.9) (26).

To categorize responders and nonresponders, we 1) determined twice the typical error (2× TE) of maximal exercise testing for $\dot{V}O_{2max}$ estimation (27–31) and 2) defined clinic effectiveness (CE) for change in $\dot{V}O_{2max}$ (10). TE is an adaptable form of within-subject variation; the TE of measurement reflects the reliability of measurement within groups in repeated trials, or the coefficient of variation (32). The TE for $\dot{V}O_{2max}$ was calculated using the change from PRE to POST in the CONT group using the following equation (32):

$$TE = \frac{SD_{diff}}{\sqrt{2}}$$

where SD_{diff} is the SD of the $\dot{V}O_{2max}$ difference in the CONT group, which estimates measurement error and the within-subject variability caused by changes in behavioral or environmental factors during the intervention period (18). This value was multiplied by two and expressed as a percentage of the measurement's mean (33). We calculated a 2× TE of 4.09 $mL \cdot min^{-1} \cdot kg^{-1}$.

Clinic effectiveness (CE) was used as another threshold to categorize exercise "responders" and "nonresponders." CE is the minimally important difference between two groups and represents the improvement considered worthwhile by a given treatment (34). In our study, the CE for $\dot{V}O_{2max}$ was set at 1 $mL \cdot kg^{-1} \cdot min^{-1}$. This level was chosen because each one unit increase in $\dot{V}O_{2max}$ is associated with a 16% predicted reduction in cancer mortality (10).

Association to cancer mortality risk. Our study population was at high risk for breast cancer. Therefore, we sought to further categorize change in $\dot{V}O_{2max}$ by predicted risk reduction in cancer mortality. The relation between changes in fitness capacity to risk of cancer mortality was assessed by distributing change in $\dot{V}O_{2max}$ across 1 $mL \cdot kg^{-1} \cdot min^{-1}$ categories via histogram plots at CONT, LOW, and HIGH groups, respectively. Each 1 $mL \cdot kg^{-1} \cdot min^{-1}$ category is associated with a 16% reduction in cancer mortality (10).

Statistical analysis. Sociodemographic factors (age, race, ethnicity, and education level) and baseline clinical characteristics (BMI and $\dot{V}O_{2max}$) were compared using Fisher's exact test for categorical variables and one-way ANOVA for continuous variables. In addition, the number of exercise "nonresponders" was compared between groups by Fisher's exact test. Normality was tested by Shapiro–Wilk test to assess changes in $\dot{V}O_{2max}$ from baseline to follow-up by groups. To estimate the probability density function of the associated risk reduction in cancer mortality, the normal density estimation curve was applied when the data are normally distributed (control group), whereas the kernel density estimation curve was used when the data were nonnormally distributed (intervention groups). Statistical analyses were conducted using SAS 9.4 (SAS Inc., Cary, NC). Statistical significance was set at an alpha level of 0.05.

RESULTS

Characteristics of the 125 participants are presented in Table 1. The mean age of participants was 34.6 ± 6.8 yr, and the mean BMI was 26.1 ± 6.0 $kg \cdot m^{-2}$. Participants were predominantly White (84.8%) and non-Hispanic (93.6%). We observed no significant between-group differences for age ($P = 0.68$), BMI ($P = 0.51$), $\dot{V}O_{2max}$ preintervention ($P = 0.26$), race ($P = 0.67$), ethnicity ($P = 0.54$), and education level ($P = 0.37$). The WISER Sister study recruited women at high risk for breast cancer, and documentation of risk status by genetic testing or prediction model is given in Table 1. The comparison between individuals who withdrew from the study and individuals who completed the study has been previously discussed (35). Further, demographic and clinical characteristics were not different between responders and nonresponders in the intervention groups (data not shown).

Observed individual $\dot{V}O_{2max}$ responses in the CONT (Fig. 1A), LOW (Fig. 1B), and HIGH (Fig. 1C) groups are presented. Although 2× TE (dashed line) is a relatively robust threshold for the classification of "responders," it was calculated from tests approximately 6 months apart and likely represents change in the control group, rather than technical error or the coefficient of variation. Therefore, we chose CE (dotted line) as a better representative threshold. Participants were dichotomously classified as "responders" (Black) and "nonresponders" (White) based on the CE threshold of 1 $mL \cdot kg^{-1} \cdot min^{-1}$. There was a significant difference between groups in the number of nonresponders as exercise dose increased ($P < 0.01$): CONT ($n = 35$, 74.5%), LOW ($n = 11$, 28.2%), and HIGH ($n = 2$, 5.1%).

We next examined the adherence level of exercise "nonresponders." Overall, the average adherence level (adherence defined as proportion of total prescribed minutes completed within target heart rate range for the full study [22]) was 85% in the low-dose group and 81% in the high-dose group. We present individuals sorted by adherence level (Fig. 2). Given the adherence rate to the intervention, there were only 3 of 11 exercise "nonresponders" in the low-dose group that were nonadherent (<75% adherence), and their lack of adherence explains their lack of change in $\dot{V}O_{2max}$ (Fig. 2A). However, 73% of "nonresponders" in the low-dose exercise group were true "nonresponders" as they did not improve their $\dot{V}O_{2max}$ despite high adherence to the exercise prescription. Similarly, in the high-dose group, both "nonresponders" had high adherence (>90%) (Fig. 2B). The low-dose group maintained a significantly higher percentage of clinical nonresponders among participants who were adherent to the intervention (23.5%) compared with the high-dose group (5.6%) ($P = 0.04$). In addition, compared with age-appropriate general population $\dot{V}O_{2max}$ norms, we observed that 57% of our study population was at good, excellent, or superior levels of fitness at baseline, and this increased to 66% by the follow-up exercise test (36).

Predicted cancer mortality risk reduction by dose of exercise was assessed (Fig. 3). In the CONT group (Fig. 3A), we observed a shift toward an increase in cancer mortality risk.

TABLE 1. Characteristics of 125 participants at study baseline.

Characteristic	Total Sample ($N = 125$)	Control ($n = 47$)	Low Dose ($n = 39$)	High Dose ($n = 39$)	P
Age (mean ± SD), yr	34.6 ± 6.8	34.3 ± 7.6	35.4 ± 6.1	34.2 ± 6.4	0.68
BMI (mean ± SD), $kg \cdot m^{-2}$	26.1 ± 6.0	26.7 ± 6.3	26.1 ± 6.2	25.2 ± 5.6	0.51
$\dot{V}O_{2max}$ (mean ± SD), $mL \cdot kg^{-1} \cdot min^{-1}$	32.6 ± 6.9	31.6 ± 7.4	32.2 ± 6.1	34.0 ± 7.1	0.26
Race, *n* (%)					0.67
White	106 (84.8)	39 (83.0)	32 (82.0)	35 (89.7)	
Non-White	19 (15.2)	8 (17.0)	7 (18.0)	4 (10.3)	
Ethnicity, *n* (%)					0.54
Hispanic	8 (6.4)	4 (8.5)	3 (7.7)	1 (2.6)	
Non-Hispanic	117 (93.6)	43 (91.5)	36 (92.3)	38 (97.4)	
Education level, *n* (%)					0.37
≤High school degree	3 (2.4)	3 (6.4)	0	0	
Some college	29 (23.2)	12 (25.5)	9 (23.1)	8 (20.5)	
≥College degree	93 (74.4)	32 (68.1)	30 (76.9)	31 (79.5)	
BRCA gene mutation status, *n* (%)					0.35
Positive	43 (34.4)	14 (29.8)	16 (41.0)	13 (33.3)	
Negative	11 (8.8)	7 (14.9)	1 (2.6)	3 (7.7)	
Not tested	71 (56.8)	26 (55.3)	22 (56.4)	23 (59.0)	
>18% lifetime risk of developing breast cancer, *n* (%)					
Gail[a]	50 (40.0)	18 (69.2)	18 (85.7)	14 (82.4)	0.40
Claus[b]	83 (66.4)	30 (65.2)	27 (69.2)	26 (68.4)	0.91

[a]A Gail score is not calculated for women below the age of 35 yr.
[b]A Claus score is not calculated for women who lack female first and/or degree relatives with breast cancer.

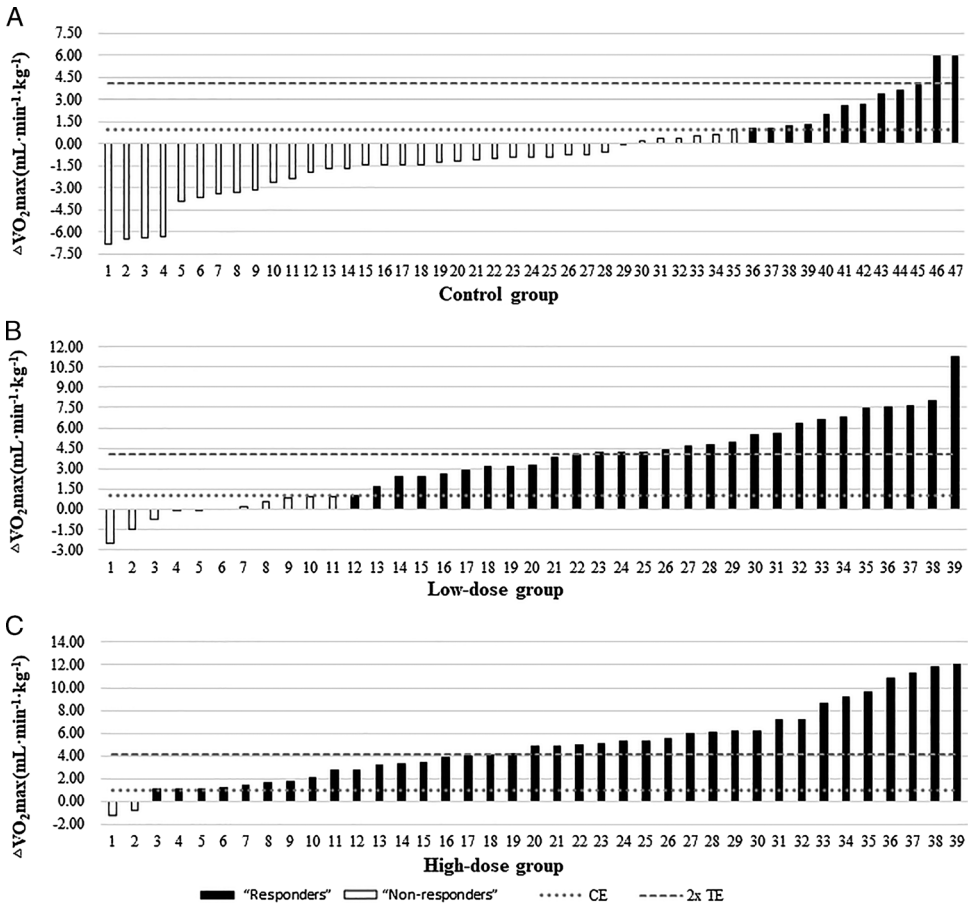

FIGURE 1—A, Observed individual $\dot{V}O_{2max}$ response in CONT group and CE threshold-based dichotomous classification of responders and nonresponders. B, Observed individual $\dot{V}O_{2max}$ response in low-dose group and CE threshold-based dichotomous classification of responders and nonresponders. C, Observed individual $\dot{V}O_{2max}$ response in high-dose group and CE threshold-based dichotomous classification of responders and nonresponders.

In the low-dose (Fig. 3B) and high-dose groups (Fig. 3C), the distribution of cancer mortality risk shifted toward a decrease in cancer risk (peak kernel density estimation fitted between −80% and −64%). A greater number of participants reduced their cancer mortality risk in the high-dose group (94.9%) compared with the low-dose group (87.2%), although the difference was not significant ($P = 0.43$).

DISCUSSION

The current study investigated change in $\dot{V}O_{2max}$ at the individual level after a 6-month aerobic exercise intervention among premenopausal women at elevated breast cancer risk. We found that exercise "nonresponders" occurred in both low-dose and high-dose groups independent of relative adherence to the exercise intervention. We observed that increasing the volume of exercise dose (via exercise duration) significantly decreased the number of "nonresponders." Nonresponders were classified by clinical effectiveness, which was defined as the change in $\dot{V}O_{2max}$ associated with reduced risk from cancer mortality. Increasing the volume of exercise dose did not provide additional benefit for predicted decreases in cancer mortality risk.

In addition to the aforementioned findings, we addressed an important methodological issue in terms of the classification of "responders" and "nonresponders." We adopted the CE threshold for the classification of individual responses. We observed more "responders" to exercise with CE threshold compared with 2× TE. This is because 2× TE is a statistical measure referring to a change that is equal to two SE of the mean from the first test, but our exercise tests were 6 months apart. Thus, 2× TE may overestimate technical error in measurement, and instead reflect actual physiological change over 6 months. As a population at high risk of breast cancer, our participants face a serious threat of death from cancer. Thus, our selection of CE, which relates changes in $\dot{V}O_{2max}$ to cancer mortality risk, is reasonable and clearly fits clinical meaningfulness.

The WISER Sister study has measured several biomarkers of breast cancer risk. Variables related to body composition, estrogen sensitive breast tissue, estrogen and progesterone levels, adipokine levels, and cytokine levels have all been reported previously (23–25,35). Exercise training–induced changes in these variables have not been linked to clinical outcomes. Therefore, change in $\dot{V}O_{2max}$ is presently the strongest biomarker available from our data set for predicting how change after an exercise intervention can affect future cancer risk. Although we chose to classify "responders" and "nonresponders"

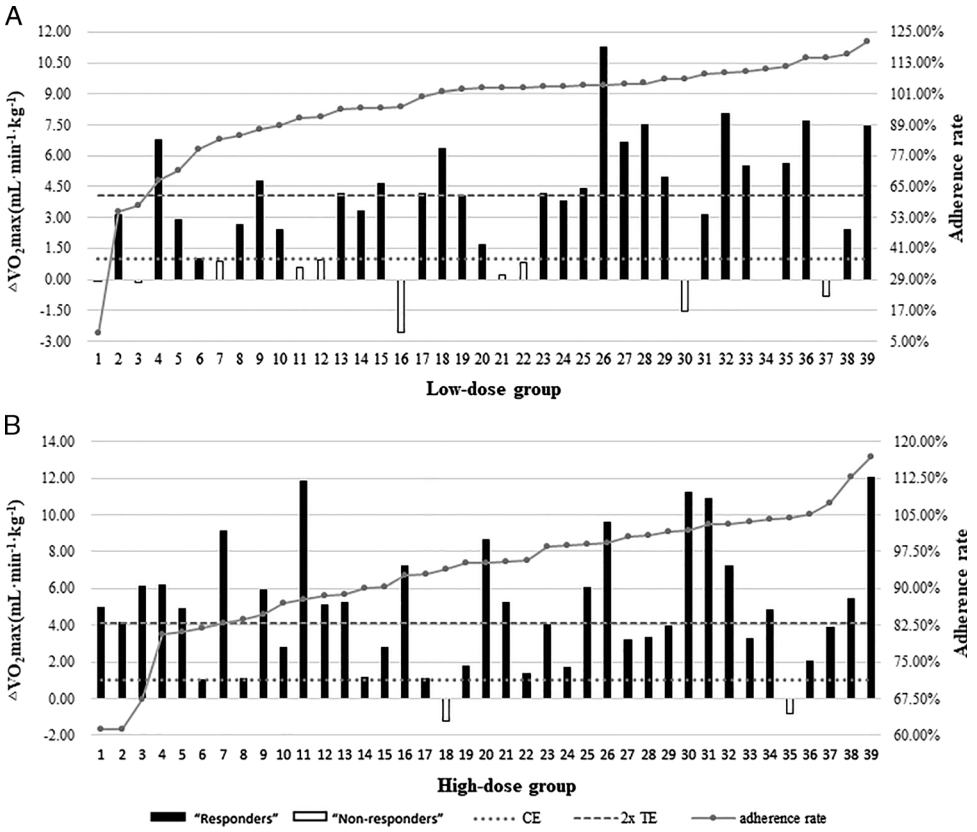

FIGURE 2—A, Observed individual $\dot{V}O_{2max}$ responses in low-dose group sorted by adherence rate and CE threshold-based dichotomous classification of responders and nonresponders. B, Observed individual $\dot{V}O_{2max}$ responses in high-dose group sorted by adherence rate and CE threshold-based dichotomous classification of responders and nonresponders.

to exercise based on $\dot{V}O_{2max}$, it is still likely that individuals who did not improve their $\dot{V}O_{2max}$ may have experienced other benefits from exercise.

Findings of the current study provide useful implications for exercise prescription decision making. As our study population is at high risk of breast cancer, determining an appropriate amount of exercise to reduce the associated cancer mortality is important. Although we observed that a higher exercise dose is more beneficial in improving $\dot{V}O_{2max}$, it did not significantly increase the number of participants with a predicted

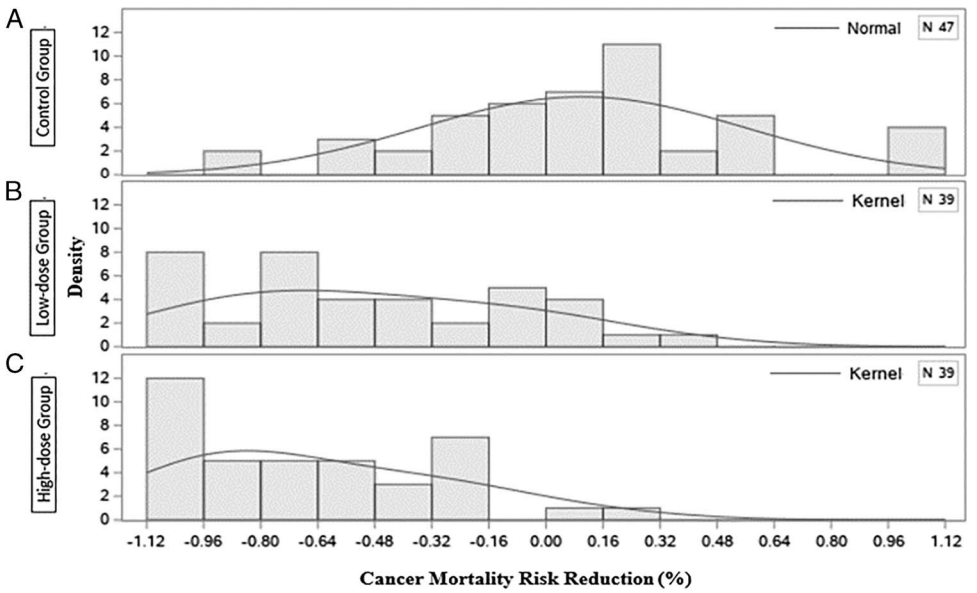

FIGURE 3—A, Change in $\dot{V}O_{2max}$-associated cancer mortality risk reduction in CONT group. B, Change in $\dot{V}O_{2max}$-associated cancer mortality risk reduction in low-dose group. C, Change in $\dot{V}O_{2max}$-associated cancer mortality risk reduction in high-dose group.

reduction in cancer mortality risk. This may indicate that 150 min·wk^{-1} is sufficient to control the risk of cancer mortality for the majority of people. Yet, for those that fail to increase $\dot{V}O_{2max}$ at 150 min·wk^{-1}, these individuals may benefit from increasing their exercise duration. Overall, our observations are consistent with current U.S. Department of Health and Human Services and American College of Sports Medicine guidance: for substantial health benefits, adults should do at least 150 to 300 min·wk^{-1} of moderate-intensity aerobic physical activity (37).

Identification of exercise "nonresponders" can provide useful information for developing personalized medicine. As $\dot{V}O_{2max}$ is one of the best clinical predictors of all-cause mortality (second only to smoking status), doing $\dot{V}O_{2max}$ testing after an exercise prescription would allow a clinician to determine efficacy of the exercise prescription (38). Similar to thyroid dysfunction, a physician prescribes a drug and retests thyroid levels for appropriate response. Just as a physician would modulate the drug prescription based on follow-up testing, so too can an exercise physiologist. Our study has provided the exercise physiologist with evidence to further prescribe additional duration of aerobic exercise at the same intensity. Future studies should determine whether increasing exercise intensity will decrease rate of nonresponders. It appears that high-intensity interventions also result in nonresponders (28,31); thus, more work on exercise prescriptions is necessary to understand how to dose and prescribe exercise modalities.

Nonpharmacological cancer prevention methods are particularly important for our study population as, currently, effective preventative measures are limited to prophylactic bilateral mastectomies, bilateral oophorectomies, and selective estrogen receptor modulators (39,40). These options are expensive and carry their own risks in the short- and long-term settings. Although not necessarily a replacement for these therapies, aerobic exercise can reduce breast cancer risk, delay onset, and prove to be a valuable preventative measure in high-risk individuals (41–45).

There are two major strengths of our study: 1) high exercise adherence and 2) consistency in exercise intensity and exercise type between groups. Adherence to the exercise intervention is an important factor to assess the accuracy of classifying exercise nonresponders. Without accounting for individual exercise adherence, the density of clinical nonresponders can be overestimated. Our study rigorously assessed adherence to the prescribed exercise intervention using both self-reported logs and objective monitoring. We observed some women did not improve their fitness capacity despite high adherence levels in both exercise intervention groups, which were true clinical "nonresponders" to exercise. Also, this secondary analysis examines modulation of the frequency, intensity, time, and type principle of exercise physiology. To assess the volume of exercise via an increase in time (150 or 300 min·wk^{-1}), we strictly controlled the exercise intensity and type between groups.

Although the current study explored CE and 2× TE for the classification of "responders" and "nonresponders," it is important to note that there are several other different thresholds that can be used (46). For instance, a fixed proportion of participants with the lowest training response were classified as "nonresponders" in some studies, regardless of the magnitude of change in the outcome of interest (47,48). Other groups have set a threshold of 0.5 metabolic equivalents of task (0.5 MET, equals to 1.75 mL·kg^{-1}·min^{-1} $\dot{V}O_{2max}$) and found three exercise "nonresponders" among 29 healthy, recreationally active participants (10.3%) after 4 wk of structured exercise training (33). Furthermore, some pointed out a concept of the smallest worthwhile change as a meaningful value to define their threshold in identifying "nonresponders," which is quite similar to the definition of CE we used (32,49). It is worth mentioning that Swinton et al. (49) recommended choosing the smallest worthwhile change that is lower than the expected change for most individuals. This argument is consistent with our study methodological issue that the value of CE we adopted is lower than the 2× TE we calculated. Using a different threshold will significantly affect the picture of individuals classified as responders and nonresponders (46). As there remains lack of consistency as to how "nonresponders" should be defined, the threshold should be carefully considered in the research context, e.g., what the exercise is prescribed for, who is the main population, how long is the intervention period, and what are desired outcomes.

Other limitations include that our study population was predominantly educated non-Hispanic White women. The incidence of breast cancer is similar between non-Hispanic White and Black women, yet the mortality rate among Black women due to breast cancer is 42% higher (50). Although our findings provide promise, the implications of our findings exclude populations from diverse racial and ethnic backgrounds. Future studies should assess the association between the change in cancer-specific mortality in a larger cohort of more diverse women with greater disease-specific mortality end points.

In conclusion, this study supports the application of a CE threshold to categorize clinical exercise "nonresponders" and demonstrates a dose–response effect via time spent exercising on decreasing the number of "nonresponders" to exercise. The 150-min·wk^{-1} exercise volume may also be sufficient to decrease the predicted risk of cancer mortality for women at high risk of developing breast cancer. Based on our findings, future studies should assess the modulation of dosed exercise prescriptions (frequency, intensity, time, and type).

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The authors have no conflicts of interests to disclose.

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