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Physical Activity during Adolescence and Early Adulthood and Breast Cancer Risk before Age 40 Years

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ABSTRACT

Background: Breast cancer incidence is increasing in women under age 40, underscoring the need for research on breast cancer risk factors for younger women.

Methods: We used data from an international family cohort (n = 26,348) to examine whether recreational physical activity (RPA) during adolescence and early adulthood is associated with breast cancer risk before age 40. The cohort includes 2,502 women diagnosed with breast cancer before age 40, including 2,408 diagnosed before study enrollment (68% within 5 years of enrollment). Women reported their average hours per week of moderate and strenuous RPA during adolescence (12–17 years) and early adulthood (25–34 years), which were converted to total age-adjusted metabolic equivalents per week and categorized into quartiles. We conducted attained age analyses until age 40 (follow-up time began at age 18) using Cox proportional hazards regression models adjusted for study center, race and ethnicity, and education.

Results: Being in the highest versus lowest quartile of RPA during adolescence and early adulthood were respectively associated with 12% [HR (95% confidence interval, or CI), 0.88 (0.78–0.98)] and 16% [HR (95% CI), 0.84 (0.74–0.95) lower breast cancer risks before age 40. Being in the highest quartile of RPA during both adolescence and early adulthood (Pearson correlation = 0.52) versus neither time point was associated with a 22% lower risk [HR (95% CI), 0.78 (0.68–0.89)].

Conclusions: Findings suggest that RPA during adolescence and early adulthood may lower breast cancer risk before age 40.

Impact: Policies promoting physical activity during adolescence and early adulthood may be important for reducing the growing burden of breast cancer in younger women.

Introduction

Breast cancer incidence has increased over time in women under age 40 across the globe (1–3). In the United States, the overall incidence of invasive breast cancer increased by 0.54% per year between 2004 and 2017 in women under 40; distant-stage disease increased by 3.54% per year during this same timeframe (4). Genetic factors cannot explain the increase in breast cancer incidence over just a few decades, nor can changes in screening practices, given that women under age 40 are younger than the recommended age for routine mammography screening (5). Increasing obesity rates are also unlikely to explain the increase in breast cancer incidence in younger women, as has been suggested for colorectal cancer (6), given that adiposity is associated with a lower risk for premenopausal breast cancer (7–9). Other, possibly modifiable, factors are thus likely to explain incidence trends, suggesting tremendous potential for breast cancer risk reduction in younger women. However, few studies have focused on identifying strategies for reducing breast cancer risk in younger women prior to age 40.

Recreational physical activity (RPA), also sometimes referred to as leisure activity, may be important for reducing breast cancer risk in younger women. Extensive epidemiological evidence supports that, irrespective of body size, RPA in middle and later adulthood is associated with lower risk for both premenopausal breast cancer (usually defined as under age 55 years) and postmenopausal breast cancer (10–12). There is also evidence suggesting that RPA at younger ages may be important for reducing breast cancer risk (13). This includes RPA during adolescence, which is the period in life when the breast tissue is rapidly developing and thus potentially more susceptible to exogenous factors such as physical activity that may regulate hormone levels (14–16). Adolescence is also the period in life when RPA levels dramatically decline, particularly in girls (17, 18), and when adulthood RPA levels are established (19). Given the long latency of tumorigenesis, we hypothesize that RPA during adolescence may be important for reducing breast cancer risk specifically before age 40. However, there is currently limited data to

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support this hypothesis as few cohorts are powered to examine associations specifically in women diagnosed before age 40. This is a notable research gap given that breast tumors in younger women often exhibit different biological features and may thus arise from different pathways than breast tumors in older women (20). It is possible that modifiable factors such as RPA may influence breast cancer risk differently in younger women compared with what has been observed in older populations.

In this study, we leveraged data from a large international family cohort (21) to examine if RPA during adolescence and early adulthood is associated with breast cancer risk before age 40. The cohort is enriched for women with a breast cancer family history, which increases the risk for breast cancer at a younger age; (22, 23) it is thus uniquely suited to examine breast cancer risk before age 40 (includes 2,502 breast cancer cases diagnosed before age 40). We previously used this cohort to conduct a prospective analysis of RPA and breast cancer risk until age 80 years (24). Here, we extend this research by conducting a combined retrospective and prospective analysis of RPA and breast cancer risk specifically before age 40.

Materials and Methods

Study sample

We used data from two family-based cohorts for this analysis (21), the Breast Cancer Family Registry (BCFR; ref. 25) and the Kathleen Cuningham Foundation Consortium for Research into Familial Breast Cancer (kConFab) Follow-Up Study (26, 27). The BCFR is a collaboration of six breast cancer family studies from the United States, Canada, and Australia [average age at study enrollment = 49.8 years, standard deviation (SD) = 14.5; ref. 25]. Recruitment to the BCFR began in 1996, at which time population-based case families were recruited through cancer registries, oversampling for early onset cases and those with a breast cancer family history and other predictors of genetic risk; multiple-case families were recruited through clinics and community outreach. The kConFab was established in 1997 and has collected data from >1,300 breast cancer families recruited through family cancer clinics in Australia and New Zealand [average age at study enrollment = 49.7 years, SD = 15.9; refs. 26, 27]. Information on breast cancer diagnoses has been collected over time through self-reports, relative reports, and cancer registry linkages. Breast cancer diagnoses have been pathologically confirmed for 89% of women in our sample. The BCFR and kConFab were approved by the institutional review board at each participating study center; all participants provided written informed consent.

The BCFR and kConFab include a total of 31,639 women, including 18,854 women unaffected with breast cancer at study enrollment and 12,785 women affected with breast cancer at study enrollment. In the present study, we excluded women with missing data on RPA during adolescence ($n = 4{,}534$) or early adulthood ($n = 490$), or covariates ($n = 265$). We further excluded two women who were diagnosed with breast cancer before the age of 18 years, resulting in a final analytic sample of 26,348 (hereafter referred to as the full cohort). In our main analysis, we included women who were diagnosed with breast cancer before age 40 before study enrollment ($n = 2{,}408$) to ensure an adequate sample size for the analysis of breast cancer risk before age 40. We conducted secondary analyses excluding women older than age 45 years at study enrollment ($n = 15{,}987$) or diagnosed with breast cancer > 5 years prior to study enrollment ($n = 282$), leaving 10,079 women (hereafter referred to as the restricted cohort). Flow charts of the selection criteria for the full and restricted cohorts are provided in the Supplementary Materials (Supplementary Figs. S1 and S2).

Measures of RPA

At study enrollment, participants were asked by questionnaire, "How often did you participate in strenuous exercise activities or sports (e.g., swimming laps and running) when you were aged 12 to 17 years, 18 to 24 years, and 25 to 34 years, respectively?" Participants were given the following response options for each age interval: none, ½ hour per week, 1 hour per week, 1½ hours per week, 2 hours per week, 3 hours per week, 4 to 6 hours per week, 7 to 10 hours per week, or ≥11 hours per week, on average. A similar question was asked about moderate exercise activities or sports (e.g., brisk walking and golf). We used responses corresponding to ages 12 to 17 years to evaluate adolescent RPA. We used responses corresponding to ages 25 to 34 years to evaluate RPA in recent early adulthood for most participants ($n = 25{,}227$). We used responses corresponding to ages 18 to 24 years to evaluate RPA in recent early adulthood for participants who were <25 years at study enrollment, breast cancer diagnosis, or bilateral risk–reducing mastectomy ($n = 1{,}121$).

We converted hours per week of moderate and strenuous RPA to total metabolic equivalents (METs) per week (1 hour moderate = 4 METs; 1 hour strenuous = 7 METs; ref. 28); the midpoint was used if a range of hours per week was reported (e.g., 4–6 hours moderate converted to 5 hours = 20 METs) and ≥11 was coded as 11 hours per week. Consistent with our previous study (24), we adjusted the RPA measures for age at study enrollment to account for negative correlations. We did this by regressing log-transformed average METs per week on age at study enrollment to obtain age-adjusted residuals. We then categorized age-adjusted METs per week during adolescence and early adulthood into quartiles [quartile 1 (Q1) = least active to Q4 = highly active]. We also created a four-level variable that categorized individuals based on their RPA during both adolescence and early adulthood: (i) *not highly active during either timepoint*—Q1–Q3 during both adolescence and early adulthood; (ii) *highly active during adolescence only*—Q4 during adolescence and Q1–Q3 during early adulthood; (iii) *highly active during early adulthood only*—Q1–Q3 during adolescence and Q4 during early adulthood; and (iv) *highly active during both timepoints*—Q4 during both adolescence and early adulthood.

Statistical analysis

We conducted attained age analyses using multivariable Cox proportional hazards regression models to estimate HR and 95% confidence intervals (CI). The proportionality assumption was assessed by evaluating Schoenfeld residuals. Follow-up time was calculated from age 18 years to age at first breast cancer diagnosis, age at bilateral risk–reducing mastectomy, age at last follow-up visit, or age 40, whichever of these events occurred first (see Supplementary Materials, Supplementary Fig. S3). Models were stratified by decade of birth and adjusted for study center, race and ethnicity (non-Hispanic White vs. otherwise), and education (high school degree or general education degree or less, some college or vocational school, or bachelor's or higher degree), the latter of which was used as a proxy for early life social environment. We used a robust variance estimator to account for the family structure of the cohort.

We examined the separate associations of RPA during adolescence and early adulthood with breast cancer risk before age 40, using the previously described quartile variables. We tested linear trends across quartiles based on the Wald test, modeling RPA quartiles as a continuous term using the median value for each

quartile. We also examined the joint association of RPA during adolescence and early adulthood with breast cancer risk before age 40, using the previously defined four-level combined variable. To further explore whether RPA needs to be maintained between the two timepoints to reduce breast cancer risk before age 40, we fitted a model that included RPA during adolescence as a dichotomous variable [highly active (Q4) vs. otherwise (Q1–Q3)], RPA during early adulthood categorized into quartiles, and a cross-product term between the two RPA variables.

We fitted cross-product term models to examine whether associations between RPA and breast cancer risk were modified by *BRCA1* and *BRCA2* pathogenic variants (hereafter referred to as *BRCA1/2* PVs) status; women who did not undergo genetic testing were grouped with women who received testing and did not have PVs identified. We also examined whether associations were modified by family history of breast cancer defined as none, second-degree relative(s) only, or first-degree relative(s). In addition to breast cancer risk overall (counting all breast cancer diagnoses as events), we separately examined estrogen receptor (ER)–positive breast cancer risk and ER-negative breast cancer risk. In the analysis of ER-positive breast cancer risk, only ER-positive breast cancer cases were counted as events; ER-negative and ER-unknown breast cancer cases were censored at age at diagnosis. A similar approach was used to evaluate ER-negative breast cancer risk. All statistical analyses were conducted using Stata 15.1 (RRID: SCR_012763).

Sensitivity analyses

We conducted a sensitivity analysis excluding pathologically confirmed ductal carcinoma *in situ* cases ($n = 120$) and non-pathologically confirmed breast cancer cases ($n = 259$) to evaluate whether associations changed when we restricted the analysis to pathologically confirmed invasive breast cancer cases. We conducted a sensitivity analysis excluding participants for whom we defined RPA during early adulthood at ages 18 to 24 years ($n = 1{,}121$). This was done to evaluate whether associations changed when we used a consistent definition of RPA in early adulthood (i.e., ages 25–34 years) for all observations. To explore whether associations were possibly explained by other breast cancer risk factors, we conducted a sensitivity analysis further adjusting models for cigarette smoking, alcohol consumption, hormonal birth control use, parity, breastfeeding, and body mass index, all measured at study enrollment. Finally, we conducted a sensitivity analysis where we excluded 787 cases diagnosed with breast cancer more than 2 years before study enrollment from the restricted cohort to evaluate whether associations changed when we used a stricter inclusion criterion for the restricted cohort (diagnosed within 2 vs. 5 years of enrollment).

Data availability

The data generated in this study are available upon request from the corresponding author.

Table 1. Characteristics of the full cohort, $n = 26{,}348$.

Characteristic	Mean	SD	*n*	%
Age at study enrollment, years	49.5	14.6		
Decade of birth year				
<1950			11,833	44.9
1950–1959			6,723	25.5
1960–1969			4,777	18.1
≥1970			3,015	11.4
METs/week of RPA during adolescence, ages 12–17 years	43.1	33.3		
METs/week of RPA during early adulthood, ages 25–34 years	26.5	26.9		
Race and ethnicity				
Hispanic			2,665	10.1
Non-Hispanic Asian			1,609	6.1
Non-Hispanic Black			1,824	6.9
Non-Hispanic White			19,532	74.1
Other			718	2.7
Education at study enrollment				
< High school degree/GED			8,784	33.3
Some college/vocational			9,727	36.9
≥ Bachelor's degree			7,837	29.7
BRCA1 or *BRCA2* pathogenic variant				
No[a]			23,900	90.7
Yes			2,448	9.3
Family history of breast cancer				
None			4,564	17.3
Second-degree relative(s) only			3,962	15.0
First-degree relative(s)			17,822	67.6
Breast cancer cases			2,502	9.5
ER-positive breast cancer			784	31.3[b]
ER-negative breast cancer			630	25.2[b]
ER-unknown breast cancer			1,088	43.5[b]

Abbreviations: ER, estrogen receptor; GED, general education degree; METs, metabolic equivalents; RPA, recreational physical activity; SD, standard deviation.
[a]Includes women who did not undergo genetic testing and women who received testing and had no known PVs.
[b]Denominator is the total number of breast cancer cases in the full cohort ($n = 2{,}502$).

Results

Study sample characteristics

There were 2,502 breast cancer cases diagnosed before age 40 in the full cohort. The average age at study enrollment was 49.5 years (SD = 14.6), and women reported an average of 43.1 (SD = 33.3) and 26.5 (SD = 26.9) METs per week of RPA during adolescence and early adulthood, respectively (**Table 1**). See the Supplementary Materials (Supplementary Table S1) for sample characteristics stratified by RPA categories. Average METs per week of RPA during adolescence and early adulthood were correlated (Pearson correlation coefficients = 0.52); see Supplementary Materials, Supplementary Table S2, for the cross-tabulation of quartiles. The average METs per week of RPA during adolescence (Supplementary Fig. S4A) and early adulthood (Supplementary Fig. S4B) were generally higher in individuals who were younger at study enrollment and in those born in later decades (Supplementary Table S3). See the Supplementary Materials for a comparison of individuals who were included in versus excluded from the full cohort (Supplementary Table S4) and descriptive characteristics of the restricted cohort (Supplementary Table S5).

RPA during adolescence and breast cancer risk before age 40

In the full cohort overall, being in the highest (Q4) versus lowest (Q1) quartile of RPA during adolescence was associated with a 12% lower breast cancer risk before age 40 [HR (95% CI), 0.88 (0.78–0.98); **Table 2**]. When stratified by *BRCA1/2* PV status, being in the highest versus lowest quartile of RPA during adolescence was only associated with lower breast cancer risk before age 40 in women without known *BRCA1/2* PVs [HR (95% CI), 0.83 (0.73–0.95)]; however, we did not find statistical evidence of heterogenous effects by *BRCA1/2* PV status (interaction term *P*-value = 0.83). We did find statistical evidence of heterogenous effects by family history of breast cancer (interaction term *P*-value <0.001), such that being in the highest versus lowest quartile of RPA during adolescence was only associated with lower breast cancer risk before age 40 in women without a family history of breast cancer [HR (95% CI), 0.62 (0.52–0.73)]. Being in the highest versus lowest quartile of RPA during adolescence was associated with a 30% lower risk of ER-positive breast cancer before age 40 [HR (95% CI), 0.70 (0.56–0.86)]. RPA during adolescence was not associated with ER-negative breast cancer risk before age 40.

RPA during early adulthood and breast cancer risk before age 40

Being in the highest versus lowest quartile of RPA during early adulthood was associated with a 16% lower overall risk of breast cancer before age 40 [HR (95% CI), 0.84 (0.74–0.95); **Table 3**], and a 28% lower risk of ER-positive breast cancer [HR (95% CI), 0.72 (0.58–0.91)]. As with RPA during adolescence, RPA during early adulthood was not associated with ER-negative breast cancer risk, nor was it associated with breast cancer risk in women with known *BRCA1/2* PVs or with a first-degree family history of breast cancer.

Table 2. HRs and 95% CIs for the association of recreational physical activity during adolescence, ages 12 to 17 years, with breast cancer risk before age 40 in the full cohort, $n = 26{,}348$.

		Quartile of age-adjusted METs per week of RPA during adolescence					
		Q1	Q2	Q3	Q4		
Outcome		Avg METs/week: 7.9 ± 6.7	Avg METs/week: 26.7 ± 8.2	Avg METs/week: 49.2 ± 13.3	Avg METs/week: 88.6 ± 22.9		
Stratifying variable	Breast cancer events	HR (95% CI)[a]	HR (95% CI)[a]	HR (95% CI)[a]	HR (95% CI)[a]	*P*-trend	Interaction term *P*-value[b]
Overall breast cancer risk[c]	2,502	ref.	1.01 (0.91–1.13)	0.92 (0.82–1.03)	0.88 (0.78–0.98)	0.02	
By *BRCA*1/2 PV status							0.83
None[d]	1,891	ref.	0.99 (0.88–1.12)	0.89 (0.78–1.01)	0.83 (0.73–0.95)	0.003	
Any	611	ref.	1.05 (0.82–1.34)	1.00 (0.79–1.27)	0.92 (0.72–1.18)	0.54	
By family history of breast cancer							<0.001
None	1,013	ref.	0.82 (0.70–0.95)	0.74 (0.63–0.87)	0.62 (0.52–0.73)	<0.001	
Second degree only	546	ref.	1.23 (0.98–1.55)	0.88 (0.69–1.13)	0.92 (0.71–1.19)	0.24	
First degree	943	ref.	1.07 (0.89–1.29)	1.09 (0.91–1.31)	1.15 (0.95–1.39)	0.15	
ER-positive breast cancer risk[e]	784	ref.	0.93 (0.77–1.13)	0.79 (0.65–0.96)	0.70 (0.56–0.86)	<0.001	
ER-negative breast cancer risk[f]	630	ref.	1.27 (1.02–1.57)	0.95 (0.75–1.19)	0.99 (0.78–1.25)	0.59	

Abbreviations: Avg METs/week, average metabolic equivalents per week; CI, confidence interval; ER, estrogen receptor; HR, hazard ratio; PV, pathogenic variant; Q, quartile; RPA, recreational physical activity.

[a]Estimates are stratified by decade of birth and adjusted for study center, race and ethnicity, and education.

[b]The *P* value was calculated using the Wald test statistic evaluating the cross-product term in the model.

[c]All breast cancer diagnoses are counted as events, including ER-positive, ER-negative, and ER-unknown breast cancers.

[d]Includes women who received genetic testing and not known to carry pathogenic variants, as well as women who did not undergo genetic testing.

[e]Only ER-positive breast cancer diagnoses are counted as events; ER-negative and ER-unknown breast cancers are censored at the age of diagnosis.

[f]Only ER-negative breast cancer diagnoses are counted as events; ER-positive and ER-unknown breast cancers are censored at the age of diagnosis.

Table 3. HRs and 95% CIs for the association of recreational physical activity during early adulthood, ages 25 to 34 years, with breast cancer risk before age 40 in the full cohort, $n = 26{,}348$.

		Quartile of age-adjusted METs per week of RPA during early adulthood					
		Q1	Q2	Q3	Q4		
Outcome		Avg METs/week: 1.8 ± 2.8	Avg METs/week: 13.7 ± 5.9	Avg METs/week: 28.5 ± 10.4	Avg METs/week: 63.2 ± 26.0		
Stratifying variable	Breast cancer events	HR (95% CI)[a]	HR (95% CI)[a]	HR (95% CI)[a]	HR (95% CI)[a]	*P*-trend	Interaction term *P*-value[b]
Overall breast cancer risk[c]	2,502	ref.	1.03 (0.92–1.15)	0.94 (0.84–1.06)	0.84 (0.74–0.95)	0.04	
By *BRCA*1/2 PV status							0.90
None[d]	1,891	ref.	1.03 (0.91–1.17)	0.92 (0.80–1.04)	0.81 (0.70–0.93)	0.02	
Any	611	ref.	1.03 (0.81–1.30)	0.99 (0.78–1.26)	0.83 (0.65–1.07)	0.39	
By family history of breast cancer							0.002
None	1,013	ref.	1.08 (0.93–1.26)	0.94 (0.80–1.11)	0.69 (0.58–0.83)	0.01	
Second degree only	546	ref.	0.90 (0.71–1.14)	0.96 (0.75–1.22)	0.72 (0.55–0.93)	0.07	
First degree	943	ref.	1.00 (0.83–1.20)	0.97 (0.80–1.18)	1.08 (0.88–1.32)	0.77	
ER-positive breast cancer risk[e]	784	ref.	1.12 (0.93–1.36)	1.02 (0.83–1.24)	0.72 (0.58–0.91)	0.17	
ER-negative breast cancer risk[f]	630	ref.	1.09 (0.88–1.35)	0.92 (0.72–1.16)	0.85 (0.67–1.08)	0.33	

Abbreviations: Avg METs/wk, average metabolic equivalents per week; CI, confidence interval; ER, estrogen receptor; HR, hazard ratio; PV, pathogenic variant; Q, quartile; RPA, recreational physical activity.

[a]Estimates are stratified by decade of birth and adjusted for study center, race and ethnicity, and education.

[b]The *P* value was calculated using the Wald test statistic evaluating the cross-product term in the model.

[c]All breast cancer diagnoses are counted as events, including ER-positive, ER-negative, and ER-unknown breast cancers.

[d]Includes women who received genetic testing and not known to carry pathogenic variants, as well as women who did not undergo genetic testing.

[e]Only ER-positive breast cancer diagnoses are counted as events; ER-negative and ER-unknown breast cancers are censored at the age of diagnosis.

[f]Only ER-negative breast cancer diagnoses are counted as events; ER-positive and ER-unknown breast cancers are censored at the age of diagnosis.

Joint association of RPA during adolescence and early adulthood with breast cancer risk before age 40

In the model using the combined RPA variable, women who were highly active during both adolescence and early adulthood had a 22% lower risk of breast cancer before age 40 compared with women who were not highly active during either timepoint [HR (95% CI), 0.78 (0.68–0.89); **Table 4**]. When stratified by *BRCA1/2* PV status, this association was only observed in women without known *BRCA1/2* PVs. However, in the sensitivity analysis that further adjusted for other breast cancer risk factors, this association was observed in both women with and without known *BRCA1/2* PVs (see Supplementary Materials, Supplementary Table S6). In the cross-product term model, being in the highest versus lowest quartile of RPA during early adulthood was not associated with breast cancer risk before 40 among women who were not highly active during adolescence (**Fig. 1A**). However, among women who were highly active during adolescence (**Fig. 1B**), being in the highest versus lowest quartile of RPA during early adulthood was associated with a 33% lower risk of breast cancer before age 40 [HR (95% CI), 0.67 (0.51–0.88)]. Results were consistent in the restricted cohort compared with the full cohort (see Supplementary Materials, Supplementary Fig S5A and S5B; Supplementary Table S7).

Discussion

This study provides some of the first data supporting that RPA during adolescence and early adulthood may be associated with lower breast cancer risk before age 40. We found evidence of a multiplicative interaction between RPA at the two timepoints, such that RPA during early adulthood was only associated with lower breast cancer risk before 40 in women who were in the highest quartile of RPA during adolescence. RPA during early adulthood was not associated with lower breast cancer risk before age 40 in women who were in the lower three quartiles of RPA during adolescence. Further, we found that women who were in the highest quartile of RPA during both adolescence and early adulthood had a lower breast cancer risk before age 40 compared with women who were not in the highest quartile of RPA during either timepoint. Women who were in the highest quartile of RPA during one timepoint, but not the other, did not have a lower breast cancer risk before age 40. These findings suggest that women might need to be highly active during both adolescence and early adulthood to reduce their risk of breast cancer before age 40.

This finding that RPA may need to be high in both adolescence and early adulthood to reduce breast cancer risk before age 40 differs from what we found previously for breast cancer risk until age 80 years (24). In our previous study, in which <1% of cases were diagnosed before 40, RPA in adulthood was associated with lower breast cancer risk irrespective of RPA levels during adolescence (24). This suggests that the timing of RPA may be important when assessing breast cancer risk at different ages, as the associations may vary depending on the age at which breast cancer risk is evaluated. Hoewever, more longitudinal studies are needed to better understand how the timing of RPA affects breast cancer risk across the life course, especially given that we relied on retrospectively reported RPA data and had limited information on potential confounders (e.g., diet during

Table 4. HRs and 95% CIs for the association of recreational physical activity during both adolescence and early adulthood with breast cancer risk before age 40 in the full cohort, $n = 26{,}348$.

Outcome		Recreational physical activity during adolescence and early adulthood				
		Not highly active during either timepoint[a]	Highly active during adolescence only[b]	Highly active during early adulthood only[c]	Highly active during both time points[d]	
Stratifying variable	Breast cancer events	HR (95% CI)[e]	HR (95% CI)[e]	HR (95% CI)[e]	HR (95% CI)[e]	Interaction term *P*-value[f]
Overall breast cancer risk[g]	2,502	ref.	1.00 (0.88–1.13)	0.92 (0.81–1.05)	0.78 (0.68–0.89)	
By *BRCA*1 or 2 PV status						0.98
None[h]	1,891	ref.	0.98 (0.85–1.13)	0.91 (0.78–1.05)	0.74 (0.63–0.86)	
Any	611	ref.	1.04 (0.81–1.32)	0.90 (0.69–1.17)	0.77 (0.58–1.01)	
By family history of breast cancer						<0.001
None	1,013	ref.	0.90 (0.75–1.08)	0.82 (0.68–1.00)	0.55 (0.44–0.67)	
Second degree only	546	ref.	0.94 (0.72–1.23)	0.75 (0.57–0.99)	0.75 (0.56–1.00)	
First degree	943	ref.	1.07 (0.87–1.31)	1.07 (0.86–1.32)	1.13 (0.92–1.40)	
ER-positive breast cancer risk[i]	784	ref.	0.96 (0.77–1.20)	0.83 (0.66–1.06)	0.56 (0.42–0.73)	
ER-negative breast cancer risk[j]	630	ref.	1.06 (0.83–1.35)	0.95 (0.73–1.23)	0.77 (0.59–1.01)	

Abbreviations: CI, confidence interval; ER, estrogen receptor; HR, hazard ratio; PV, pathogenic variant

[a]Includes individuals who were in the lower three quartiles (Q1–Q3) of recreation physical activity during both adolescence and early adulthood ($n = 16{,}836$).

[b]Includes individuals who were in the highest quartile (Q4) of recreational physical activity during adolescence and in the lower three quartiles (Q1–Q3) of recreation physical activity during early adulthood ($n = 3{,}133$).

[c]Includes individuals who were in the lower three quartiles (Q1–Q3) of recreational physical activity during adolescence and in the highest quartile (Q4) of recreation physical activity during early adulthood ($n = 2{,}914$).

[d]Includes individuals who were in the highest quartile (Q4) of recreation physical activity during both adolescence and early adulthood ($n = 3{,}465$).

[e]Estimates are stratified by a decade of birth and adjusted for study center, race and ethnicity, and education.

[f]The *P*-value was calculated using the Wald test statistic evaluating the cross-product term in the model.

[g]All breast cancer diagnoses are counted as events, including ER-positive, ER-negative, and ER-unknown breast cancers.

[h]Includes women who received genetic testing and not known to carry pathogenic variants, as well as women who did not undergo genetic testing.

[i]Only ER-positive breast cancer diagnoses are counted as events; ER-negative and ER-unknown breast cancers are censored at the age of diagnosis.

[j]Only ER-negative breast cancer diagnoses are counted as events; ER-positive and ER-unknown breast cancers are censored at the age of diagnosis.

early life) that may track with RPA (18). Therefore, it will be important for future studies to utilize younger cohorts in which prospective data can be collected on RPA and other exposures in early life.

Although this study provides some of the first data on the relationship between RPA during adolescence and breast cancer risk specifically before 40, there have been previous studies that evaluated RPA during adolescence with premenopausal breast cancer risk (usually defined as <55 years). The Nurses' Health Study II was the largest study to evaluate RPA during adolescence in association with premenopausal breast cancer risk (29, 30). Consistent with our findings, the Nurse's Health Study II found that being in the highest versus lowest category of RPA during adolescence was associated with a 25% lower risk of premenopausal breast cancer after 6 years of follow-up and 15% lower risk after 15 years of follow-up (29, 30). However, other smaller studies did not find an association between RPA during adolescence and premenopausal breast cancer risk (31–33). Inconsistent findings across studies might be attributed to differences in sample characteristics and size, study design (e.g., case-control vs. cohort study), covariate adjustment, and exposure measurement. Previous studies of premenopausal breast cancer risk, to our knowledge, did not examine whether there was a multiplicative interaction between RPA during adolescence and early adulthood. Continued research is thus needed on the role of RPA across the life course in breast cancer risk in younger women; the urgency of this research is underscored by the global increase in breast cancer incidence in women under age 40 (2).

The biological mechanisms by which RPA may reduce breast cancer risk before 40 are not fully understood. However, they are likely independent of body fat regulation because higher adiposity is associated with a lower risk of premenopausal breast cancer risk, which contrasts with the increased risk observed for postmenopausal breast cancer (7). Mechanisms that might operate independently of changes in adiposity include the effects of RPA on estrogen metabolism, insulin sensitivity, chronic low-level inflammation, oxidative stress, and immune function (34, 35). When we examined associations by ER subtype, we found that RPA during adolescence and early adulthood were consistently associated with ER-positive breast cancer risk, which is the subtype that has been increasing over time in younger women (36). This might suggest that RPA is operating through mechanisms specific to ER-positive breast cancer (e.g., estrogen metabolism). Additional studies are needed to better

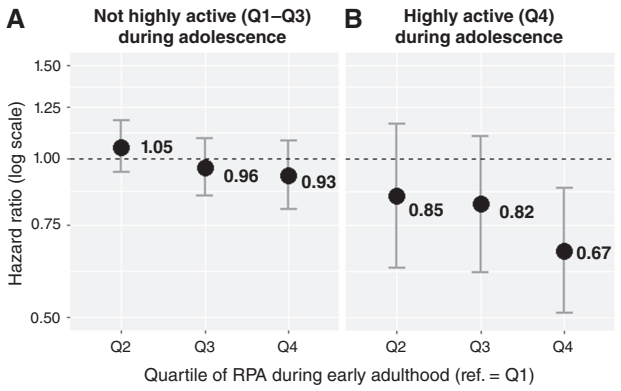

Figure 1.

HRs and 95% CIs for the association of recreational physical activity (RPA) during early adulthood with breast cancer risk before age 40 for individuals who were highly active vs. not highly active during adolescence in the full cohort, $n = 26{,}348$. **A,** shows HRs and CIs for individuals not in the highest quartile of adolescent RPA (Q1–Q3), whereas (**B**) shows results for those in the highest quartile of adolescent RPA (Q4). Quartile 1 (Q1) of early adulthood RPA serves as the reference. HRs and CIs are estimated from a multivariable Cox model, stratified by birth decade adjusted for study center, race and ethnicity, and education, and includes an interaction term between adolescent and early adulthood RPA. The overall interaction *P*-value was 0.21, with a one-degree-of-freedom *P*-value of 0.04 for Q4 vs. Q1 in early adulthood.

understand the role of RPA in ER-specific breast cancer risk before age 40 years, along with more mechanistic research.

One of the key strengths of this study is the use of a family-based cohort that was enriched for women at increased familial/genetic risk. This allowed us to explore whether associations varied by *BRCA1/2* PV status or by family history of breast cancer. When we stratified by these factors, we found that RPA during adolescence and early adulthood was only associated with lower breast cancer risk before age 40 in women without known *BRCA1/2* PVs and without a first-degree family history of breast cancer in the main analysis. However, in sensitivity analyses, we found that an association between RPA during adolescence and early adulthood with breast cancer risk before age 40 in women with known *BRCA1/2* PVs may have been obscured by other baseline risk factors, such as lifestyle, parity, and body mass index. We note that previous studies in women with *BRCA1/2* PVs have found evidence that RPA during adolescence may be associated with lower breast cancer risk in premenopausal women. This includes a previous case-control study that found that being in the highest versus lowest quartile of moderate RPA during adolescence was associated with lower risk of premenopausal breast cancer in women with *BRCA1/2* PVs (443 matched pairs; odds ratio, 0.62; 95% CI, 0.30–0.96; ref. 37). Another study found that being more physically active as a teenager was associated with delayed breast cancer onset in women with *BRCA1/2* PVs (38). Therefore, further studies with larger samples of women with *BRCA1/2* PVs and more detailed data on covariates across the life course are needed to better understand how RPA interacts with genetic susceptibility to influence breast cancer risk in younger women.

This study has limitations, the main one of which is that we were not able to conduct a purely prospective analysis. We used retrospectively reported data on RPA during adolescence and early adulthood and included prevalent breast cancer cases ($n = 765$ diagnosed more than 5 years before study enrollment), which may have led to differential exposure misclassification bias and survivorship bias. However, by including prevalent cases, we reduced the potential for selection bias from depletion of susceptibles (i.e., women unaffected by breast cancer at study enrollment may have lower absolute risk for disease), which may be a major concern when examining breast cancer risk at younger ages (39). The questionnaire that we used to measure RPA was previously used and validated in a different US cohort (40), but self-reported RPA is known to be overestimated (41). Nevertheless, prior studies have demonstrated the reliability and validity of using self-reported measures of RPA for rank ordering physical activity levels (i.e., stratifying more physically active individuals from less physically active individuals; refs. 42–44). Therefore, our use of categorical RPA measures likely minimized measurement error. We were also missing data on RPA during adolescence or early adulthood for 16% of the original cohort, which may have introduced selection bias, especially given that there were differences between individuals who were included versus excluded from the analysis. Moreover, our measures of RPA were limited in that we did not ask participants to report the specific types of sports and activities that they engaged in at different ages, which would have allowed for more accurate estimations of their total METs per week during adolescence and early adulthood. We may have introduced recall bias into the study by including a wide age range at study enrollment, although self-reported RPA levels in our study were comparable to those reported by the general population of US women (45). We attempted to minimize this type of bias by using age-adjusted measures of RPA and associations were consistent between the full cohort (no restriction on age at study enrollment) and the restricted cohort (restricted to age ≤45 years at study enrollment), providing support for our overall study conclusions. We were also limited in that we did not account for other types of physical activity (e.g., transportation, employment, and daily living) across the life course, and thus our assessment of physical activity is likely incomplete. However, previous studies support that RPA is more strongly associated with reduced breast cancer risk than other types of physical activity (10, 46). Furthermore, because we were interested in physical activity in early life, certain types of physical activity such as occupational activity were less relevant to this study. Finally, we had limited data on other early-life risk factors that may operate as confounders (e.g., diet and socioeconomic status). Nevertheless, this study is an important step toward understanding the role of RPA during adolescence and early adulthood in breast cancer risk in younger women.

In conclusion, this study provides evidence that RPA during adolescence and early adulthood may reduce breast cancer risk before 40. These findings support an investment in younger cohorts that can be followed prospectively over time to provide a deeper understanding of the role of RPA and other early-life risk factors in modifying breast cancer risk across the life course. These findings also underscore why the steep decline in physical activity levels that commonly occurs during adolescence is a pressing public health concern (17, 18). Policies promoting physical activity during adolescence, especially for girls, may thus be important for reducing the growing burden of breast cancer in younger women, along with providing other health benefits.

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Authors' Contributions

R.D. Kehm: Conceptualization, formal analysis, funding acquisition, visualization, writing–original draft, writing–review and editing. **J.M. Genkinger:** Visualization, writing–review and editing. **J.A. Knight:** Writing–review and editing. **R.J. Maclnnis:** Visualization, methodology, writing–review and editing. **Y. Liao:** Data curation, writing–review and editing. **S. Li:** Formal analysis, methodology, writing–review and editing. **P.C. Weideman:** Data curation, writing–review and editing. **W.K. Chung:** Writing–review and editing. **A.W. Kurian:** Writing–review and editing. **S.V. Colonna:** Writing–review and editing. **I.L. Andrulis:** Funding acquisition, writing–review and editing. **S.S. Buys:** Funding acquisition, writing–review and editing. **M.B. Daly:** Funding acquisition, writing–review and editing. **E.M. John:** Funding acquisition, writing–review and editing. **J.L. Hopper:** Funding acquisition, methodology, writing–review and editing. **M.B. Terry:** Conceptualization, funding acquisition, methodology, writing–review and editing.

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Note

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