Association between estimated cardiorespiratory fitness and breast cancer: a prospective cohort study

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ABSTRACT

Objective To examine the association between cardiorespiratory fitness (CRF) and the risk of breast cancer in postmenopausal women.

Methods This study used data from 17 840 cancer-free postmenopausal women with a CRF assessment from the UK Biobank. High estimated CRF (eCRF) was categorised as being ≥80th percentile within 10-year age bands. Fine and Gray regression was used to examine the association between eCRF and breast cancer risk, accounting for both non-breast cancer diagnoses and all-cause mortality as competing risks. Age was used as the time scale. Several different models were produced, including those adjusting for known breast cancer risk factors, and stratified by measures of body fat (body mass index and per cent body fat).

Results Over a median follow-up of 11.0 years there were 529 cases of invasive breast cancer, 1623 cases of non-breast cancer disease and 241 deaths. With adjustment for breast cancer risk factors, high eCRF was associated with a 24% (subdistribution HR (SDHR) 0.76, 95% CI 0.60 to 0.97) lower risk of breast cancer. When stratified by measures of body fat, we found evidence of effect measure modification. Mainly, having high eCRF was only associated with a lower risk of breast cancer among those classified as having overweight/obesity (SDHR 0.33, 95% CI 0.11 to 1.01) or percentage body fat above the 1st quintile (SDHR 0.65, 95% CI 0.45 to 0.94).

Conclusion Having higher CRF may be a protective factor against breast cancer in postmenopausal women but only for women with elevated body fat.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Higher body mass index (BMI) or per cent body fat and lower physical activity are risk factors for breast cancer in postmenopausal women.

WHAT THIS STUDY ADDS

⇒ Findings from this study suggest that having high cardiorespiratory fitness (CRF) may be associated with a lower risk of breast cancer in postmenopausal women.
⇒ The relationship between CRF and breast cancer appears to be modified by BMI and per cent body fat whereby CRF may only be associated with a lower risk of breast cancer in those with overweight/obesity or with a percentage body fat above the first quintile.
⇒ CRF was significantly associated with breast cancer, independent of physical activity.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ CRF may be a new target for clinicians to decrease postmenopausal women's risk of breast cancer, in particular for women with elevated body fat percentage.
⇒ Consistent participation in physical activity to improve CRF may be required to lower a woman's risk of breast cancer.

INTRODUCTION

Established postmenopausal breast cancer risk factors include having a family history of the disease,[1 2] the use of hormone replacement therapy,[2–4] early age at menarche[2 5] and increased body mass index (BMI).[6–8] One example of a potentially modifiable risk factor is physical activity. Prior research has found that participating in moderate to vigorous physical activity is associated with a lower risk of breast cancer, especially in postmenopausal women.[8]

Cardiorespiratory fitness (CRF) is the ability of a body's respiratory and circulatory system to provide oxygen to skeletal muscles during sustained physical activity. The better these systems are at delivering oxygen, the longer an activity can be maintained at a given endurance. This is an indication of physical fitness. CRF is, therefore, an assessment of the cumulative interrelationship between physical activity,[9] and other lifestyle (eg, smoking),[10] physiological (eg, adiposity)[11 12] and genetic factors.[13]

The aerobic hypothesis put forth by Koch *et al* postulates that a key mechanism of disease and health relates to how well the body can metabolise oxygen (which is partly assessed by CRF).[14] Studies of rodents bred for high aerobic capacity (an assessment of CRF) have found that higher aerobic capacity is associated with greater longevity,[14] as well as a lower incidence of risk factors (eg, insulin resistance) associated with chronic diseases including breast cancer.[15] There is also substantial evidence in humans to support that higher CRF is associated with a lower risk of disease and death.[16] However, while having higher inherent CRF is associated with lower breast cancer incidence and severity in rats,[17] no study to date has examined the relationship between CRF and breast cancer risk in humans.[17] The objective of this study was to examine the association between CRF and incident invasive breast cancer in postmenopausal women. Understanding the relationship between CRF and risk may inform interventions for breast cancer prevention.

METHODS

Study population

The UK Biobank study is a large population-based cohort that recruited approximately 500 000 adults aged 37–73 years from 2006 to 2010.[18] Participants completed comprehensive questionnaires capturing information on sociodemographic characteristics, lifestyle factors and medical history at baseline. A detailed description of the recruitment process and population characteristics have been described elsewhere.[19] Follow-up is ongoing and includes linkage to administrative databases, including the National Cancer and Death Registries. Participants provided written consent to the UK Biobank study personnel prior to initiating the study.

In 2009, the UK Biobank added a CRF assessment to the baseline protocol. For the current analysis, the sample was restricted to postmenopausal women who completed one of three CRF protocols (N=26 838) (see details on the assessment below).[20] Menopausal status at the time of CRF assessment was determined using an algorithmic approach. Women were categorised as being postmenopausal if they were >1 year older than the age their period stopped or if they had not had a period for >365 days at baseline. Women with a history of double oophorectomy at baseline were also classified as postmenopausal. Lastly, women were categorised as postmenopausal if no other information was available and they were>55 years at baseline.

Women were excluded if they had a personal history of any cancer (n=3524) or a history of mastectomy (n=18) at baseline (figure 1). As decided a priori, women with missing information on important covariates (N=5460) (eg, BMI and physical activity) were also excluded. The final sample analysed included 17 840 postmenopausal women.

Patient and public involvement

This study uses secondary data, therefore, there was no direct contact between the researchers and the participants for this study. In addition, there was no public involvement in the conceptualisation, creation or dissemination of this manuscript.

Exposure

CRF was assessed using a submaximal bicycle test without gas analysis.[20] Participants completed a questionnaire prior to CRF assessment to determine the risk of complications. Those classified as having minimal risk were tested at 50% of their predicted maximal workload (protocol 1), those with small risk were tested at 35% of their predicted maximal workload (protocol 2), and those with medium risk were tested at a constant workload (protocol 3). Those at high risk of an adverse event were not eligible for the general CRF protocol and therefore are not included in the study sample. Heart rate was monitored throughout, and workload was captured at the end of the CRF assessment. Linear regression, using the formula recommended in the literature, was used to interpolate workload at a predicted maximum heart rate.[21 22] Peak oxygen consumption (VO_2 peak) was calculated using the formula: 7+(10.8×predicted maximum workload)/weight in kilograms),[23] which is the method employed for other CRF studies from the UK Biobank.[21 22]

Estimated CRF (eCRF) was classified as a nominal three-level categorical variable: low (<20th percentile), moderate (20th to <80th percentile) and high eCRF (≥80th percentile) within 10-year age bands, consistent with existing CRF literature.[24] Alternative classifications of eCRF were also examined within 10-year age bands: (1) low fitness (less than vs greater than or equal to 20th percentile)[25] and (2) high fitness (less than vs greater than or equal to 80th percentile).[26] Other functional forms of eCRF considered can be found in online supplemental materials.

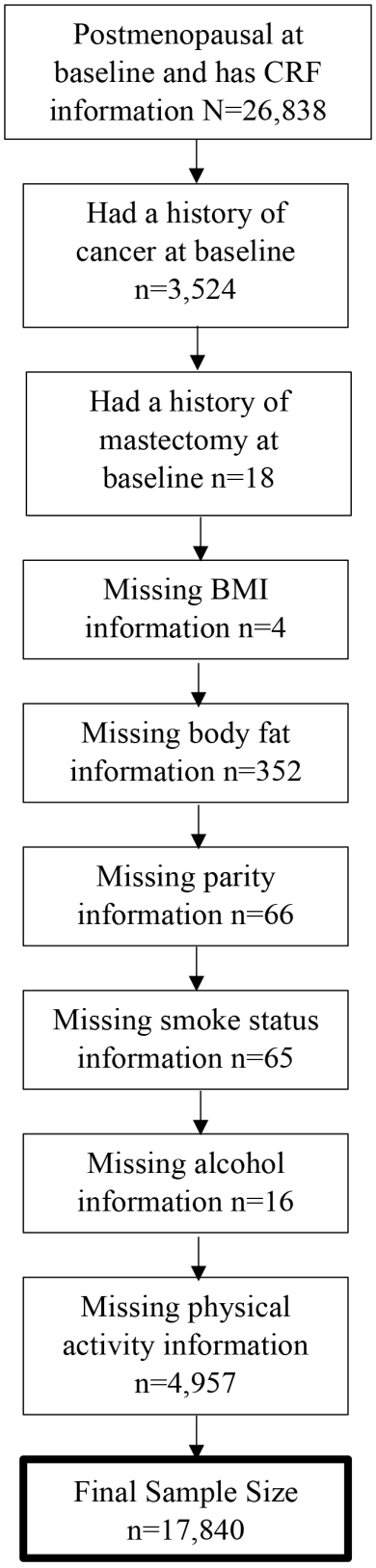

Figure 1 Flow chart of exclusion criteria of postmenopausal women from the UK Biobank with a valid CRF assessment. BMI, body mass index; CRF, cardiorespiratory fitness.

Outcome

Time from baseline to incident cancer diagnosis was captured through linkage to the National Cancer Registry and categorised based on International Classification of Disease 10th revision (ICD-10) codes. Information on primary cause of death was obtained from the National Health Service Information Centre for participants in England and Wales, and the National Health Service Central Register for participants in Scotland. The primary outcome was a diagnosis of invasive breast cancer (ICD-10 codes C50). The occurrence of a non-breast cancer diagnosis and all-cause mortality were both treated as competing risks. Individuals were followed from baseline until the first occurrence of any of the above-mentioned outcomes or the end of the follow-up period (25 June 2021) at which point they were right censored.

Covariates

Several variables associated with CRF and/or breast cancer risk were identified as potential confounders based on existing literature. All covariates were measured at baseline/time of CRF assessment. The following covariates were treated as nominal variables: (1) race (white, black or other (Asian, mixed, other, missing)); (2) education (secondary (advanced levels, advanced subsidiary levels or equivalent; ordinary levels, general certificate of secondary education or equivalent; certificate of secondary education or equivalent), postsecondary (college or university; national vocational qualification, higher national diploma, higher national certificate or equivalent; other professional qualification (eg, teacher, nurse)) or missing (none of the above, missing)); (3) alcohol consumption (never, special occasions only, one to three times a month, once to twice a week, three or four times a week); (4) smoking status (never, current, previous); protocol (protocol 1 (minimal risk), protocol 2 (small risk), and protocol 3 (medium risk). Protocol was examined as a nominal variable as there was no hierarchical order to protocol. Other covariates included: first degree (mother, sister, father, brother) family history of breast cancer (yes, no); number of pregnancies (nulliparous, 1, 2, ≥3); age at menarche (<13 years, ≥13 years); physical activity (≤or>50th percentile of metabolic task equivalent minutes of physical activity per week); BMI (underweight/normal weight (<25 kg/m^2) or overweight/obesity (≥ 25 kg/m^2)); and body fat percentage measured using bioelectric impedance analysis (first quintile, yes/no)). For women with missing information for age at menarche (N=696), the median age at menarche (13 years) was used. The proportion of women using hormone replacement therapy at baseline was low (n=381, 2.1%) and adjustment for this variable did not meaningfully change the result; therefore, it was not included in the multivariable model. Self-reported physical activity was assessed using a modified version of the International Physical Activity Questionnaire short-form and MET minutes per week estimates using standard procedures.[27]

Statistical analysis

Standardised differences were used to compare the distribution of variables by eCRF category. A mean standardised difference greater than 10% was considered clinically meaningful.[28]

Cumulative incidence functions, stratified by the three-category eCRF variable, were estimated for invasive breast cancer (the primary outcome), where other cancers and all-cause mortality were treated as competing events. Differences in the estimates of cumulative incidence were formally compared using Gray's test.[29]

Fine and Gray regression models[30] were used to examine the unadjusted and multivariable adjusted association between eCRF and hazard of breast cancer, with other cancer and all-cause mortality as competing events. Age was used as the timescale to anchor the analysis to a clinically meaningful time point (ie, attained age, rather than time since the arbitrary baseline assessment).

Four models were produced: (1) an unadjusted model, (2) a minimally adjusted model adjusted for potential confounders of the relationship between eCRF and breast cancer (ethnicity, smoke status, alcohol frequency use and physical activity), (3) a fully adjusted model with all variables included in the minimally adjusted model and including additional established breast cancer risk factors: education, family history of breast cancer, age at menarche, number of live births, as well as protocol number and (4) fully adjusted model restricted to individuals who completed the eCRF protocol 1 (N=15 147, 84.9%).

We did not adjust for BMI or per cent body fat in any models because it was highly colinear with eCRF (Pearson's r=−0.82 and r=0.80, respectively). Instead, we presented models stratified by BMI (overweight/obesity yes/no) and per cent body fat (first quintile yes/no) categories. This allowed us to control for the potential confounding effects of BMI and per cent body fat, and to assess whether they modified the association between eCRF and risk. Lastly, the potential impact of reverse causality on the findings were assessed using the fully adjusted model by setting the index date to 6 months, 1 year and 2 years after CRF assessment.

All analyses were conducted using SAS V.9.4; a two-sided alpha of 0.05 was considered statistically significant.

RESULTS

Table 1 shows the characteristics of the study population. The median age at eCRF assessment/baseline was 60 years (IQR 56–64) (table 1). Most women in the study sample were white (92.5%) and had completed some type of postsecondary education (60.0%). Approximately 12% of women had a first-degree relative with a history of breast cancer. The median BMI was 25.9 kg/m^2, the median body fat percentage was 36.8%, and the mean VO_2peak was 20.5 mL/kg/min.

Table 2 shows the characteristics of the study population stratified by eCRF categories. The greatest imbalance in covariates was observed for BMI (mean standardised difference=223%) and body fat percentage (mean standardised difference=213%). As expected, a greater proportion of individuals in the lower fitness category also had a higher BMI and body fatness above the first quintile.

Over a median follow-up of 11.0 years (range >0.0 to 12.2 years), 529 (3.0%) women were diagnosed with invasive breast cancer, 1623 (9.1%) with other cancers and 241 (1.4%) died (table 1). Cumulative incidence function for breast cancer with other cancers and all-cause mortality as competing events in the full study population and by eCRF category are presented in figures 2 and 3, respectively. Women with high eCRF had a lower cumulative incidence of breast cancer compared with those with low to moderate eCRF (figure 3A). However, the results of the Gray's test were not statistically significant (p=0.09). Further, while women in their mid-60s to early 70s with low eCRF had a higher cumulative incidence of other cancers compared with those with moderate and high eCRF, the differences were also not statistically significant (p=0.30; figure 3B). For all-cause mortality, however, the result of the Gray's test was significant (p<0.0001) finding that women in their mid 60s to late-70s with

Table 1 Characteristics of postmenopausal women included in the analysis from the UK Biobank

Characteristics	N=17 840
Follow-up time (years), median (min, max)	11.0 (>0.0 to 12.2)
Age (years), median (IQR)	60 (56–64)
Age categories, n (%)	
40 to <50	869 (4.9)
50 to <60	6886 (38.6)
60 t o<70	10 002 (56.1)
≥70 years	81 (0.5)
BMI (kg/m^2), median (IQR)	25.9 (23.4–29.1)
BMI categories, n (%)	
Underweight/normal weight	7332 (41.1)
Overweight	6892 (38.6)
Obesity	3616 (20.3)
Body fat percentage, median (IQR)	36.8 (32.2–41.2)
Body fat percentage categories	
First quintile (≤20th percentile)	3591 (20.1)
Second quintile (>20th to 40th percentile)	3569 (20.0)
Third quintile (>40th to 60th percentile)	3497 (19.6)
Fourth quintile (>60th to 80th percentile)	3632 (20.4)
Fifth quintile (>80th percentile)	3551 (19.9)
Ethnicity, n (%)	
White	16 502 (92.5)
Black	387 (2.2)
Other*	951 (5.3)
Education, n (%)	
Less than postsecondary†	4498 (25.2)
Postsecondary‡	10 702 (60.0)
Missing§	2640 (14.8)
Family history of breast cancer (Yes)¶, n (%)	2064 (11.6)
Age at menarche (years), median (IQR)	13.0 (12.0–14.0)
Parous (yes), n (%)	14 416 (80.8)
No of live births, median (IQR)	2 (1–2)
No of live births category, n (%)	
Nulliparous	3424 (19.2)
One	2274 (12.8)
Two	8048 (45.1)
Three or more	4094 (23.0)
Age at first birth** (years), n (%)	
<20	1050 (8.7)
20 to <25	3833 (31.6)
25 to <30	4868 (40.1)
30 to <35	1915 (15.8)
≥35	462 (3.8)
Hormone replacement therapy use, n (%)	381 (2.1)
Smoking status, n (%)	
Never	7789 (43.7)
Current	1177 (6.6)
Previous	8874 (49.7)
Alcohol frequency, n (%)	
Never	1572 (8.8)
Special occasions only	2.683 (15.0)
1–3 times a month	2175 (12.2)
Once or twice a week	4306 (24.1)
3 or 4 times a week	3833 (21.5)
Daily	3271 (18.3)
MET-minutes per week††, median (IQR)	1879.5 (924.0–3666.0)
Protocol	
1 (minimal risk)‡‡	15 147 (84.9)
2 (small risk)§§	2064 (11.6)
3 (medium risk)¶¶	629 (3.5)
Exposure	
VO_2peak (mL/kg/min), mean±SD	20.5±2.1
eCRF level, n (%)	
Low eCRF	3566 (20.0)
Moderate eCRF	10.704 (60.0)
High eCRF	3570 (20.0)
Outcome	
Breast cancer, n (%)	529 (3.0)
Other cancer, n (%)	1623 (9.1)
Death, n (%)	241 (1.4)

*Asian, mixed, other and missing.
†Advanced levels, advanced subsidiary levels or equivalent; ordinary levels, general certificate of secondary education or equivalent; certificate of secondary education or equivalent.
‡College or university; national vocational qualification, higher national diploma, higher national certificate or equivalent; other professional qualification (eg, teacher, nurse)
§None of the above or missing.
¶Self-reported history of their father, mother, sister and/or brother having had breast cancer.
**N=22 396.
††Three types of physical activity were self reported using a modified version of the IPAQ short form: walking, moderate and vigorous physical activity. Data were cleaned using standardised procedures, and then minutes of physical activity were multiplied by corresponding MET values for walking (3.3 METs), moderate (4.0 METs) and vigorous (8.0 METs) physical activity to determine total weekly METs of physical activity.
‡‡Participants who complete protocol 1 (aka minimal risk) for the eCRF assessment work at a maximum of 50% of their predicted workload.
§§Participants who complete protocol 2 (aka small risk) for the eCRF assessment work at a maximum of 35% of their predicted workload.
¶¶Participants who complete protocol 3 (aka medium risk) for the eCRF assessment worked at a constant workload.
%, per cent; BMI, body mass index; eCRF, estimate cardiorespiratory fitness; IQR, interquartile range; max, maximum; MET, metabolic task equivalent; min, minimum; n, sample size; SD, standard deviation.

low eCRF had the highest and women with moderate eCRF the lowest, cumulative incidence of all-cause mortality (figure 3C).

Adjusted subdistribution HR (SDHR) and 95%CIs for the relationship between eCRF and breast cancer are presented in table 3. Notably, there was a little difference in the results for the different models. In the fully adjusted model, women with high eCRF had a 24% lower risk of developing breast cancer compared with women with low to moderate eCRF (SDHR 0.76, 95% CI 0.60 to 0.97).

When models were stratified by BMI or per cent body fat, there was evidence of effect measure modification for the relationship between eCRF and breast cancer risk (table 4). Specifically, among women with overweight/obesity those with high eCRF were at a 67% (SDHR 0.33, 95% CI 0.11 to 1.01) lower risk of developing breast cancer than those with low to moderate eCRF. Conversely, women without overweight/obesity and with high eCRF did not appear to be at a significantly lower risk of developing breast cancer than those without overweight/obesity with low to moderate eCRF (SDHR 0.94, 95% CI 0.70 to 1.25). The same pattern was observed when we stratified by per cent body fat categories. Specifically, among women with per cent body fatness

Table 2 Characteristics of postmenopausal women with available eCRF assessment from the UK Biobank

Characteristics	Low eCRF	Moderate eCRF	High eCRF	Standardised differences
Sample size, n (%)	4558 (20.0)	13 675 (60.0)	4560 (20.0)	--
Follow-up time (years), median (min, max)	11.0 (0.1 to 12.0)	11.0 (>0.0 to 12.2)	11.0 (>0.0 to 12.1)	3.2
Age (years), median (IQR)	61 (56–64)	60 (56–64)	60 (56–64)	2.6
Age categories, n (%)				
40 to <50	173 (4.9)	522 (4.9)	174 (4.9)	0.1
50 to <60	1377 (38.6)	4133 (38.6)	1378 (38.6)	0.0
60 to <70	2000 (56.1)	6001 (56.1)	2001 (56.1)	0.1
≥70 years	16 (0.5)	48 (0.5)	17 (0.5)	0.3
BMI (kg/m^2), median (IQR)	32.4 (29.8–35.4)	25.9 (24.1–27.9)	22.0 (20.7–23.3)	**223.1**
BMI categories, n (%)				
Underweight/normal weight	63 (1.8)	3955 (37.0)	3314 (92.8)	**229.5**
Overweight	893 (25.0)	5743 (53.7)	256 (7.2)	**76.2**
Obesity	2610 (73.2)	1006 (9.4)	0 (0.0)	**120.1**
Body fat percentage, median (IQR)	44.1 (41.2–46.9)	36.9 (33.6–39.9)	29.5 (26.0–32.5)	**212.6**
Body fat percentage categories				
1st quintile (≤20th percentile)	26 (0.7)	1289 (12.0)	2276 (63.8)	**118.7**
2nd quintile (>20th to 40th percentile)	63 (1.8)	2562 (23.9)	944 (26.4)	**50.6**
3rd quintile (>40th to 60th percentile)	240 (6.7)	2973 (27.8)	284 (8.0)	**38.8**
4th quintile (>60th to 80th percentile)	859 (24.1)	2709 (25.3)	64 (2.0)	**48.8**
5th quintile (>80th percentile)	2378 (66.7)	1171 (10.9)	2 (0.1)	**129.4**
Ethnicity				
White	3304 (92.7)	9955 (93.0)	3243 (90.8)	5.3
Black	151 (4.2)	203 (1.9)	33 (0.9)	**14.3**
Other*	111 (3.1)	546 (5.1)	294 (8.2)	**15.0**
Education, n (%)				
Less than postsecondary†	898 (25.2)	2727 (25.5)	873 (24.5)	1.6
Postsecondary‡	2080 (58.3)	6402 (59.8)	2220 (62.2)	
Missing§	420 (11.8)	1264 (11.8)	380 (10.6)	5.8
Family history of breast cancer (yes)¶, n (%)	527 (11.6)	1599 (11.7)	493 (10.8)	2.5
Age at menarche (years), median (IQR)	13.0 (11.0–14.0)	13.0 (12.0–14.0)	13.0 (12.0–14.0)	**14.7**
Parous (yes), n (%)	2882 (80.8)	8784 (82.1)	2750 (77.0)	8.3
No of live births, median (IQR)	2 (1–2)	2 (1–2)	2 (1–2)	9.0
No of live births category, n (%)				
Nulliparous	684 (19.2)	1920 (17.9)	820 (23.0)	8.3
One	474 (13.3)	1334 (12.5)	466 (13.1)	1.7
Two	1529 (42.9)	4975 (46.5)	1544 (43.3)	4.8
Three or more	879 (24.7)	2475 (23.1)	740 (20.7)	9.3
Age at first birth**, n (%)				
<20	265 (11.0)	620 (8.3)	165 (7.2)	7.9
20 to <25	870 (36.2)	2361 (31.7)	602 (26.4)	**12.5**
25 to <30	920 (38.3)	2980 (40.0)	968 (42.5)	3.1
30 to <35	283 (11.8)	1198 (16.1)	434 (19.0)	9.4
≥35	66 (2.8)	286 (3.8)	110 (4.8)	5.3
Hormone replacement therapy use, n (%)	71 (2.0)	237 (2.2)	73 (2.0)	1.0
Smoking status, n (%)				
Never	1540 (43.2)	4637 (43.3)	1612 (45.2)	2.6
Current	243 (6.8)	671 (6.3)	263 (7.4)	2.9
Previous	1783 (50.0)	5396 (50.4)	1695 (47.5)	3.9
Alcohol frequency, n (%)				
Never	386 (10.8)	833 (7.8)	353 (9.9)	7.0
Special occasions only	739 (20.7)	1472 (13.8)	472 (13.2)	**13.4**
1–3 times a month	542 (15.2)	1274 (11.9)	359 (10.1)	**10.4**
Once or twice a week	839 (23.5)	2658 (24.8)	809 (22.7)	3.4
3 or 4 times a week	623 (17.5)	2386 (22.3)	824 (23.1)	9.3
Daily	437 (12.3)	2081 (19.4)	753 (21.1)	**15.9**
MET-minutes per week††, median (IQR)	1473 (693.0–3013)	1908.0 (959.0–3657.0)	2228.5 (1092.0–4266.0)	**20.7**

Continued

Table 2 Continued

Characteristics	Low eCRF	Moderate eCRF	High eCRF	Standardised differences
Protocol				
1 (minimal risk)‡‡	2797 (78.4)	9162 (85.6)	3188 (89.3)	**19.9**
2 (small risk)§§	560 (15.7)	1195 (11.2)	309 (8.7)	**14.5**
3 (medium risk)¶¶	209 (5.9)	347 (3.2)	73 (2.0)	**13.2**
Exposure				
VO_2peak (mL/kg/min), mean±SD	16.9±1.1	20.5±1.2	24.3±1.5	**378.8**
Outcome				
Breast cancer, n (%)	115 (3.2)	329 (3.1)	85 (2.4)	3.4
Other cancer, n (%)	349 (9.9)	967 (9.0)	307 (8.6)	2.7
Death, n (%)	69 (1.9)	109 (1.0)	63 (1.8)	5.1
Crude incident rates for breast cancer (per 10 000 person-years)	31.0	29.4	22.7	--

Standardised differences greater than 10% are bolded to indicate clinically meaningful differences. One standardised difference was calculated by first calculating a unique standardised difference for all possible pairwise. Standardised differences less than 0 were multiplied by –1, and then the average of the three standardised differences was calculated.
*Asian, mixed, other and missing.
†Advanced levels, advanced subsidiary levels or equivalent; ordinary levels, general certificate of secondary education or equivalent; certificate of secondary education or equivalent.
‡College or university; national vocational qualification, higher national diploma, higher national certificate or equivalent; other professional qualification (eg, teacher, nurse).
§None of the above or missing.
¶Self-reported history of their father, mother, sister and/or brother having had breast cancer.
**Low fit n=4418, moderate fit n=13 766, high fit n=4212.
††Three types of physical activity were self reported using the modified version of the IPAQ short form: walking, moderate and vigorous physical activity. Data were cleaned using standardised procedures, and then minutes of physical activity were multiplied by corresponding MET values for walking (3.3 METs), moderate (4.0 METs) and vigorous (8.0 METs) physical activity to determine total weekly METs of physical activity.
‡‡Participants who complete protocol 1 (aka minimal risk) for the eCRF assessment work at a maximum of 50% of their predicted workload.
§§Participants who complete protocol 2 (aka small risk) for the eCRF assessment work at a maximum of 35% of their predicted workload
¶¶Participants who complete protocol 3 (aka medium risk) for the eCRF assessment worked at a constant workload
%, per cent; BMI, body mass index; eCRF, estimate cardiorespiratory fitness; IQR, interquartile range; max, maximum; min, minimum; n, sample size; SD, standard deviation.

above the 1st quintile, having high eCRF was associated with a 35% lower risk of developing breast cancer than women with low to moderate eCRF (SDHR 0.65, 95% CI 0.45 to 0.94). Among women with a body fat percentage within the first quintile, there was no significant association between having high eCRF and breast cancer compared with women with low to moderate eCRF (SDHR 1.41, 95% CI 0.86 to 2.32). Results from the unadjusted, minimally adjusted and fully adjusted models restricted to protocol 1 were one again similar.

Several other functional forms of eCRF were considered and results are presented in online supplemental table 1. Results were consistent when using alternative categorisations of eCRF.

To examine the potential impact of reverse causality on our results, analyses were performed setting the index date (ie, start of follow-up) to 6 months, 1 year and 2 years after CRF assessment (online supplemental table 2). In these analyses, the effect estimates for high eCRF were slightly attenuated, with wider CIs (likely due to the smaller number of events). Overall, all effect

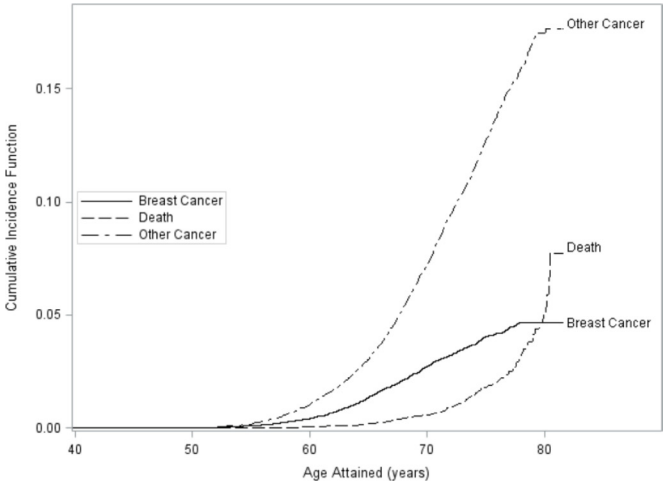

Figure 2 Cumulative incidence function curves for invasive breast cancer, other cancers and all-cause mortality in postmenopausal women.

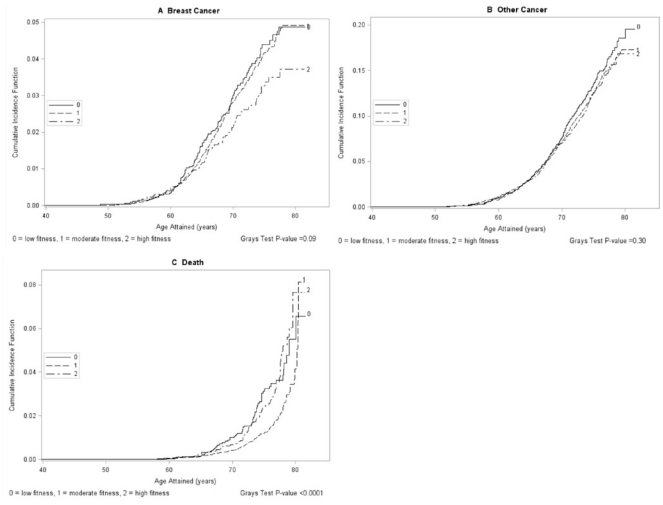

Figure 3 Cumulative incidence function curves for invasive breast cancer (A), other cancers (B) and all-cause mortality (C) by eCRF.

Table 3 SDHR and 95% CI for the relationship between eCRF and breast cancer among postmenopausal women in the UK Biobank

Exposure†	Unadjusted‡ (N=17 840)	Minimally adjusted‡ (N=17 840)	Fully adjusted§ (N=17 840)	Adjusted & restricted to protocol 1§ (N=15 147)
Three category fitness 1				
Low (<20th percentile) (N=3566)	Ref	Ref	Ref	Ref
Moderate (20th to <80th percentile) (N=10 704)	0.95 (0.77 to 1.18)	0.94 (0.76 to 1.17)	0.94 (0.76 to 1.16)	1.03 (0.81 to 1.32)
High (≥80th percentile) (N=3570)	0.75 (0.57 to 0.99)*	0.74 (0.56 to 0.98)*	0.73 (0.55 to 0.97)*	0.79 (0.57 to 1.08)
Low Fitness				
No (N=14 274)	Ref	Ref	Ref	Ref
Yes (N=3566)	1.11 (0.90 to 1.36)	1.12 (0.91 to 1.38)	1.13 (0.91 to 1.39)	1.03 (0.81 to 1.31)
High fitness				
No (N=14 720)	Ref	Ref	Ref	Ref
Yes (N=3570)	0.78 (0.62 to 0.98)*	0.77 (0.61 to 0.98)*	0.76 (0.60 to 0.97)*	0.77 (0.60 to 0.99)*

Fine and Gray regression analysis with other cancer, and all-cause mortality treated as competing risks was used to produce SDHRs. Age was used as a timescale to anchor findings to a clinically meaningful time point instead of arbitrary time point (ie, time since CRF assessment).
*Statistically significant (p<0.05).
†Sample sizes are based on the whole sample (ie, all those with an eCRF assessment using any of the three protocols).
‡Estimates adjusted for ethnicity (white, black, other), smoke status (never, current, previous), alcohol use frequency (never, special occasions only, 1–3 times a month, once or twice a week, 3 or 4 times a week, daily) and physical activity (categorised as ≤50th percentile vs >50th percentile of MET minutes per week).
§Estimates are adjusted for all variables in the minimally adjusted model and education (secondary, postsecondary, missing), family history of breast cancer, age at menarche (<or≥13 years of age), number of live births (nulliparous, 1, 2, 3 or more children) and protocol (1, 2, 3) if relevant.
BMI, body mass index; CI, confidence interval; eCRF, estimated cardiorespiratory fitness; SDHR, subdistribution HR.

estimates remained below one and were similar regardless of the number of events excluded, and the model presented.

DISCUSSION

In this population of postmenopausal, primarily white, women from the UK Biobank, we observed that having high eCRF was associated with an approximately 24% lower risk of breast cancer compared with having low or moderate eCRF. However, when we stratified by BMI or per cent body fat, the estimated association for eCRF was limited to individuals with overweight/obesity or per cent body fat above the first quintile and not in their leaner counterparts. Taken together, this may suggest that CRF is a protective factor for breast cancer, but only among women with overweight/obesity or those with per cent body fat above the first quintile.

Previous research has found that having a higher CRF can decrease a person's risk of developing[31] and dying from cardiometabolic conditions,[32] but the relationship between CRF and breast cancer incidence has not been examined. One study to date has examined the association between CRF and breast cancer mortality in women, finding that higher CRF is associated with lower breast cancer mortality.[33] Consistent with these findings, we observed that women with high eCRF have a lower risk of breast cancer.

CRF increases as a result of sustained physical activity. It is well established that increased physical activity can decrease a woman's risk of developing breast cancer.[34 35] In fact, a meta-analysis of 73 studies that incorporated many different physical activity assessments observed that women who participate in physical activity have, on average, a 25% lower risk of breast cancer.[34] This association was more pronounced in women who participated in sustained moderate to vigorous physical activity, or physical activity across their lifetime.[34] This could suggest that physical activity alone is not enough to reduce a woman's risk of breast cancer but rather the improvement in CRF is what is decreasing risk. Consistent with this, in the current study, eCRF was associated with a significantly lower risk of breast cancer even after adjustment for physical activity. In fact, the effect estimate for eCRF was essentially unchanged. These findings suggest that participation in sustained physical activity leading to increased CRF may be necessary to significantly lower a woman's risk of developing breast cancer.

Several functional forms of eCRF were assessed. Despite this, only estimates of high eCRF such as those in the 60th–75th percentile or greater were significantly associated with risk. Prior studies have observed a dose response relationship between CRF and non-cancer-related outcomes and death.[36–38] In the current study, we did not observe a dose response. Instead, we observed a potential threshold effect of high eCRF. This may mean that a higher level of CRF is needed to have meaningful improvements in breast cancer risk. However, CRF values from the Cooper Clinic in the USA, which first proposed percentile cut-offs for characterising the association between CRF and health risk are substantially higher than those that would likely be seen in the general population. The Fitness Registry and the Importance of Exercise National Database (FRIEND) cohort was developed to determine normative CRF values in the USA. They found that while the 25th percentile of VO_2max for women between the ages of 60–69 (which is similar to the median age in the current study) at the Cooper Clinic was 25.1 mL/kg/min,[39] women of the same age in the FRIEND cohort who were in the 75th percentile had a VO_2max of 23.8 mL/kg/min. The VO_2max reported in the FRIEND cohort is similar to the 75th percentile of VO_2peak for the current study (22.2 mL/kg/min). This suggests that the 20th percentile CRF cut-off (proposed by the Cooper Clinic) and observed as having a protective association with health outcomes is more closely associated with our 80th percentile cut-off and may contribute to why we observed our threshold effect. The issue of unrepresentative CRF thresholds is not restricted to the Cooper Clinic study. Several cohorts[40 41] with CRF measurements (eg, the National Health and Nutrition Examination Survey) also have substantially higher CRF values than what would be expected in the general population (ie, individuals in the FRIEND cohort). The higher CRF values present in these existing cohorts suggest a need for more representative CRF cohort studies to establish relevant thresholds related to CRF, and risk of disease and death.

A bidirectional relationship is thought to exist between CRF and both BMI and per cent body fat. That is, having a higher CRF is associated with a lower body fat percentage.[42] Conversely, having

Table 4 SDHR (95% CI) for the relationship between eCRF and breast cancer risk stratified by category of BMI and per cent body fat among postmenopausal women from the UK Biobank

Exposure	Unadjusted† (N=17 840)		Minimally adjusted†‡ (N=17 840)		Fully adjusted†§ (N=17 840)		Adjusted and restricted to protocol 1†§ (N=15 147)	
BMI categories	Without OWOB (N=7332)	With OWOB (N=10 508)	Without OWOB (N=7332)	With OWOB (N=10 508)	Without OWOB (N=7332)	With OWOB (N=10 508)	Without OWOB (N=6518)	With OWOB (N=8629)
High fitness								
No¶	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Yes**	0.91 (0.69 to 1.21)	0.33 (0.11 to 1.02)	0.94 (0.71 to 1.25)	0.33 (0.10 to 1.01)	0.94 (0.70 to 1.25)	0.33 (0.11 to 1.01)	0.89 (0.66 to 1.21)	0.38 (0.12 to 1.18)
Quintiles of per cent body fat	1st quintile (N=3737)	2nd–5th quintile (N=14 103)	1st quintile (N=3737)	2nd–5th quintile (N=14 103)	1st quintile (N=3737)	2nd–5th quintile (N=14 103)	Low body fat (N=3360)	High body fat (N=11 787)
High fitness								
No††	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Yes‡‡	1.38 (0.85 to 2.25)	0.66 (0.45 to 0.96)*	1.40 (0.86 to 2.29)	0.66 (0.45 to 0.95)*	1.41 (0.86 to 2.32)	0.65 (0.45 to 0.94)*	1.33 (0.79 to 2.24)	0.68 (0.46 to 1.00)

Fine and Gray regression analysis with other cancer, and all-cause mortality treated as competing risks was used to produce SDHRs. Age was used as a timescale to anchor findings to a clinically meaningful time point instead of arbitrary time point (ie, time since CRF assessment).
*Statistically significant (p<0.05).
†Sample sizes are based on the whole sample (ie, all those with an eCRF assessment using any of the three protocols).
‡Estimates adjusted for ethnicity (white, black, other), smoke status (never, current, previous), alcohol use frequency (never, special occasions only, 1–3 times a month, once or twice a week, 3 or 4 times a week, daily) and physical activity (categorised as ≤50th percentile versus >50th percentile of MET minutes per week).
§Estimates are adjusted for all variables in the minimally adjusted model and education (secondary, postsecondary, missing), family history of breast cancer, age at menarche (<or≥13 years of age), number of live births (nulliparous, 1, 2, 3 or more children) and protocol (1, 2, 3) if relevant.
¶Sample size in whole population is n=4018 and n=10 252 for without and with overweight/obesity, respectively.
**Sample size in whole population is n=3314 and n=256 for without and with overweight/obesity, respectively.
††Sample size in whole population is n=1315 and n=12 955 for body fat within and greater than the first quintile, respectively.
‡‡Sample size in whole population is n=2276 and n=1294 for body fat within and greater than the first quintile, respectively.
BMI, body mass index; eCRF, estimated cardiorespiratory fitness; MET, metabolic task equivalent; OWOB, overweight/obesity; SDHR, subdistribution HR.

higher levels of body fat is associated with a lower CRF.[43] CRF and BMI have also each been found to modify the association of the other with chronic diseases such as diabetes[44 45] and all-cause mortality.[46] When we stratified by BMI or per cent body fat, individuals with overweight/obesity or per cent body fat above the first quintile with high eCRF were at a lower risk of breast cancer than those with low to moderate eCRF, but not their leaner counterparts with similar CRF levels. While BMI and per cent body fat may still be cofounders of the relationship between eCRF and breast cancer, the fact that the effect estimates were different depending on the category of BMI and per cent body fat is also suggestive of effect measure modification. This could be mechanistically explained by the relationship between body fatness, physical activity and eCRF to oestrogen and chronic inflammation.

Following menopause, body fat becomes the primary source of oestrogen in the body[47] and oestrogen exposure is strongly associated with breast cancer risk.[48] Obesity is associated with chronic systemic inflammation.[49–52] In addition to oestrogen, chronic inflammation is thought to mediate the relationship between obesity and an increased risk of breast cancer in postmenopausal women.[53] Conversely, higher CRF and physical activity are associated with both lower levels of circulating endogenous estrogen[54 55] and lower levels of systemic inflammation.[51 52 56] Given CRF and measures of body fatness may both impact breast cancer risk through similar pathways may explain why CRF is only associated with a lower risk among those with elevated body fatness as individuals may need to have elevated inflammation or oestrogen in order to see a benefit.

Given that some events occurred shortly after CRF assessment, there is a potential for reverse causality. Although one study suggested that women with a recent breast cancer diagnosis have lower CRF than sedentary women without a history of cancer,[57] the comparison was biased as controls that were younger and leaner, both factors associated with a higher CRF. There is no paper that has repeat measures of CRF in women prior to and at diagnosis of breast cancer, but early-stage breast cancer is primary an asymptomatic disorder. It is therefore unlikely that it is associated with lower CRF levels. Nonetheless, we assessed for the potential impact of reverse causality in sensitivity analyses by setting the index date to 6 months, 1 year and 2 years after CRF assessment. Using the new index date there was an attenuation of the effect estimate (from 24% to 16% lower risk) along with reduced precision, which could suggest some impact of reverse causality on the results. However, all the effect estimates remained below one, and the attenuation of the effect estimates was similar when the index was set to 6 months and 2 years post-CRF assessment, with the reduction in precision likely due to the smaller number of events. These results support the findings that CRF may be an independent predictor of breast cancer risk and identify the need for future studies to assess CRF over time to determine if CRF can change as a result of breast cancer.

There are several strengths and limitations of the current analysis that warrant mentioning. A limitation is that the gold-standard method for capturing CRF (ie, a maximal treadmill test with oxygen expiration capture) was not used. Further, participants completed slightly different versions of the CRF assessment based on their estimated risk of adverse events, potentially introducing some measurement error into the analysis. To account for this potential measurement bias, we conducted an analysis restricted to those with protocol 1 (the protocol most closely resembling a submaximal CRF assessment). Overall, results were similar to those reported in the full sample. We also only had one measurement of eCRF per participant, which does not allow us to explore the impact of temporal changes in this measurement over time or how these temporal changes may impact risk. Nonetheless, exercise-based CRF assessments are rare, thus the availability of a submaximal assessment to estimate CRF on more than 17 500 participants is a strength of this study. Lastly, approximately 93% of participants in our sample from the UK Biobank identified as white, which may mean our findings do not generalise to non-white populations.

Other important strengths include the quality of other measures: (1) weight and height were measured by trained professionals; (2) many confounders were captured using standardised questionnaires that used the same wording as other established population-based cohorts and (3) outcome measures were assessed by administrative databases in a publicly funded healthcare system, allowing for complete follow-up. While there are multiple methods to assess body fat, dual-X-ray-absorptiometry is often considered the gold standard. However, dual-X-ray-absorptiometry assessed body fat was only available for a small proportion of individuals who also had a CRF assessment and there were very few events in this group (n=1). However, per cent body fat assessed using bioelectrical impedance analysis was available in most individuals. Notably, research from the UK Biobank found that results for the association between body fat and breast cancer risk were similar whether per cent body fat was assessed using dual-X-ray-absorptiometry or bioelectrical impedance analysis.[58]

Menopausal status is an important modifier for some breast cancer risk factors including BMI[6] and physical activity.[59] Since most women in the sample were 50 years or older at baseline, we could not examine the association between CRF and risk in premenopausal women. This remains an important area of study for future research. We also had limited information on dietary habits. While dietary information is available through the UK Biobank, there is only limited evidence that a few dietary factors may be associated with a woman's risk of developing breast cancer[60] and some of these (eg, calcium intake) were not measured by the UK Biobank.

In conclusion, this is the first study to examine the relationship between eCRF and breast cancer risk. Findings from this study suggest that high eCRF may be a protective factor for breast cancer in postmenopausal women, in particular those with overweight/obesity or per cent body fat above the first quintile. This work contributes to our understanding of the relationship between several interrelated risk factors for breast cancer (eg, elevated body fatness, physical inactivity) with the goal of informing preventive interventions. Findings from this study support the notion that physical activity, with the particular goal of increasing CRF, may be beneficial to reduce breast cancer risk in postmenopausal with an elevated body fat.

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Contributors RAGC was responsible for: conceptualisation, data curation, formal analysis, methodology, software and writing—original draft, and takes overall responsibility as the guarantor. JAK was responsible for the conceptualisation and writing—review and editing. RS was responsible for conceptualisation, methodology and writing—review and editing. JDB was responsible for conceptualisation, supervision and writing—review and editing.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by University of Toronto (#38620). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data may be obtained from a third party and are not publicly available. Data are owned by the UK Biobank study. Qualified researchers can access the data by completing a short application form and paying a data access fee.

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