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Original Article

# Estimated cardiorespiratory fitness in relation to overall, breast and prostate cancer incidence: the Norwegian HUNT study

Jin Wang, MSc[a,b], Xiao-Mei Mai, PhD[c], Yi-Qian Sun, PhD[d,e,f,*]

[a] Cancer Center, Department of Ultrasound Medicine, Zhejiang Provincial People's Hospital, Affiliated People's Hospital, Hangzhou Medical College, Hangzhou, Zhejiang, China
[b] Department of Neuromedicine and Movement Science, NTNU, Norwegian University of Science and Technology, Trondheim, Norway
[c] Department of Public Health and Nursing, NTNU, Norwegian University of Science and Technology, Trondheim, Norway
[d] Department of Clinical and Molecular Medicine, NTNU, Norwegian University of Science and Technology, Trondheim, Norway
[e] Department of Pathology, Clinic of Laboratory Medicine, St. Olavs Hospital, Trondheim, Norway
[f] Center for Oral Health Services and Research Mid-Norway (TkMidt), Trondheim, Norway

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ABSTRACT

*Purpose:* To investigate the relationships between the estimated cardiorespiratory fitness (eCRF) and the incidence of overall, breast, and prostate cancer in a large prospective cohort study.
*Methods:* We included 46,968 cancer-free adults who participated in the second survey of the Trøndelag Health Study in Norway. Sex-specific non-exercise algorithms were used to estimate CRF. eCRF was classified into sex and age-specific tertiles, that is, into low, medium and high levels. Cox proportional hazards models were used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs).
*Results:* Over a median of 22.1 years' follow-up, there were 7752 overall, 858 breast and 1376 prostate cancer cases. Medium and high levels of eCRF were associated with a reduced incidence of overall cancer in a dose-response manner in all participants (HR 0.96; 95% CI, 0.90–1.01 and HR 0.85; 95% CI, 0.79–0.91, respectively, and *P*-value for trend <.001). No association was observed between eCRF and breast cancer incidence in women. Only the high level of eCRF seemed to be associated with a reduced incidence of prostate cancer in men (HR 0.85; 95% CI, 0.72–1.02).
*Conclusions:* eCRF may be a practical and cost-effective means of investigating the association between the CRF and cancer incidence.



## Introduction

Globally, new cancer cases rose to 19.3 million in 2020 and are predicted to reach 28.4 million by 2040 [1]. Breast cancer is the world's most commonly diagnosed cancer, with nearly 2.3 million new cases in 2020, and prostate cancer cases reached 1.4 million in 2020 [1]. Diverse factors cause cancer, including smoking, obesity, alcohol consumption and a family history of cancer, and more than half of cancer incidence today is preventable [2,3].

Cardiorespiratory fitness (CRF) is an expression of maximal oxygen uptake ($VO_{2max}$) [4]. It reflects the ability to transport oxygen from the atmosphere to the body cells during physical activity (PA). Because oxygen delivery in the body involves numerous organs and body systems, such as the gas exchange function of the respiratory system, the blood circulation of the cardiovascular system and the metabolic function of the muscular system [4], CRF reflects the general health status of the body. Although more than half of CRF is determined by genes, age, and sex, habitual PA remains an important way of improving fitness [5]. Nevertheless, higher CRF has been associated with a lower risk of cardiovascular disease and mortality, independent of PA and other risk predictors [6–8].

*Abbreviations:* ACLS, The Aerobics Center Longitudinal Study; ACSM, American College of Sports Medicine; BMI, body mass index; CI, confidence interval; CRF, cardiorespiratory fitness; eCRF, estimated cardiorespiratory fitness; HR, hazard ratio; HRT, hormone replacement treatment; HUNT, the Trøndelag Health Study; LRT, likelihood ratio test; MET, metabolic equivalent of task; PA, physical activity; RHR, resting heart rate; WC, waist circumference.

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* Corresponding author: Department of Clinical and Molecular Medicine, NTNU, Norwegian University of Science and Technology, Trondheim, Norway. Tel.: +47 73598407.

*E-mail address:* yi-qian.sun@ntnu.no (Y.-Q. Sun).

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The gold standard measurement of CRF is the laboratory exercise test by analyzing the ventilatory gas exchange during maximal effort exercise on a treadmill or bicycle ergometer [4], which is not applicable to everyone, such as individuals with disabilities and those who are unable to exert themselves. Moreover, such a CRF test is time-consuming and costly, and it requires specialized equipment and trained workers. This makes it impractical to perform exercise-measured CRF in large populations. Thus, non-exercise algorithms have been developed to calculate estimated CRF (eCRF) based on health indicators that can be easily obtained [9,10]. The variables often included in the algorithms are age, waist circumference (WC), resting heart rate (RHR), and PA, which can be easily measured during a clinical examination or obtained through questionnaires. However, it is noteworthy that heterogeneity may exist between different algorithms. A study showed that eCRF was a useful predictor of stroke incidence among white but not among black participants using the algorithm generated from predominantly white participants [11]. Thus, algorithms derived from one population may not be applicable to another population.

Previous studies have reported an inverse association between exercise-measured CRF and cancer incidence and mortality [12–18]. Almost all these studies were conducted among men, and the sample size was generally small. With regard to the incidence of site-specific cancer, studies were either scarce for breast cancer or inconsistent for prostate cancer, showing no, inverse or positive associations [19–21]. To date, only a few studies have investigated the relationship between the eCRF and cancer mortality among the US population [22–24]. No studies have investigated eCRF in relation to the incidence of overall or site-specific cancer in a large population.

Thus, the aim of our study was to investigate the potential association between the eCRF and the incidence of overall cancer in a prospective cohort of Norwegians. We also aimed to study the relationships between the eCRF and the incidence of breast and prostate cancer, as they are the most common types of cancer in women and men, respectively. The applied eCRF algorithms were derived from the same Norwegian population.

## Methods

### *Study population and data collection*

The study population was derived from the Trøndelag Health Study (HUNT). HUNT is one of the largest population-based health surveys in Norway, covering about 123,000 Norwegian participants aged 20 years or older in four different surveys: HUNT1 (1984–1986), HUNT2 (1995–1997), HUNT3 (2006–2008) and HUNT4 (2017–2019) [25,26]. The HUNT data were collected via clinical measures, questionnaires, interviews, and biological samples. Participants were followed up by linking the HUNT surveys with national health or other registers in Norway.

In our study, we included all participants who participated in HUNT2 ($n$ = 65,226) from 1995 to 1997. Participants with missing information on WC, RHR or PA were excluded because these variables were necessary for the estimation of CRF ($n$ = 16,804). We further excluded participants who were diagnosed with cancer before their participation in HUNT2 ($n$ = 1454). Ultimately, the analysis dataset included a total of 46,968 participants (23,375 men and 23,593 women).

### *Estimated cardiorespiratory fitness (eCRF) as the exposure variable*

Sex-specific non-exercise algorithms obtained from the HUNT population were used to estimate CRF [27,28]. The algorithms were initially derived from a healthy population of more than 2000 women and men, respectively, in the HUNT3 survey (mean age of 48 years) and adapted to the HUNT2 survey. They explained 52% and 58% of the variance in peak oxygen uptake ($VO_{2peak}$) for women and men, respectively, in HUNT2 [28]. They showed high comparability with other non-exercise prediction algorithms in terms of the included variables, such as age, body composition, PA and RHR, as well as the variation explained and the error estimates [10,29,30]. The algorithms for calculating eCRF in peak oxygen consumption (mL/kg/min) were as follows [28]:

$$\text{For women: } 78.00 - (0.297 \times \text{Age}) - (0.270 \times \text{WC}) - (0.110 \times \text{RHR}) + (2.674 \times \text{PA}_{\text{ACSM}});$$

$$\text{For men: } 105.91 - (0.334 \times \text{Age}) - (0.402 \times \text{WC}) - (0.144 \times \text{RHR}) + (3.102 \times \text{PA}_{\text{ACSM}}).$$

Waist circumference and RHR were measured at clinical examinations [25]. Waist circumference was measured horizontally at the height of the umbilicus to the nearest 1.0 cm while the participant was standing with their arms hanging relaxed. A Dinamap 845XT (Critikon Inc) was used by trained nurses or technicians to measure RHR after the participant had been seated for two minutes, and the mean of three measurements was recorded. The information on age and PA was retrieved from self-administered questionnaires. We classified $\text{PA}_{\text{ACSM}}$ into two categories according to the response to questions about the duration and intensity of PA [31]. $\text{PA}_{\text{ACSM}} = 1$ if the participant met the American College of Sports Medicine (ACSM) recommendation [32], that is, moderate-intensity cardiorespiratory exercise training for ≥30 minutes (min) a day on ≥5 days a week for a total of ≥150 minutes a week, or vigorous-intensity cardiorespiratory exercise training for ≥20 minutes a day on ≥3 days a week for a total of ≥75 minutes a week; $\text{PA}_{\text{ACSM}} = 0$ for participants not meeting the recommendation. eCRF was derived from the given equations, and participants were classified into sex and age-specific tertiles (regarded as low, medium, and high levels) within each 10-year age interval [28]. We also adopted the Aerobics Center Longitudinal Study (ACLS) approach to categorize participants based on eCRF into sex- and age-specific 20% low, 40% medium and 40% high groups [33].

### *Cancer incidence as the outcome variable*

The HUNT population data were linked to the data from the Cancer Registry of Norway. The unique eleven-digit Norwegian personal identification number was used for the linkage. Participants were followed up from the baseline participation date in HUNT2 until one of the following circumstances occurred: 1) the first diagnosis of any/breast/prostate cancer, 2) death, 3) emigration from Norway, or 4) the end of follow-up on December 31, 2018. The International Classification of Diseases Tenth Revision (ICD-10) coding was used to identify the types of cancer in the Cancer Registry of Norway. In this study, we focused on the incidence of overall cancer as well as incidence of breast (C50) and prostate (C61) cancer specifically.

### *Covariates*

Age, sex, body mass index (BMI), PA level, sitting hours/day, smoking status, alcohol consumption, education, economic difficulties, severe disease and a family history of cancer were identified as potential confounders *a priori* based on previous knowledge and a directed acyclic graph [34] when the relationship between the eCRF and the risk of overall cancer was assessed. Information on the mentioned covariates was obtained via clinical examination or self-administered questionnaires in the HUNT2 survey. Height and weight were measured when participants wore light clothes,

without shoes. Body mass index was calculated as body weight divided by height squared (kg/m²), and participants were categorized as underweight (<18.5 kg/m²), normal weight (18.5–24.9 kg/m²), overweight (25.0–29.9 kg/m²) and obesity (>30.0 kg/m²). Participants were asked to report their average hours of light (no sweating or not being out of breath) and hard PA (sweating or out of breath), with the following response options for each intensity: none, <1 hour, 1–2 hours and ≥3 hours. We classified participants, based on PA levels, as inactive (no any activity, or ≤2 hours light activity), low (≥3 hours light activity only, or ≤2 hours light activity and <1 hour hard activity), moderate (≥3 hours light activity and <1 hour hard activity, or 1–2 hours hard activity regardless of light activity) and high (≥3 hours hard activity regardless of light activity) [31]. Moderate or high levels of PA in the HUNT data were assumed to meet the ACSM recommendation ($PA_{ACSM} = 1$), and inactive or low level of PA was assumed to not meet the ACSM recommendation ($PA_{ACSM} = 0$). In terms of sitting hours/day, participants were categorized as ≤4, 5–7 and ≥8. Smoking status was classified as never smoked, former smoker <10 pack-years (pyrs), former smoker 10–20 pyrs, former smoker >20 pyrs, current smoker <10 pyrs, current smoker 10–20 pyrs and current smoker >20 pyrs. Alcohol consumption was categorized as never, 1–4 times/month and ≥5 times/month. The categorization of educational years was <10, 10–12 and ≥13. Economic difficulties were defined as "yes" or "no" based on the question "During the last year, has it, at any time, been difficult to meet the costs of food, transportation, housing, and such?" For severe disease, we classified participants as "yes" if they had experienced myocardial infarction (heart attack), angina pectoris (chest pain), stroke/brain hemorrhage or diabetes previously and as "no" if they had never experienced these diseases. Family history of cancer was classified as "yes" or "no" by using the following question: "Have your relatives (mother, father, brother, sister, and child) had cancer, or do they have it now?"

To study breast cancer as an outcome in women, we added hormone replacement treatment (HRT) as an additional confounder [35]. The HRT question was asked as follows: "Have you taken estrogen in any form (not for birth control)?" Answers were classified as never having used and ever having used. To study prostate cancer as an outcome in men, marital status was added as an additional covariate [36]. Marital status was categorized as single, widow/divorced/separated and married/registered partner. A separate "unknown" category was defined for missing information on the covariates and was included in the analysis. The categorizations of covariates in the present study were commonly used in the previous HUNT publications [31,37].

### *Statistical analysis*

The baseline characteristics of the participants were presented by the sex and age-specific tertiles for eCRF (as low, medium, and high levels). Cox proportional hazards models were used to evaluate the potential associations between the eCRF and the incidence of overall, breast and prostate cancer, respectively. eCRF was used as a categorical variable (low, medium, and high levels), and the *P*-value for trend was calculated by treating the categorical variable as an ordinal variable. We also used the ACLS eCRF categories (20% low, 40% medium, and 40% high) to examine the relationship with overall cancer incidence. Crude and adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) are presented. Age was used as the time scale and was therefore adjusted in both the crude and adjusted Cox models. The potential confounding factors included in the adjusted Cox models for overall cancer were sex, BMI, PA level, sitting hours/day, smoking status, alcohol consumption, education, economic difficulties, severe disease and a family history of cancer. For breast cancer in women, HRT was additionally adjusted. For prostate cancer in men, marital status was additionally adjusted. Schoenfeld residuals were used to test the proportional hazards assumption for both the exposure variable and all the potential confounding factors. The *tvc* option for the *stcox* command in Stata was used to model non-proportional hazards if a covariate did not satisfy the proportional hazards assumption. The possible effect modification by sex regarding the association between the eCRF and the incidence of overall cancer was evaluated via the likelihood ratio test (LRT). To reduce the possibility of reverse causality due to existing but undiagnosed cancer during the early years of follow-up, sensitivity analyses were performed by excluding the first three years' follow-up. All statistical analyses were performed with STATA, Release 17 (StataCorp LP, College Station, Texas).

## Results

Among the 46,968 participants, 7752 participants were diagnosed with cancer over a median of 22.1 years of follow-up. As compared with participants with medium or high eCRF levels (Table 1), participants with the low eCRF level were more likely to be obese and physically inactive, and they were also less educated and had more economic difficulties. The distributions of baseline characteristics across eCRF tertile categories were similar between women and men (Table 1).

As compared to participants having the low eCRF level, those with the medium and high eCRF levels had HRs of 0.96 (95% CI, 0.90–1.01) and 0.85 (95% CI, 0.79–0.91), respectively, for the incidence of overall cancer (*P*-value for trend <.001, Table 2). Among women, only the high eCRF level appeared to be inversely associated with the incidence of overall cancer (*P*-value for trend = .09). Among men, both the medium and high eCRF levels were inversely associated with overall cancer incidence (*P*-value for trend <.001). The reduction in the incidence of overall cancer associated with the high eCRF level was 9% in women (HR 0.91; 95% CI, 0.81–1.02) and 19% (HR 0.81; 95% CI, 0.74–0.89) in men. However, the LRT test did not show effect modification by sex ($P = .72$). We also performed an analysis of the incidence of overall cancer, using the ACLS approach to categorize eCRF as 20% low, 40% medium and 40% high [33]. The results are presented as Supplementary Table 1 and were similar to those in Table 2. In the sensitivity analysis performed after excluding the first three years' follow-up, the estimates for the association between the eCRF, in tertiles, and overall cancer incidence were similar to the main results for all participants, as well as for women and men, respectively (Supplementary Table 2).

During the follow-up, there were 858 breast cancer cases in women and 1376 prostate cancer cases in men. No association was observed between the eCRF and breast cancer incidence in women (Table 3). Nevertheless, the high eCRF level seemed to be associated with a reduced HR for the incidence of prostate cancer in men (HR 0.85; 95% CI, 0.72–1.02). After the exclusion of the first 3 years of follow-up in the sensitivity analysis (Supplementary Table 3), the associations between eCRF and breast and prostate cancer incidence did not change substantially.

## Discussion

### *Main findings*

We observed an inverse dose-response association between the eCRF and the incidence of overall cancer in all participants and in men. In women, the high eCRF level appeared to be inversely associated with overall cancer incidence. However, there was no clear evidence showing effect modification by sex. No association was

**Table 1**
Baseline characteristics of 46, 968 participants from the HUNT Study, stratified by eCRF tertile categories in women and men

| | eCRF level in women ($n$ = 23, 593) | | | eCRF level in men ($n$ = 23, 275) | | |
|---|---|---|---|---|---|---|
| | Low | Medium | High | Low | Medium | High |
| **N** | 7866 | 7864 | 7863 | 7793 | 7793 | 7789 |
| **Age at baseline (years)** | 47.4 ± 16.7 | 46.5 ± 16.4 | 45.2 ± 16.2 | 48.2 ± 16.2 | 47.3 ± 15.9 | 46.3 ± 15.9 |
| **WC (cm)** | 90.2 ± 10.9 | 78.7 ± 7.4 | 72.2 ± 6.1 | 99.5 ± 8.5 | 90.7 ± 5.8 | 84.2 ± 5.9 |
| **RHR (bpm)** | 79.8 ± 13.2 | 74.2 ± 10.9 | 68.3 ± 9.7 | 77.1 ± 12.9 | 69.5 ± 10.5 | 62.9 ± 9.6 |
| **eCRF (mL/kg/min)** | 31.5 ± 6.7 | 36.2 ± 6.1 | 39.8 ± 5.8 | 39.7 ± 7.3 | 45.5 ± 6.5 | 50.2 ± 6.5 |
| **BMI** | | | | | | |
| Normal weight | 1398 (17.8) | 3825 (48.6) | 5814 (73.9) | 901 (11.7) | 2574 (33.0) | 4843 (62.2) |
| Under weight | 15 (0.2) | 45 (0.6) | 173 (2.2) | 1 (0.0) | 7 (0.1) | 66 (0.9) |
| Overweight | 3305 (42.0) | 3344 (42.5) | 1776 (22.6) | 4207 (54.0) | 4696 (60.3) | 2805 (36.0) |
| Obesity | 3074 (39.1) | 631 (8.0) | 94 (1.2) | 2658 (34.1) | 512 (6.6) | 69 (0.9) |
| Unknown | 74 (0.9) | 19 (0.2) | 6 (0.1) | 26 (0.3) | 4 (0.1) | 6 (0.1) |
| **Recommended PA is met** | 2114 (26.9) | 4046 (51.5) | 6584 (83.7) | 2435 (31.3) | 4635 (59.5) | 6642 (85.3) |
| **PA level** | | | | | | |
| Inactive | 4107 (52.2) | 2592 (33.0) | 869 (11.1) | 3353 (43.0) | 1809 (23.2) | 605 (7.8) |
| Low | 2038 (25.9) | 1934 (24.6) | 1359 (17.3) | 2351 (30.2) | 1879 (24.1) | 1081 (13.9) |
| Moderate | 1098 (14.0) | 2087 (26.5) | 3446 (43.8) | 1287 (16.5) | 2395 (30.7) | 3232 (41.5) |
| High | 214 (2.7) | 498 (6.3) | 1050 (13.4) | 461 (5.9) | 1091 (14.0) | 2211 (28.4) |
| Unknown | 409 (5.2) | 753 (9.6) | 1139 (14.5) | 341 (4.4) | 619 (7.9) | 660 (8.5) |
| **Sitting hours/day** | | | | | | |
| ≤4 h | 1978 (25.2) | 2111 (26.8) | 2091 (26.6) | 1440 (18.5) | 1747 (22.4) | 1862 (23.9) |
| 5–7 h | 2068 (26.3) | 2031 (25.8) | 2089 (26.6) | 1819 (23.3) | 1873 (24.0) | 1954 (25.1) |
| ≥8 h | 2137 (27.2) | 2159 (27.5) | 2223 (28.3) | 2679 (34.4) | 2605 (33.4) | 2507 (32.2) |
| Unknown | 1683 (21.4) | 1563 (19.9) | 1460 (18.6) | 1855 (23.8) | 1568 (20.1) | 1466 (18.8) |
| **Smoking (pack-years)** | | | | | | |
| Never smoked | 3517 (44.8) | 3645 (46.4) | 3919 (49.8) | 2770 (35.5) | 3024 (38.8) | 3591 (46.1) |
| Former smoker <10 | 1110 (14.1) | 1173 (14.9) | 1128 (14.4) | 992 (12.7) | 1131 (14.5) | 1083 (13.9) |
| Former smoker 10–20 | 269 (3.4) | 272 (3.5) | 223 (2.8) | 687 (8.8) | 606 (7.8) | 443 (5.7) |
| Former smoker >20 | 95 (1.2) | 70 (0.9) | 67 (0.9) | 566 (7.3) | 403 (5.2) | 284 (3.7) |
| Current smoker <10 | 1145 (14.5) | 1136 (14.5) | 1085 (13.8) | 664 (8.5) | 688 (8.8) | 636 (8.2) |
| Current smoker 10–20 | 890 (11.3) | 808 (10.3) | 698 (8.9) | 703 (9.0) | 663 (8.5) | 605 (7.8) |
| Current smoker >20 | 415 (5.3) | 351 (4.5) | 317 (4.0) | 753 (9.7) | 692 (8.9) | 587 (7.5) |
| Unknown | 425 (5.4) | 409 (5.2) | 426 (5.4) | 658 (8.4) | 586 (7.5) | 560 (7.2) |
| **Alcohol consumption** | | | | | | |
| Never | 3633 (46.2) | 2975 (37.8) | 2611 (33.2) | 1940 (24.9) | 1674 (21.5) | 1708 (21.9) |
| 1–4 times/month | 3244 (41.2) | 3726 (47.4) | 3871 (49.2) | 4086 (52.4) | 4184 (53.7) | 4244 (54.5) |
| ≥ 5 times/month | 424 (5.4) | 619 (7.9) | 866 (11.0) | 1325 (17.0) | 1495 (19.2) | 1431 (18.4) |
| Unknown | 565 (7.2) | 544 (6.9) | 515 (6.6) | 442 (5.7) | 440 (5.7) | 406 (5.2) |
| **Education (years)** | | | | | | |
| <10 | 3100 (39.4) | 2518 (32.0) | 2123 (27.0) | 2510 (32.2) | 2072 (26.6) | 1766 (22.7) |
| 10–12 | 2437 (31.0) | 2382 (30.3) | 2190 (27.9) | 3104 (39.8) | 3196 (41.0) | 3073 (39.5) |
| ≥13 | 2145 (27.3) | 2784 (35.4) | 3412 (43.4) | 1976 (25.4) | 2376 (30.5) | 2785 (35.8) |
| Unknown | 184 (2.3) | 180 (2.3) | 138 (1.8) | 203 (2.6) | 149 (1.9) | 165 (2.1) |
| **Economic difficulties** | | | | | | |
| No | 3643 (46.3) | 4132 (52.5) | 4411 (56.1) | 3614 (46.4) | 3984 (51.1) | 4201 (53.9) |
| Yes | 2326 (29.6) | 1926 (24.5) | 1692 (21.5) | 1822 (23.4) | 1655 (21.2) | 1502 (19.3) |
| Unknown | 1897 (24.1) | 1806 (23.0) | 1760 (22.4) | 2357 (30.3) | 2154 (27.6) | 2086 (26.8) |
| **Severe disease ever** | | | | | | |
| No | 6925 (88.0) | 7113 (90.5) | 7191 (91.5) | 6705 (86.0) | 6871 (88.2) | 6899 (88.6) |
| Yes | 683 (8.7) | 517 (6.6) | 450 (5.7) | 9,21 (11.8) | 799 (10.3) | 733 (9.4) |
| Unknown | 258 (3.3) | 234 (3.0) | 222 (2.8) | 167 (2.1) | 123 (1.6) | 157 (2.0) |
| **Family history of cancer** | | | | | | |
| No | 5777 (73.4) | 5853 (74.4) | 5906 (75.1) | 6034 (77.4) | 5917 (75.9) | 5971 (76.7) |
| Yes | 2089 (26.6) | 2011 (25.6) | 1957 (24.9) | 1759 (22.6) | 1876 (24.1) | 1818 (23.3) |
| **HRT** | | | | | | |
| Never having used | 4988 (63.4) | 5012 (63.7) | 5088 (64.7) | – | – | – |
| Ever having used | 1112 (14.1) | 1227 (15.6) | 1276 (16.2) | – | – | – |
| Unknown | 1766 (22.5) | 1625 (20.7) | 1499 (19.1) | – | – | – |
| **Marital status** | | | | – | – | – |
| Single | 1809 (23.0) | 1867 (23.7) | 2070 (26.3) | 2442 (31.3) | 2316 (29.7) | 2451 (31.5) |
| Widow/divorced/separated | 1434 (18.2) | 1320 (16.8) | 1221 (15.5) | 746 (9.6) | 692 (8.9) | 605 (7.8) |
| Married/register partner | 4603 (58.5) | 4654 (59.2) | 4538 (57.7) | 4591 (58.9) | 4772 (61.2) | 4715 (60.5) |
| Unknown | 20 (0.3) | 23 (0.3) | 34 (0.4) | 14 (0.2) | 13 (0.2) | 18 (0.2) |

Abbreviations: BMI = body mass index; bpm = beats per minute; eCRF = estimated cardiorespiratory fitness; HRT = hormone replacement treatment; PA = physical activity; RHR = resting heart rate; WC = waist circumference.
Data presented as mean ± standard deviation for continuous variables or number of participants (column percentage) for categorical variables.
eCRF was classified into sex and age-specific tertiles. Low level: the lowest tertile; medium level: the middle tertile; and high level: the highest tertile.

**Table 2**
The association between eCRF and incidence of overall cancer in the HUNT study

| eCRF | Cases | IR (per 1000 person-years) | Crude HR* | 95% CI | Adjusted HR† | 95% CI |
|---|---|---|---|---|---|---|
| **All (*n* = 46, 968)** | | | | | | |
| Low | 2684 | 9.07 | 1.00 | Reference | 1.00 | Reference |
| Medium | 2633 | 8.68 | 0.96 | 0.91–1.01 | 0.96 | 0.90–1.01 |
| High | 2435 | 7.85 | 0.88 | 0.83–0.93 | 0.85 | 0.79–0.91 |
| *P*-value for trend | | | <.001 | | <.001 | |
| **Women (*n* = 23, 593)** | | | | | | |
| Low | 1168 | 7.68 | 1.00 | Reference | 1.00 | Reference |
| Medium | 1147 | 7.38 | 0.97 | 0.89–1.05 | 0.98 | 0.90–1.08 |
| High | 1072 | 6.77 | 0.90 | 0.83–0.98 | 0.91 | 0.81–1.02 |
| *P*-value for trend | | | .02 | | .09 | |
| **Men (*n* = 23, 375)** | | | | | | |
| Low | 1516 | 10.55 | 1.00 | Reference | 1.00 | Reference |
| Medium | 1486 | 10.05 | 0.95 | 0.88–1.02 | 0.93 | 0.86–1.01 |
| High | 1363 | 8.99 | 0.85 | 0.79–0.91 | 0.81 | 0.74–0.89 |
| *P*-value for trend | | | <.001 | | <.001 | |

Abbreviations: BMI = body mass index; CI = confidence interval; eCRF = estimated cardiorespiratory fitness; HR = hazard ratio; IR = incidence rate; PA = physical activity.
eCRF was classified into sex and age-specific tertiles. Low level: the lowest tertile; medium level: the middle tertile; and high level: the highest tertile.
* Age was used as the time scale.
† Age was used as the time scale and further adjusted for sex, BMI, PA level, sitting hours, smoking (pack-years), alcohol consumption, education, economic difficulties, severe disease and family history of cancer in all participants. Sex was not included in the analysis for women and men, respectively.

**Table 3**
The associations between eCRF and incidence of breast cancer in women as well as incidence of prostate cancer in men in the HUNT Study

| eCRF | Cases | IR (per 1000 person-years) | Crude HR* | 95% CI | Adjusted HR† | 95% CI |
|---|---|---|---|---|---|---|
| **Breast cancer** | | | | | | |
| Low | 265 | 1.74 | 1.00 | Reference | 1.00 | Reference |
| Medium | 320 | 2.06 | 1.20 | 1.02–1.42 | 1.13 | 0.94–1.36 |
| High | 273 | 1.72 | 1.03 | 0.87–1.22 | 0.94 | 0.75–1.18 |
| **Prostate cancer** | | | | | | |
| Low | 423 | 2.94 | 1.00 | Reference | 1.00 | Reference |
| Medium | 488 | 3.30 | 1.12 | 0.99–1.28 | 1.02 | 0.88–1.18 |
| High | 465 | 3.07 | 1.05 | 0.92–1.19 | 0.85 | 0.72–1.02 |

Abbreviations: BMI = body mass index; CI = confidence interval; eCRF = estimated cardiorespiratory fitness; HR = hazard ratio; IR = incidence rate; PA = physical activity.
eCRF was classified into sex and age-specific tertiles. Low level: the lowest tertile; medium level: the middle tertile; and high level: the highest tertile.
* Age was used as the time scale.
† Age was used as the time scale and further adjusted for BMI, PA level, sitting hours, smoking (pack-years), alcohol consumption, education, economic difficulties, severe disease and family history of cancer. Hormone replacement treatment was additionally adjusted in the model for breast cancer. Marital status was additionally adjusted for prostate cancer.

observed between the eCRF and breast cancer incidence. Nevertheless, the high eCRF level only seemed to be associated with a reduced incidence of prostate cancer.

### *Comparison with previous studies*

To our knowledge, this is one of the first prospective cohort studies to investigate the association between the eCRF calculated based on non-exercise algorithms and cancer incidence in a large and homogenous population. Previous studies have examined the relationship between the eCRF and all-cancer mortality in the US population [22,23]. Vainshelboim et al. demonstrated an 11% reduction in all-cancer mortality for each 1-MET increase in eCRF among both men and women [22]. Wang et al. observed a somewhat clearer association between the eCRF and all-cancer mortality in women than in men [23].

Several smaller sized population studies have mainly investigated the relationship between exercise-measured CRF and overall cancer incidence in men and demonstrated a dose-response and inverse association [12–14,18]. Our results obtained using eCRF support these findings in men. The relationship between exercise-measured CRF and overall cancer incidence in women has only been investigated in a pilot cohort of 184 veterans [15]; For each 1-MET increase in CRF, there was a 20% decrease in the risk of cancer incidence in this cohort of women. Although we did not observe a dose-response relationship between eCRF and overall cancer incidence in women, there was no effect modification by sex in our study.

We did not observe an association between the eCRF and breast cancer incidence in women. Contrastingly, Peel et al. showed an inverse association between exercise-measured CRF and breast cancer mortality among 14,811 US women [24]. However, PA was not included in the adjustment in that study, and the participants included in the analysis were restricted to married, well-educated women. Our study extends this previous study by including more participants and adjusting for more potential confounders. In addition, we studied breast cancer incidence instead of mortality.

We found the high, as compared to the low, level of eCRF seemed to be associated with a lower prostate cancer incidence. Previous studies regarding exercise-measured CRF and prostate cancer incidence have demonstrated no association [19], an inverse association [20], or a positive association [21]. Regarding the positive association, the authors interpreted it as a non-causal association, most likely due to a screening/detection bias in men

who were fitter [21]. In addition, prostate cancer was self-reported through mail-back health surveys in the cited study.

*Potential biological mechanisms*

The underlying mechanisms via which higher levels of CRF reduce cancer incidence are not fully understood. As mentioned above, CRF reflects the general health status of the body. Good CRF may help to improve the integrated function of body systems, such as increasing blood circulation and muscle protein synthesis [4]. For example, Vainshelboim et al. point out that good CRF may reduce the risk of lung cancer by improving lung ventilation and lung perfusion to reduce the interaction time of potential carcinogens in the airways [38]. However, cancer is a broad and complex disease, and the mechanisms behind the relationship between CRF and cancer may vary between cancer sites. In this regard, future research addressing the biological roles of CRF in the prevention of site-specific cancer is warranted.

*Strengths and limitations*

Scientific evidence regarding eCRF in relation to cancer incidence in large population studies is scarce. Our study showed that eCRF may be a practical means of investigating such relationships in large populations when exercise-measured CRF is difficult to obtain from all participants. The follow-up duration in our study was long, and the relatively large sample size allowed us to study both all cancer and site-specific forms of cancer. Moreover, we included many important socio-demographic and lifestyle factors as confounders in the adjustment, which strengthened the validity of results. The ascertainment of cancer outcomes was highly accurate based on the Cancer Registry of Norway. We also excluded participants with a cancer diagnosis at baseline and excluded the first three years' follow-up in the sensitivity analysis to minimize reverse causality.

However, our study has several limitations. First, the distributions of several baseline characteristics differed between the included and exclude participants (Supplementary Table 4). The excluded participants were older, less educated and more likely to be women and had more severe disease. Although the percentages of overall cancer cases were similar among the included and excluded participants, the percentages of breast and prostate cases were relatively higher in the included than in the excluded participants. Thus, caution should be taken when we interpret our results, because selection bias cannot be excluded. Second, the misclassification of PA due to self-reporting and measurement error for WC and RHR was possible, which may have led to the misclassification of eCRF. However, this misclassification could be regarded as non-differential misclassification. Third, we were unable to evaluate how changes in eCRF level over time would affect the cancer incidence using the one-time eCRF at baseline. Fourth, heterogeneity regarding the included variables, variants explained and error estimates among different algorithms may exist [39]. Thus, algorithms derived from one population may not be applicable to another population [11]. In this study, we used the algorithms obtained from the same HUNT population, which may have provided more accurate values of eCRF. Fifth, some of the observed associations had imprecise estimates due to insufficient statistical power, warranting further confirmation from larger population studies. Sixth, although we adjusted for the most important confounders, we were not able to exclude residual confounding due to unknown factors. Finally, the participants in our study were mainly European, which may limit the generalizability of our results to other populations.

In summary, we found an inverse dose-response association between eCRF and the incidence of overall cancer in the Norwegian HUNT population. No association was observed between the eCRF and breast cancer incidence, but the high level of eCRF appeared to be associated with lower prostate cancer incidence. Our study suggests that eCRF may be a practical and cost-effective means of investigating the association between the CRF and cancer incidence.

## Ethics approval

All participants gave their informed consent for participation in HUNT. The current study was approved by the Norwegian Regional Committees for Medical and Health Research Ethics (2019/337 REK sør-østA).

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## Authors' contributions

**JW, XMM** and **YQS** performed literature search and contributed to the study design. **XMM** and **YQS** were responsible for data collection. **JW** and **YQS** conducted statistical analyses and wrote the initial draft of the manuscript. **JW, XMM** and **YQS** participated in the data interpretation, contributed to statistical analyses and manuscript writing with important intellectual content and approved the final version of the manuscript.

## Availability of data and materials

Data from the HUNT Study that are used in research projects will, when reasonably requested by others, be made available on request to the HUNT Data Access Committee (hunt@medisin.ntnu.no). The HUNT data access information describes the policy regarding data availability (https://www.ntnu.edu/hunt/data).

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## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.annepidem.2022.11.008.

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