Dose/Exposure Relationship of Exercise and Distant Recurrence in Primary Breast Cancer

Davide Soldato, MD[1]; Stefan Michiels, PhD[2]; Julie Havas, MS[1]; Antonio Di Meglio, MD, PhD[1]; Martina Pagliuca, MD[1,3]; Maria Alice Franzoi, MD[1]; Barbara Pistilli, MD[4]; Neil M. Iyengar, MD[5,6]; Paul Cottu, MD, PhD[7]; Florence Lerebours, MD[8]; Charles Coutant, MD[9]; Aurélie Bertaut, MD, PhD[9]; Oliver Tredan, MD, PhD[10]; Laurence Vanlemmens, MD[11]; Christelle Jouannaud, MD[12]; Iona Hrab, MD[13]; Sibille Everhard, PhD[14]; Anne-Laure Martin, PharmD[14]; Fabrice André, MD, PhD[1,4]; Ines Vaz-Luis, MD, PhD[1,4,15]; and Lee W. Jones, PhD[5,6]

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ABSTRACT

PURPOSE Postdiagnosis exercise is associated with lower breast cancer (BC) mortality but its link with risk of recurrence is less clear. We investigated the impact and dose-response relationship of exercise and recurrence in patients with primary BC.

METHODS Multicenter prospective cohort analysis among 10,359 patients with primary BC from 26 centers in France between 2012 and 2018 enrolled in the CANcer TOxicities study, with follow-up through October 2021. Exercise exposure was assessed using the Global Physical Activity Questionnaire-16, quantified in standardized metabolic equivalent of task–hours per week (MET-h/wk). We examined the dose/exposure response of pretreatment exercise on distant recurrence-free interval (DRFI) for all patients and stratified by clinical subtype and menopausal status using inverse probability treatment weighted multivariable Cox models to estimate hazard ratios (HRs).

RESULTS For the overall cohort, the relationship between exercise and DRFI was nonlinear: increasing exercise ≥ 5 MET-h/wk was associated with an inverse linear reduction in DRFI events up to approximately 25 MET-h/wk; increasing exercise over this threshold did not provide any additional DRFI benefit. Compared with <5 MET-h/wk, the adjusted HR for DRFI was 0.82 (95% CI, 0.61 to 1.00) for ≥ 5 MET-h/wk. Stratification by subtype revealed the hormone receptor−/human epidermal growth factor receptor 2− (HR−/HER2−; HR, 0.59 [95% CI, 0.38 to 0.92]) and HR−/HER2+ (HR, 0.37 [95% CI, 0.14 to 0.96]) subtypes were preferentially responsive to exercise. The benefit of exercise was observed especially in the premenopausal population.

CONCLUSION Postdiagnosis/pretreatment exercise is associated with lower risk of DRFI events in a nonlinear fashion in primary BC; exercise has different impact on DRFI as a function of subtype and menopausal status.

ACCOMPANYING CONTENT

Data Supplement

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INTRODUCTION

The concept that engagement in exercise at the time of diagnosis or change in exercise after diagnosis of primary breast cancer (BC) might influence disease outcomes is of considerable interest.[1] Most work in this context has focused on the link between exercise and mortality; meta-analyses show reduced risk of all-cause and BC-specific mortality among those reporting higher levels of exercise, both before and after diagnosis.[2-5] How exercise influences disease recurrence has been less studied. Corollary investigation of this question is important for at least two reasons. First, accurate assessment and adjudication of the underlying cause of death is a major challenge, especially in elderly patients with multiple comorbidities, increasing the potential for misclassification.[6,7] Hence, although the clinical importance of mortality as a study end point is undisputed, examining disease recurrence arguably provides a more rigorous evaluation of the exercise-tumor progression link, especially since evidence of recurrence is confirmed by objective radiographic tumor assessments. Second, metastasis is responsible for 90% of all BC-related deaths. Thus, adjunct strategies, particularly lifestyle interventions that have minimal toxicity, symptom control benefit (eg, improvements in quality of life and physical function[8,9]), can be administered either concurrent and/or sequential with conventional adjuvant therapy, and have the potential to further improve outcomes, are of high clinical interest.[1,10-12]

CONTEXT

Key Objective

Investigate the dose/exposure relationship of exercise and distant recurrence-free interval (DRFI) in breast cancer (BC).

Knowledge Generated

A nonlinear relationship between exercise and risk of DRFI events was observed: exercise exposure between 5 and 25 metabolic equivalent of task–hours per week was associated with the higher benefit. Engagement in higher exercise at diagnosis was associated with lower risk of DRFI events, especially in hormone receptor–negative subtype and premenopausal patients.

Relevance *(I. Cheng)*

There has been limited understanding of the relationship between exercise dose and BC recurrence. Findings from the CANcer TOxicities study suggest a certain optimal range in the benefit of exercise on BC recurrence for specific subtypes of BC, encouraging further biological, epidemiological, and clinical research in this area.*

*Relevance section written by *JCO* Associate Editor Iona Cheng, PhD, MPH.

In addition, most previous work has examined the exercise-disease outcomes link under the assumption that BC is a single disease, or at most evaluating the differential impact of exercise on the basis of hormone receptor (HR) status,[3,4,13-15] but whether certain tumor subtypes are more or less responsive has received limited attention.

If exercise does lower disease recurrence after BC, identifying the optimal or most appropriate dose by subtype to confer such benefit is critical to guide clinical recommendations.[1] Previous work has generally adopted an unbiased split selection approach, classifying patients into discrete classifications (from minimal to high exercise) on the basis of exercise distribution within the cohort sample.[13-15] This approach uses statistics to define exercise classifications and, perhaps more importantly, adopts the overarching assumption that exercise affects disease outcomes in a linear fashion. However, the relationship between exercise dose and BC recurrence has not been rigorously evaluated. We leveraged data from the CANcer Toxicities (CANTO) prospective study[16] to investigate the dose/exposure-response relationship of exercise and recurrence in women with primary BC.

METHODS

CANTO (ClinicalTrials.gov identifier: NCT01993498) is a prospective cohort study that enrolled patients diagnosed with stage I-III BC at 26 institutions in France between March 2012 and September 2018.[16] Informed consent was obtained before study participation at all institutions. CANTO received ethical approval (ID-RCB:2011-A01095-36,11-039). All patients are assessed at diagnosis before any form of anticancer therapy and longitudinally during follow-up visits at 1 (corresponding to 3-6 months after completion of primary treatment), 2, 4, and 6 years after diagnosis. Details on protocol and variables collection were previously described.[16] The exposure variable was exercise and it was assessed in person during study visits using the Global Physical Activity Questionnaire-16 (GPAQ-16).[17] Details of the GPAQ-16 and calculation of exercise exposure in CANTO have been previously reported.[18] Briefly, exercise dose, including leisure and travel time physical activity, was calculated by multiplying the frequency of activity sessions per week by average session duration, weighted by the appropriate standardized metabolic equivalent of task (MET) value to derive a total MET-hours per week (MET-h/wk). Among the 11,400 patients available at the data lock of the analyses (October 2021), we excluded 1,041 patients with missing exercise data at baseline, for an overall analytic cohort of 10,359 patients. We assessed potential selection bias by comparing baseline covariates between responders and nonresponders to the GPAQ-16 questionnaire (Data Supplement, Table S1, online only).

The primary end point was distant recurrence-free interval (DRFI), defined according to Standardized Definitions for Efficacy End Points criteria[19] and the Definition for the Assessment of Time-to-event Endpoints in CANcer trials initiative.[20]

CANTO participants were monitored according to standard clinical practice. In case of clinical or radiologic suspicion of local or distant recurrence, objective radiographic tumor assessments and/or histological verification was performed.

Statistical Analysis

Descriptive statistics summarized clinical, socioeconomic, tumor, and treatment characteristics collected at study entry. To examine the dose/exposure-response relationship of exercise and recurrence in women with primary BC, we visually explored the relationship between DRFI events and continuous exercise exposure (MET-h/wk) by generating

TABLE 1. Description of Covariates at Diagnosis in the Overall Analytic Cohort (N = 10,359) and by Exercise Exposure at Diagnosis, Categorized as <5 MET-h/wk and ≥5 MET-h/wk

Variable	Overall Cohort (N = 10,359)	Exercise at Diagnosis <5 MET-h/wk (n = 4,205)	Exercise at Diagnosis ≥5 MET-h/wk (n = 6,154)
Age at diagnosis, years			
Mean ± SD	56.3 ± 11.2	56.2 ± 11.3	56.4 ± 11.1
Min-max	20.7-89.2	22.2-89.2	20.7-88.1
Median (IQR)	56.4 (48.2-64.9)	56.1 (48.2-64.9)	56.6 (48.2-65.0)
BMI at diagnosis, kg/m^2			
Mean ± SD	25.9 ± 5.4	26.9 ± 5.8	25.1 ± 4.9
Min-max	14.7-59.0	15.8-59.0	14.7-55.1
Median (IQR)	24.7 (22.0-28.7)	25.8 (22.7-30.1)	24.1 (21.6-27.7)
Missing, No.	41	19	22
Recreational physical activity at diagnosis, MET-h/wk			
Mean ± SD	16.6 ± 20.6	0.5 ± 1.3	27.6 ± 20.4
Min-max	0.0-75.0	0.0-4.9	5.0-75.0
Median (IQR)	9.0 (0.0-24.0)	0.0 (0.0-0.0)	20.0 (12.0-36.0)
Adherent to WHO physical activity recommendations,[a] No. (%)			
No	4,440 (42.9)	3,588 (85.3)	852 (13.8)
Yes	5,919 (57.1)	617 (14.7)	5,302 (86.2)
Menopausal status, No. (%)			
Premenopausal	3,971 (38.7)	1,635 (39.2)	2,336 (38.3)
Postmenopausal	6,300 (61.3)	2,540 (60.8)	3,760 (61.7)
Missing	88	30	58
Charlson comorbidity index, No. (%)			
0	7,593 (80.7)	2,999 (78.7)	4,594 (82.1)
≥1	1,818 (19.3)	814 (21.3)	1,004 (17.9)
Missing	948	392	556
Marital status, No. (%)			
Not partnered	2,230 (22.0)	805 (19.6)	1,425 (23.6)
Partnered	7,922 (78.0)	3,299 (80.4)	4,623 (76.4)
Missing	207	101	106
Education level, No. (%)			
Primary school	1,347 (13.3)	704 (17.4)	643 (10.7)
High school	4,652 (46.1)	2,065 (50.9)	2,587 (42.9)
College or higher	4,093 (40.6)	1,287 (31.7)	2,806 (46.5)
Missing	267	149	118
Household income, No. (%)			
<€1,500 (EUR)	1,427 (14.4)	670 (16.8)	757 (12.8)
≥€1,500 (EUR) and <€3,000 (EUR)	4,245 (42.8)	1,789 (44.9)	2,456 (41.4)
≥€3,000 (EUR)	4,239 (42.8)	1,523 (38.2)	2,716 (45.8)
Missing	448	223	225
Daily alcohol consumption behavior, No. (%)			
Less than daily	8,689 (86.0)	3,523 (86.3)	5,166 (85.9)
Daily	1,409 (14.0)	558 (13.7)	851 (14.1)
Missing	261	124	137
Tobacco use behavior, No. (%)			
Current smoker	1,815 (17.8)	880 (21.2)	935 (15.4)
Former smoker	2,295 (22.5)	899 (21.7)	1,396 (23.0)
Never smoker	6,105 (59.8)	2,370 (57.1)	3,735 (61.6)
Missing	144	56	88

(continued on following page)

TABLE 1. Description of Covariates at Diagnosis in the Overall Analytic Cohort (N = 10,359) and by Exercise Exposure at Diagnosis, Categorized as <5 MET-h/wk and ≥5 MET-h/wk (continued)

Variable	Overall Cohort (N = 10,359)	Exercise at Diagnosis <5 MET-h/wk (n = 4,205)	Exercise at Diagnosis ≥5 MET-h/wk (n = 6,154)
Tumor stage, No. (%)			
Stage I	5,039 (49.2)	1,912 (46.1)	3,127 (51.4)
Stage II	4,221 (41.2)	1,784 (43.0)	2,437 (40.0)
Stage III	975 (9.5)	454 (10.9)	521 (8.6)
Missing	124	55	69
Tumor grade, No. (%)			
Grade 1	1,840 (17.9)	731 (17.6)	1,109 (18.2)
Grade 2	5,454 (53.2)	2,172 (52.2)	3,282 (53.8)
Grade 3	2,961 (28.9)	1,257 (30.2)	1,704 (28.0)
Missing	104	45	59
Tumor subtype, No. (%)			
Hormone receptor+ HER2+	1,061 (10.3)	427 (10.2)	634 (10.4)
Hormone receptor+ HER2−	7,846 (76.3)	3,166 (75.8)	4,680 (76.6)
Hormone receptor− HER2+	392 (3.8)	166 (4.0)	226 (3.7)
Hormone receptor− HER2−	984 (9.6)	418 (10.0)	566 (9.3)
Missing	76	28	48
Axilla surgery, No. (%)			
Dissection	3,826 (37.0)	1,658 (39.5)	2,168 (35.3)
None or sentinel	6,519 (63.0)	2,542 (60.5)	3,977 (64.7)
Missing	14	5	9
Breast cancer surgery, No. (%)			
Conservative surgery	7,569 (73.2)	3,012 (71.7)	4,557 (74.2)
Mastectomy	2,776 (26.8)	1,188 (28.3)	1,588 (25.8)
Missing	5	5	9
Chemotherapy, No. (%)			
No	4,872 (47.1)	1,902 (45.3)	2,970 (48.4)
Yes	5,465 (52.9)	2,295 (54.7)	3,170 (51.6)
Missing	22	8	14
Radiotherapy, No. (%)			
No	878 (8.5)	360 (8.6)	518 (8.4)
Yes	9,448 (91.5)	3,832 (91.4)	5,616 (91.6)
Missing	33	13	20
Hormonal therapy, No. (%)			
No	1,867 (18.1)	740 (17.7)	1,127 (18.4)
Yes	8,447 (81.9)	3,445 (82.3)	5,002 (81.6)
Missing	45	20	25
Anti-HER2 therapy, No. (%)			
No	9,082 (87.9)	3,672 (87.5)	5,410 (88.2)
Yes	1,251 (12.1)	524 (12.5)	727 (11.8)
Missing	26	9	17

Abbreviations: EUR, euro; HER2, human epidermal growth factor receptor 2; MET-h/wk, metabolic equivalent of task–hours per week; SD, standard deviation.

[a]At least 150 minutes of moderate-intensity physical activity per week, corresponding to 10 MET-h/wk.

restricted cubic splines[21] from unadjusted Cox proportional hazard models for exercise exposure at diagnosis. Knots were automatically placed on the basis of percentile distribution of the continuous exposure variable (exercise). Tests for nonlinearity used the likelihood ratio test, comparing the model with the linear term with the one with the

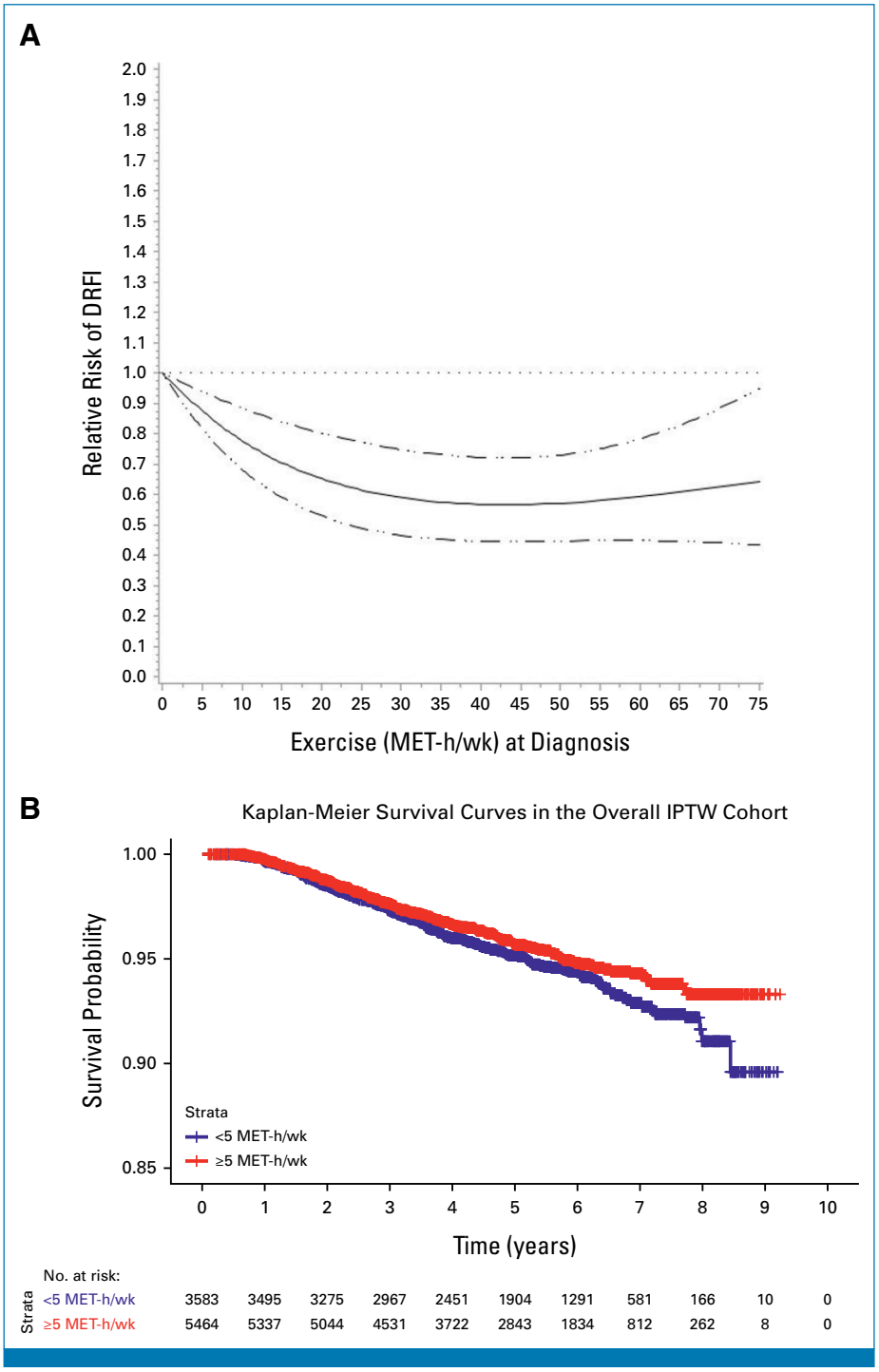

FIG 1. (A) Restricted cubic splines from Cox proportional hazard regression models showing a nonlinear relationship (test for nonlinearity $P = .0097$) between exercise at diagnosis and risk of DRFI events in the overall cohort (N = 10,359 patients). (B) Kaplan-Meier estimates of DRFI in the overall IPTW cohort according to exercise at diagnosis, categorized in <5 MET-h/wk versus ≥5 MET-h/wk. DRFI, distant recurrence-free interval; IPTW, inverse probability treatment weighted; MET-h/wk, metabolic equivalent of task–hours per week.

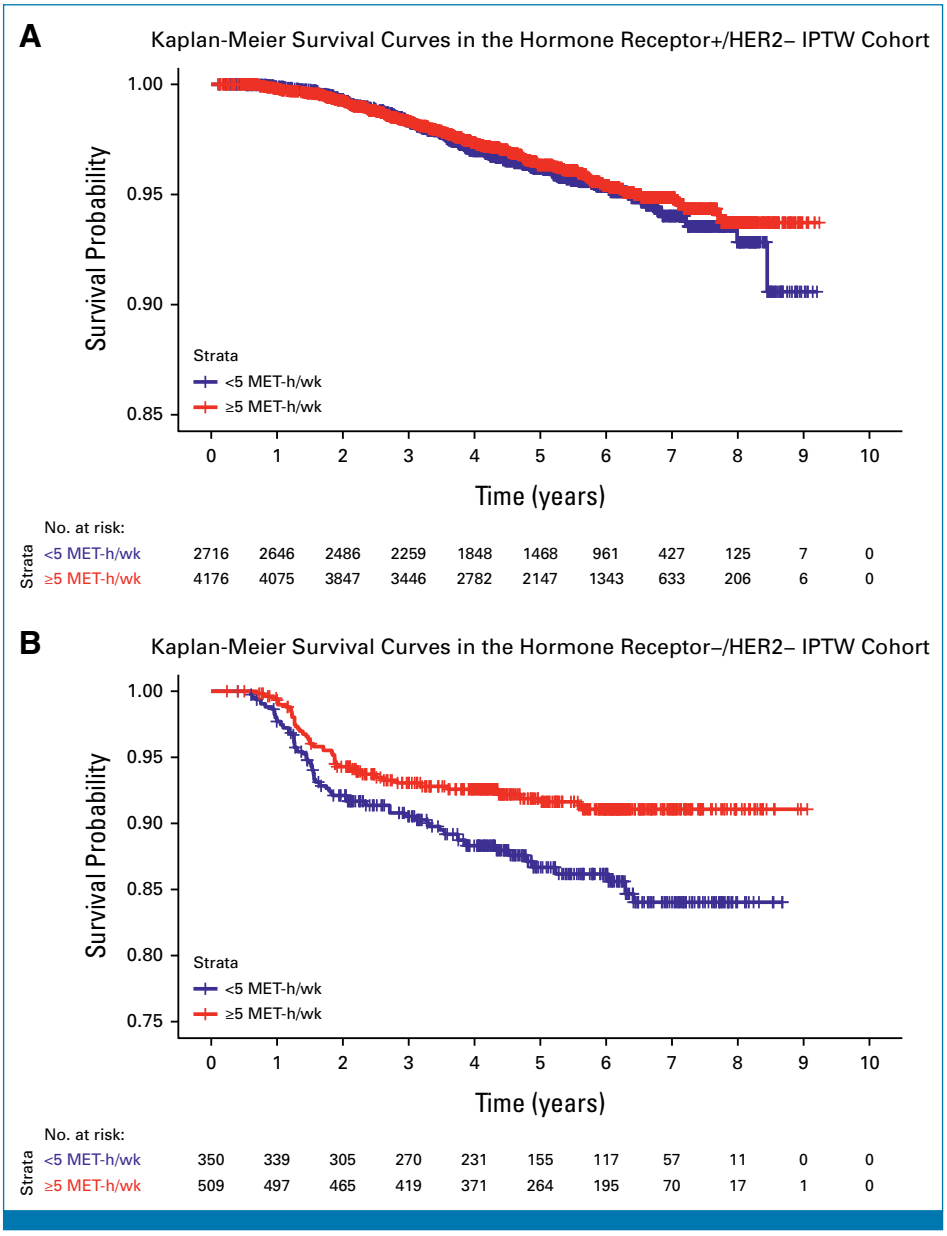

FIG 2. (A) Kaplan-Meier estimates of DRFI according to exercise at diagnosis, categorized into <5 MET-h/wk versus ≥5 MET-h/wk in the overall IPTW hormone receptor+/HER2– cohort. (B) Kaplan-Meier estimates of DRFI in <5 MET-h/wk versus ≥5 MET-h/wk in the overall IPTW hormone receptor–/HER2– cohort. DRFI, distant recurrence-free interval; HER2, human epidermal growth factor receptor 2; IPTW, inverse probability treatment weighted; MET-h/wk, metabolic equivalent of task–hours per week.

linear and cubic spline terms. Splines were generated for the overall cohort and according to BC subtype, categorized as follows: (1) hormone receptor+/human epidermal growth factor receptor 2 (HER2)–, (2) hormone receptor+/HER2+, (3) hormone receptor–/HER2+, and (4) hormone receptor–/HER2–.

To address potential confounders that could influence exercise engagement at diagnosis, we used propensity score inverse probability treatment weighted (IPTW) Cox models.[22] Variables included for weight calculation, modeled as shown in Table 1, included sociodemographic (age, marital status, education, and income), tumor-related (stage), and treatment-related (type of surgery, receipt of chemotherapy, radiotherapy, hormonal therapy, and anti-HER2 therapy) factors as well as lifestyle factors (BMI and smoking habit) and patient-reported outcome measures for overall quality of life and emotional distress. To deal with potential instability that can ensue from large weights, we used stabilized weights in subsequent analyses.[23] Distribution of covariates before and after weighting was evaluated with balancing measures (Data Supplement, Table S3) and

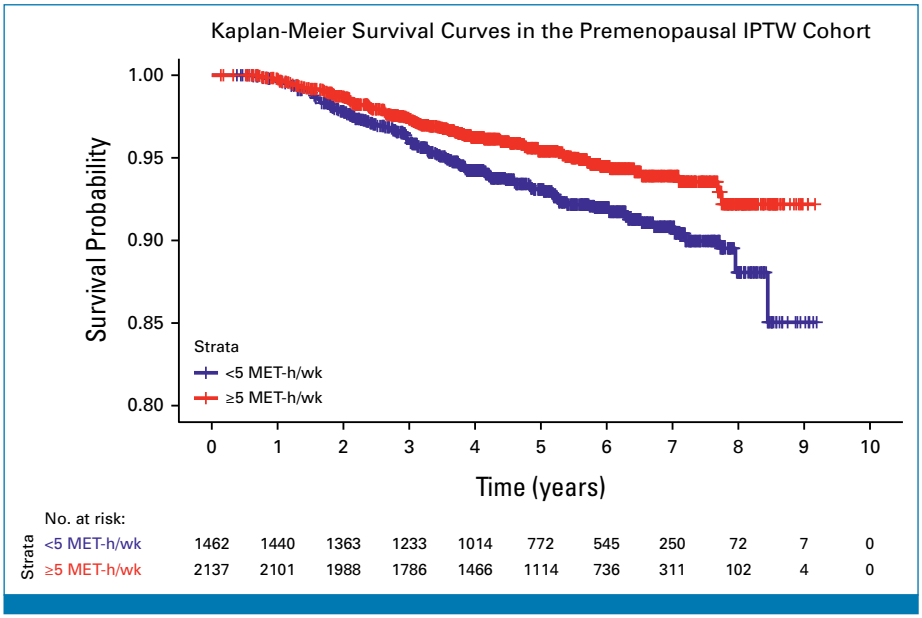

FIG 3. Kaplan-Meier estimates of DRFI according to exercise at diagnosis, categorized into <5 MET-h/wk versus ≥5 MET-h/wk in the overall premenopausal IPTW cohort. DRFI, distant recurrence-free interval; IPTW, inverse probability treatment weighted; MET-h/wk, metabolic-equivalent task-hours per week.

graphically (Data Supplement, Fig S3). After exclusion of patients with missing data in the weighting covariates (Data Supplement, Fig S1), the IPTW cohort included 9,051 patients with similar baseline characteristics as those included in the overall analytic cohort (Data Supplement, Table S2). We fit unadjusted and adjusted (by age at diagnosis, BC stage, and treatments) IPTW Cox models to evaluate the association between exercise and DRFI. The Kaplan-Meier method was used to estimate survival functions for DRFI in the IPTW cohort. Analyses were performed by subtype in the overall cohort. Furthermore, we replicated the same analyses separately in the premenopausal and postmenopausal cohorts. Distribution of covariates before and after weighting in the premenopausal cohort was evaluated with balancing measures (Data Supplement, Table S8) and graphically (Data Supplement, Fig S5).

To evaluate the potential impact of exercise over time, we selected a subcohort of patients with mature follow-up at 4 years from diagnosis. For this subcohort, exercise, assessed with the GPAQ-16, was measured at diagnosis and 1, 2, and 4 years afterward. We used marginal structural models[24,25] (MSMs) to assess whether change in exercise and over time would be associated with risk of DRFI events while accounting for time-fixed and time-varying covariates (Data Supplement, Methods). Patients with missing data in time-fixed and time-varying covariates were excluded from this analysis (Data Supplement, Fig S1).

Sensitivity Analysis

To address potential misclassification in the cause of death, a sensitivity analysis was performed using competing risk models wherein the outcome was represented by occurrence of distant disease recurrence, and death from any cause was considered as a competing event. We computed the cumulative incidence function for both events and used the Fine and Gray model to estimate the corresponding subdistribution hazard ratios (HRs) for exercise at diagnosis and adjust for covariates.

This study followed the Strengthening the Reporting of Observational Studies in Epidemiology[26] Checklist for cohort studies (Data Supplement). Statistical analysis was performed using SAS statistical software version 9.4 and R version 4.3.2; splines were generated using the LGTPHCURV9 Macro[27]; IPTW and MSMs models were generated using the WeightIt[28] and ipw[29] packages for R. Statistical significance was defined with a two-sided $P < .05$.

RESULTS

Patients' mean age (standard deviation [SD]) was 56.3 years (11.2) and 38.7% (n = 3,971) were premenopausal; 52.9% (n = 5,465) received chemotherapy and 81.9% received hormonal therapy (n = 8,447). Mean BMI (SD) was 25.9 kg/m^2 (5.4), 17.8% (n = 1,815) of patients were active smokers, and 57.1% (n = 5,919) met WHO exercise recommendations[30] (Table 1).

Pretreatment Exercise and DRFI

Over a median follow-up of 5.4 (IQR, 3.8-6.4) years, a total of 502 distant recurrences and 395 deaths (284 due to BC) were observed. In the overall cohort (N = 10,359), a nonlinear

relationship (likelihood ratio test for nonlinearity; $P = .0097$) between exercise and DRFI was observed: exercise exposure greater than approximately 5 MET-h/wk was associated with an inverse linear reduction in the risk of recurrence up to approximately 25 MET-h/wk; increasing exercise beyond this threshold did not provide any additional DRFI benefit (Fig 1A). On this basis, exercise was collapsed into two categories (1) no exercise (ie, 0 to <5 MET-h/wk: n = 4,205, 40.6%) and (2) exercise (ie, ≥ 5 MET-h/wk: n = 6,154, 59.4%).

Using this dichotomy, in the IPTW population, the 5-year DRFI was 95.1% (94.4-96.0) for <5 MET-h/wk and 95.7% (95.1-96.3) for ≥5 MET-h/wk (absolute difference, 0.6%; Fig 1B). Compared with <5 MET-h/wk, the adjusted HR for DRFI in the IPTW model was 0.82 (95% CI, 0.67 to 1.00) for ≥ 5 MET-h/wk.

Patient distribution and number of events per clinical subtype was (1) hormone receptor+/HER2− (n = 7,846; 302 events); (2) hormone receptor+/HER2+ (n = 1,061; 57 events), (3) hormone receptor−/HER2+ (n = 392; 26 events), and (4) hormone receptor−/HER2− (n = 984; 114 events). The smoothing splines revealed the dose-response relationships between exercise and DRFI risk were similar across subtypes (Data Supplement, Fig S2): an inverse relationship was observed for exposure greater than approximately 5 MET-h/wk with an attenuation of impact over approximately 25 MET-h/wk. In the IPTW population with hormone receptor+/HER2− subtype, the 5-year DRFI was 96.2% (95.4-97.0) for <5 MET-h/wk and 96.3% (95.6-97.0) for ≥5 MET-h/wk (absolute difference, 0.1%; Fig 2A); the adjusted HR for DRFI in the IPTW model was 0.89 (95% CI, 0.69 to 1.15) for ≥5 MET-h/wk. In the IPTW population with hormone receptor−/HER2− subtype, the 5-year DRFI was 86.6% (82.8-90.6) for <5 MET-h/wk and 91.6% (89.0-94.3) for ≥5 MET-h/wk (absolute difference, 5%; Fig 2B); the adjusted HR for DRFI in the IPTW model was 0.60 (95% CI, 0.38 to 0.92) for ≥5 MET-h/wk. In the IPTW population with hormone receptor−/HER2+ subtype, the 5-year DRFI was 90.0% (84.8-95.5) for <5 MET-h/wk and 96.2 (95% CI, 93.3 to 99.2) for ≥5 MET-h/wk (absolute difference, 6.2%; Data Supplement, Fig S4); the adjusted HR for recurrence was 0.37 (95% CI, 0.14 to 0.96) for ≥5 MET-h/wk. Finally, for the hormone receptor+/HER2+ subtype, we did not identify a significant relationship between exercise and DRFI, thus no additional analyses were performed.

Full results of unadjusted and adjusted IPTW models are shown in the Data Supplement (Tables S4-S7).

Pretreatment Exercise and DRFI by Menopausal Status

In the IPTW population, 3,602 patients were premenopausal (39.8%, 209 DRFI events) and 5,449 postmenopausal (60.2%, 219 DRFI events).

In the overall IPTW premenopausal cohort, the 5-year DRFI was 93.1% (91.7-94.5) for <5 MET-h/wk and 95.4% (94.4-96.4) for ≥5 MET-h/wk (absolute difference, 2.3%; Fig 3). Compared with <5 MET-h/wk, the adjusted HR for DRFI in the IPTW model was 0.64 (95% CI, 0.48 to 0.86) for ≥5 MET-h/wk (Data Supplement, Table S9). Results by subtype in the premenopausal cohort were similar to those observed in the overall cohort, with a higher magnitude of benefit observed for the hormone receptor−/HER2− subtype (Data Supplement, Tables S10-S12 and Figs S6-S8).

In the IPTW postmenopausal cohort, we did not observe any association between higher exercise at diagnosis and DRFI events, in the overall cohort or by subtype (data not shown).

Longitudinal Change in Exercise and DRFI

This subcohort included 5,256 patients (202 DRFI events). We calculated inverse probability treatment and censoring weights and multiplied them to obtain the final weights used in MSM (Data Supplement, Figs S13 and S14).

In the adjusted Cox MSM, the HR for recurrence was 0.97 (95% CI, 0.72 to 1.30) for ≥5 MET-h/wk over time.

Sensitivity Analysis

Results of the sensitivity analysis modeling distant disease recurrence as outcome and all-cause mortality as a competing risk yielded similar results as those of the primary analysis (Data Supplement, Tables S13 and S14 and Figs S9-S12).

DISCUSSION

In this large study of patients with primary BC, the relationship between pretreatment exercise and risk of DRFI events was nonlinear, suggesting a potential therapeutic range of exercise. Subgroup analyses on the basis of clinical subtype revealed exercise benefit on DRFI was only apparent for the hormone receptor−/HER2− and hormone receptor−/HER2+ subtypes. Furthermore, when stratifying analyses by menopausal status, exercise benefit was observed especially among premenopausal patients. Finally, no association with risk of DRFI events and exercise over time was observed.

Several findings are noteworthy. First, the relationship between exercise dose and DRFI events appears nonlinear. Our observational data showed higher exercise doses beyond a relatively low amount (ie, approximately 5 MET-h/wk; equivalent to approximately 90 minutes of moderate exercise per week) was associated with greater risk reductions, but this was only apparent up to a certain threshold (approximately 25 MET-h/wk; equivalent to approximately 5 hours of moderate exercise per week); doses beyond this threshold provided no additional benefit. The observed nonlinear response to increasing exposure or doses of a substance or therapy is reminiscent of hormesis.[31] Exercise doses below and above a homeostatic zone (therapeutic range) may confer suboptimal benefit. Further research is needed to validate this finding in independent observational data sets and

experimental models, explore whether hormetic response relationships are observed in other solid tumors, and elucidate the cell autonomous and/or cell nonautonomous molecular mechanisms underpinning this response.[32]

Second, our findings showing exercise is associated with lower risk of DRFI events in primary BC are different from those of recent meta-analyses. The After Breast Cancer Pooling Project that included four observational studies in primary BC (representing a total of 10,685 patients, range: 2,265-8,075 patients per study) found high (≥ 10 MET-h/wk) exercise assessed at a median of 23 months after diagnosis was not associated with recurrence (n = 1,421 total events) compared with minimal exercise (HR, 0.96 [95% CI, 0.86 to 1.18]). This association was not modified by hormone receptor status. Higher exercise was, however, associated with a reduction in hazard for BC death (HR, 0.75 [95% CI, 0.65 to 0.85]).[13] Another meta-analysis including three observational studies also found no significant associations between exercise and risk of recurrence, both in linear dose-response (HR, 0.97 [95% CI, 0.91 to 1.05]) or categorical (HR, 0.80 [95% CI, 0.56 to 1.14]) analyses.[3] Significant interstudy heterogeneity was, however, observed in both meta-analyses. The small sample sizes and low number of recurrence events in individual studies together with challenges of data harmonization related to exercise exposure—since assessment, timing, and the definition of exercise exposure differed across studies—potentially contributed to the nonsignificant findings and heterogeneity.

Third, previous work suggested that an exercise-related reduction in recurrence and BC death was confined to hormone receptor+/HER2−/low-grade tumors only[33]; in our study, the exercise-DRFI link appeared in the hormone receptor−/HER2− and hormone receptor−/HER2+ subtypes. However, our relatively short follow-up might have prevented capturing additional late recurrence events in the hormone receptor+/HER2− subtype.[34] The observation of a significant benefit in DRFI for triple-negative tumors corroborates growing preclinical data showing exercise significantly inhibits tumor progression in mouse models of triple-negative BC.[35-37] The considerable variation in the exercise-DRFI relationship within clinical subtypes might indicate heterogeneity in response to exercise. Stratification of tumors into more biologically homogeneous diseases may therefore be required to accurately identify those tumors more likely to respond to exercise therapy and appropriate dose thresholds to obtain antitumor benefit.[33]

Fourth, the benefit of exercise in reducing risk of DRFI events in this study was evident only in the premenopausal population. The majority of the studies that evaluated either BC recurrence or mortality did not find significant differences according to menopausal status,[3,38-40] and the benefit of exercise was also observed in postmenopausal patients.[41,42] Different categorization of exercise levels across studies and the short follow-up of our study might explain this difference in findings, considering that the majority of postmenopausal women are diagnosed with hormone receptor+/HER2− BC.

Finally, we found no associations between reporting higher exercise over time and risk of DRFI events. However, our analyses were limited by a reduced sample size to account for the potential effect of time-varying confounders that might influence engagement in exercise. To our knowledge, only three studies have evaluated the association between change in postdiagnosis exercise and recurrence in BC. In a secondary analysis of the Women's Healthy Eating and Living trial, meeting exercise recommendations 1 year after diagnosis was associated with higher risk of BC events (HR, 1.44 [95% CI, 1.02 to 2.03]) compared with not meeting guidelines.[43] Conversely, in the Mammary Carcinoma Risk Factor Investigation trial, increased exercise from pre- to post-diagnosis associated with improved recurrence-free survival compared with not meeting exercise guidelines (HR, 0.58 [95% CI, 0.40 to 0.84]), selection of a population of healthier survivors, and recall bias were noted as limitations of the study.[42]

Current guidelines recommend engaging in exercise during curative treatment for BC[44]; engagement in aerobic and resistance exercise is associated with reduced fatigue, preserved cardiorespiratory fitness and physical function, and improved quality of life.[8,45,46] However, whether increase or decrease in exercise levels after a BC diagnosis influences risk of recurrence remains, at present, inconclusive. Further work is needed to examine this association using prospective and ideally randomized studies to address this important clinical question.

Important study limitations require consideration. Self-reported measures of exercise exposure have well-known limitations, and therefore some misclassification, including overestimation of moderate-to-vigorous physical activity,[47,48] should be expected. Wearable devices could potentially overcome the limitations of self-reported measures.[48] Furthermore, prospective data show inverse dose-response relationship between device-captured exercise and health outcomes at smaller doses than previously reported in epidemiologic studies on the basis of self-reported exercise.[49-51] This suggests lower levels of exercise may be required to produce health benefits, although whether these findings translate to patients with breast or other types of cancer is not yet known.

Exercise levels at the point of diagnosis may have altered significantly because of the recent cancer diagnosis and therefore may not reflect normal mobility patterns levels. Some analyses were limited by a low number of recurrence events and short follow-up, especially for hormone receptor+/HER2− disease, for which recurrences are observed up to 20 years after diagnosis.[34]

We excluded from the study nonresponders to the GPAQ-16 questionnaire at diagnosis. These patients were more frequently older, with higher BMI and lower levels of education

and income; therefore, potential selection bias should be acknowledged, and results of this study are not entirely representative of a diverse population diagnosed with BC.

Additionally, limitations related to the observational nature of the study such as residual unmeasurable confounders and multiplicity of analyses must be acknowledged, and validation in independent data sets is required.

In conclusion, our data suggest the hypothesis that exercise doses below and above a homeostatic zone (therapeutic range) confer suboptimal recurrence benefit, and potential antitumor effects of exercise may be confined to only certain subtypes in primary BC. Early-phase trials evaluating whether exercise therapy has biologic antitumor activity and whether activity differs as a function of tumor molecular features are required to guide the design of larger definitive trials.

AFFILIATIONS

[1]INSERM U981—Prédicteurs moléculaires et nouvelles cibles en oncologie, Gustave Roussy, Villejuif, France
[2]INSERM U1018 CESP, Service de Biostatistique et d'Epidemiologie, Institut Gustave Roussy, Villejuif, France
[3]Division of Breast Medical Oncology, Istituto Nazionale Tumori IRCCS "Fondazione G. Pascale", Naples, Italy
[4]Medical Oncology Department, Gustave Roussy, Villejuif, France
[5]Memorial Sloan Kettering Cancer Center, New York, NY
[6]Weill Cornell Medical College, New York, NY
[7]Institut Curie, Paris, France
[8]Institut Curie Saint Cloud, Saint Cloud, France
[9]Centre Leon Berard, Lyon, France
[10]Centre Georges-Francois Leclerc, Dijon, France
[11]Centre Oscar Lambret, Lille, France
[12]Institut de Cancérologie Jean Godinot, Reims, France
[13]Centre François Baclesse, Caen, France
[14]UNICANCER, Paris, France
[15]Supportive Care and Pathways Department (DIOPP), Gustave Roussy, Villejuif, France

CORRESPONDING AUTHOR

Ines Vaz-Luis, MD, PhD; e-mail: ines.vaz-duarte-luis@gustaveroussy.fr

EQUAL CONTRIBUTION

I.V.-L. and L.W.J. contributed equally to this work.

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AUTHOR CONTRIBUTIONS

Conception and design: Davide Soldato, Neil M. Iyengar, Aurélie Bertaut, Laurence Vanlemmens, Iona Hrab, Ines Vaz-Luis, Lee W. Jones
Financial support: Ines Vaz-Luis
Administrative support: Charles Coutant, Sibille Everhard, Anne-Laure Martin, Ines Vaz-Luis
Provision of study materials or patients: Julie Havas, Barbara Pistilli, Paul Cottu, Florence Lerebours, Laurence Vanlemmens, Christelle Jouannaud, Sibille Everhard, Anne-Laure Martin, Ines Vaz-Luis
Collection and assembly of data: Barbara Pistilli, Paul Cottu, Florence Lerebours, Christelle Jouannaud, Iona Hrab, Sibille Everhard, Anne-Laure Martin
Data analysis and interpretation: Stefan Michiels, Julie Havas, Antonio Di Meglio, Martina Pagliuca, Maria Alice Franzoi, Barbara Pistilli, Neil M. Iyengar, Florence Lerebours, Charles Coutant, Aurélie Bertaut, Iona Hrab, Fabrice André, Ines Vaz-Luis, Lee W. Jones
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

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3. Cariolou M, Abar L, Aune D, et al: Postdiagnosis recreational physical activity and breast cancer prognosis: Global Cancer Update Programme (CUP Global) systematic literature review and meta-analysis. Int J Cancer 152:600-615, 2023
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51. Stamatakis E, Ahmadi MN, Gill JMR, et al: Association of wearable device-measured vigorous intermittent lifestyle physical activity with mortality. Nat Med 28:2521-2529, 2022

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Dose/Exposure Relationship of Exercise and Distant Recurrence in Primary Breast Cancer

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Davide Soldato
Honoraria: AstraZeneca
Travel, Accommodations, Expenses: Novartis

Stefan Michiels
Consulting or Advisory Role: Biophytis, Servier, Yuhan, Roche, Kedrion Biopharma, IQvia

Antonio Di Meglio
Expert Testimony: Kephren, techspert.io

Martina Pagliuca
Travel, Accommodations, Expenses: Gilead Sciences

Maria Alice Franzoi
Speakers' Bureau: Novartis (Inst)
Research Funding: Resilience Care (Inst)

Barbara Pistilli
Consulting or Advisory Role: Puma Biotechnology, Pierre Fabre, Novartis, Myriad Genetics, AstraZeneca, Daiichi Sankyo/UCB Japan
Research Funding: Pfizer (Inst), Puma Biotechnology (Inst), Merus (Inst), Daiichi-Sankyo (Inst), Gilead Sciences (Inst), AstraZeneca (Inst)
Travel, Accommodations, Expenses: Pfizer, AstraZeneca, MSD Oncology, Novartis, Pierre Fabre, Daiichi Sankyo Europe GmbH

Neil M. Iyengar
Honoraria: Total Health Conferencing, MJH Life Sciences, Curio Science, IQvia, DAVA Oncology
Consulting or Advisory Role: Novartis, Seagen, Pfizer, Tersera, AstraZeneca, Gilead Sciences, BD Biosciences
Research Funding: Novartis (Inst), American Cancer Society (Inst), National Cancer Institute (Inst), Breast Cancer Research Foundation (Inst), Conquer Cancer Foundation (Inst), SynDevRx (Inst)

Paul Cottu
Honoraria: Pfizer, Novartis (Inst), Roche, NanoString Technologies (Inst), Lilly, Daiich Sankyo, AstraZeneca, Gilead Sciences
Consulting or Advisory Role: Pfizer, Lilly
Research Funding: Pfizer (Inst)
Travel, Accommodations, Expenses: Roche, Pfizer, Lilly

Florence Lerebours
Consulting or Advisory Role: AstraZeneca, Eisai, Lilly, Roche, Novartis, Seagen, Gilead Sciences, Menarini
Travel, Accommodations, Expenses: Novartis, Pfizer, Roche, Daiichi Sankyo/Astra Zeneca, Gilead Sciences, MSD, Seagen, Lilly

Charles Coutant
Travel, Accommodations, Expenses: Roche, MSD, AstraZeneca, Pfizer, Seagen, Exact Sciences, Daiichi Sankyo, Novartis, Myriad Genetics

Olivier Tredan
Consulting or Advisory Role: Roche, Pfizer, Lilly, AstraZeneca, MSD Oncology, Daiichi Sankyo Europe GmbH, Eisai Europe, Sandoz-Novartis, Pierre Fabre, Gilead Sciences, Stemline Therapeutics, Veracyte
Research Funding: Roche (Inst), Bristol Myers Squibb (Inst), MSD Oncology (Inst), AstraZeneca (Inst), Novartis (Inst)
Travel, Accommodations, Expenses: Roche, Novartis, Pfizer, Lilly, AstraZeneca, MSD Oncology

Christelle Jouannaud
Honoraria: Pfizer, Daiichi Sankyo/Astra Zeneca, Gilead Sciences
Consulting or Advisory Role: Daiichi Sankyo/Astra Zeneca
Travel, Accommodations, Expenses: MSD Oncology, Viatris

Fabrice André
Consulting or Advisory Role: Guardant Health (Inst), AstraZeneca (Inst), Lilly, Daiichi Sankyo (Inst), Roche (Inst), Lilly (Inst), Pfizer (Inst), Owkin (Inst), Novartis (Inst), N-Power Medicine (Inst), Servier (Inst), Gilead Sciences (Inst), Boston Pharmaceuticals (Inst)
Research Funding: AstraZeneca (Inst), Novartis (Inst), Pfizer (Inst), Lilly (Inst), Roche (Inst), Daiichi (Inst), Owkin (Inst), Guardant Health (Inst)
Travel, Accommodations, Expenses: Novartis, Roche, GlaxoSmithKline, AstraZeneca

Ines Vaz-Luis
Honoraria: AstraZeneca (Inst), Amgen (Inst), Pfizer (Inst), Novartis (Inst), Sandoz
Research Funding: Resilience Care (Inst)

Lee W. Jones
Stock and Other Ownership Interests: Pacylex, illumiSonics

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