Master's thesis

NTNU
Norwegian University of Science and Technology
Faculty of Medicine and Health Sciences
Department of Neuromedicine and Movement Science

Jin Wang

# Estimated cardiorespiratory fitness in relation to overall, breast and prostate cancer incidence

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Supervisor: Xiao-Mei Mai
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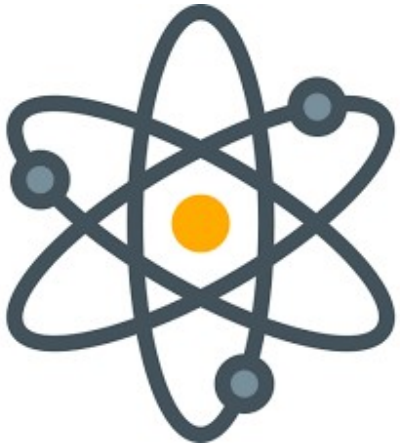
# Estimated cardiorespiratory fitness in relation to overall, breast and prostate cancer

## Introduction

The global cancer new cases have risen to **19.3 million** in 2020 with **breast cancer** occupied the world's most commonly diagnosed cancer and **prostate cancer** reached fourth place of cancer in 2020. The cancer burden has exerted immense stress on individuals, families, communities, and governments.

Although, several studies have demonstrated that a higher level of cardiorespiratory fitness (CRF) was associated with lower cancer mortality, the association between estimated CRF (eCRF), estimated from the non-exercise algorithms, and cancer incidence remains unclear.



## Purpose

**To investigate the association between**


## Study population

This prospective cohort study included 46 968 cancer-free adults who participated in the second survey of Trøndelag Health Study (HUNT2) in Norway (1995–97). The participants were followed up for a median of 22.1 years.

HUNT

## Results

An inverse dose-response association was found between eCRF and the incidence of cancer overall in the whole population, in men and women high eCRF level group.

**19% and 9%**

The risk reductions of cancer overall associated with the high eCRF level were 19% in men and 9% in women.

No association was observed between eCRF and breast cancer incidence.

High eCRF level seemed to be inversely associated with the incidence of prostate cancer.

## Methods

Two non-exercise algorithms were used to estimate CRF and then classified into tertiles.

Cox regression models were used in our study. 12 potential confounders were adjusted. Crude and adjusted hazard ratios (HRs) and 95% confidence intervals (CI) were presented.

## Conclusion

These findings suggested eCRF may be a practical and cost-effective means in studying the association between CRF and cancer incidence.

## Strengths & limitations

**T**his is the first prospective cohort study to investigate the associations between eCRF and incidence of cancer overall, breast and prostate cancer with long follow-up duration. A variety of potential confounders were adjusted, which strengthened the validity of the results.

Participants' information was only collected at baseline, we were unable to evaluate how changes in eCRF level over time would affect the cancer incidence.

## ABSTRACT

### Introduction

The total number of people diagnosed with cancer was almost doubled in the past two decades with breast cancer occupied the world's most commonly diagnosed cancer and prostate cancer reached fourth place of cancer in 2020. The cancer burden has exerted immense stress on individuals, families, communities, and governments. Although several studies have demonstrated that a higher level of cardiorespiratory fitness (CRF) was associated with lower cancer mortality, the association between CRF and cancer incidence remains unclear. We therefore, aimed to investigate the associations between estimated CRF (eCRF), estimated from the non-exercise algorithms, and incidence of cancer overall as well as breast and prostate cancer in a prospective cohort of the Norwegian population.

### Methods

This prospective cohort study included 46 968 cancer-free adults who participated in the second survey of the Trøndelag Health Study (HUNT2) in Norway (1995–97). Anthropometric measurements, lifestyle factors, and sociodemographic data were collected at baseline. Cancer ascertainment information was derived from the Cancer Registry of Norway. Two sex-specific non-exercise algorithms were used to estimate CRF and then classified into sex and age-specific tertiles within each 10 years' age interval. Cox proportional hazards models were used to evaluate the possible associations between eCRF and cancer overall, as well as with breast cancer, and prostate cancer. Crude and adjusted hazard ratios (HRs) and 95% confidence intervals (CI) were presented. The possible effect modification by sex was evaluated by the likelihood ratio test (LRT).

### Results

Over a median of 22.1 years follow-up, there was an inverse dose-response association between eCRF and the incidence of cancer overall in the whole population and men. In women, only the high eCRF level was inversely associated with the incidence of cancer overall. The risk reductions of cancer overall associated with the high eCRF level were 19% in men and 9% in women. Per 4 METs increase in eCRF was not associated with the incidence of cancer overall in women, whereas there was a 6% risk reduction for the

incidence of cancer overall in men. However, LRT did not show clear evidence for an effect modification by sex. No association was observed between eCRF and breast cancer incidence. Nevertheless, high eCRF level seemed to be inversely associated with the incidence of prostate cancer.

**Conclusion**

The eCRF had an inverse dose-response association with the cancer overall incidence in the whole population. No significant association was found between eCRF and incidence of breast cancer. Only the high level of eCRF appeared to be associated with a lower prostate cancer incidence. These findings suggested eCRF may be a practical and cost-effective means in studying the association between CRF and cancer incidence.

**Keywords:** cancer, breast cancer, prostate cancer, physical activity, cardiorespiratory fitness, estimated cardiorespiratory fitness, prospective cohort, HUNT study

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## ABBREVIATION

| | |
|---|---|
| ACSM | American College of Sports Medicine |
| ANOVA | analysis of variance |
| BMI | body mass index |
| CVD | cardiovascular disease |
| CI | confidence interval |
| CRF | cardiorespiratory fitness |
| DAG | directed acyclic graph |
| eCRF | estimated cardiorespiratory fitness |
| GCO | Global Cancer Observatory |
| HR | hazard ratio |
| HRT | hormone replacement treatment |
| HUNT | Nord-Trøndelag Health Study |
| ICD-10 | International Classification of Diseases Tenth Revision |
| LRT | likelihood ratio test |
| MET | metabolic equivalent |
| NIPH | Norwegian Institution of Public Health |
| PA | physical activity |
| pyr | pack-years |
| REK | Regional Committee for Medical Research Ethics |
| rHR | resting heart rate |
| WC | waist circumference |
| WHO | World Health Organization |

# Introduction

## 1.1 Global prevalence and burden of cancer

Cancer is a very large group of diseases, it can start in almost any organ or tissue of the body with abnormal cells growing uncontrollably, go beyond their usual boundaries to invade adjoining parts of the body, and/or spread to other organs.[1] According to the Global Cancer Observatory (GCO) report, the total number of people diagnosed with cancer was almost doubled in the past two decades. The global cancer new cases have risen to 19.3 million in 2020 and are predicted to reach 30.2 million in 2040. The mortality of cancer reached 9.9 million deaths in 2020 and will reach 16.3 million deaths in 2040 worldwide. Besides, breast cancer has become the world's most commonly diagnosed cancer with nearly 2.3 million new cases and prostate cancer has reached fourth place of cancer with 1.4 million cases in 2020.[2]

As one in 5 people will have cancer diagnosed during their lifetime and one in 6 people will die because of cancer[1], the cancer burden has been increasing over time globally which exerts immense stress on individuals, families, communities, and governments. In Europe in 2018, the financial strain in cancer health care was about €103 billion.[3] Despite the economic burden, cancer patients also face a variety of physical, psychological, or physiological problems, such as function loss, depression, anxiety, and pain. 5% to 99% of patients have reported some form of cancer-related disabilities in terms of the type and timing of cancer.[4]

In Norway, according to the report from the Norwegian Institution of Public Health (NIPH),[5] cancer is one of the main causes of death among the Norwegian population. 34 979 new cancer cases were reported in 2019, among which 18 706 were diagnosed in men, and 16 273 in women. Prostate cancer and breast cancer were the most frequent cancers in males and females respectively in the past 5 years. With the increasing cases of cancer in Norway, a considerable economic expenditure on cancer health care reached €1575 million in 2018.[4]

## 1.2 Lifestyle risk factors for cancer

There are diverse risk factors that could cause cancer, and more than half of the cancer incidence today is preventable.[6] The cancer occurrence can be prevented by modifying or avoiding the lifestyle risk factors and complying with evidence-based healthy behaviors. To date, a variety of lifestyle factors have been recognized as risk factors for cancer overall, such as obesity, smoking, alcohol consumption, sedentary behavior, and family history of cancer, etc.[6]

Among the lifestyle risk factors for cancer, there has been a growing amount of evidence showing that a higher level of physical activity (PA) is associated with a reduced risk of several cancers. For example, a pooled study of 1.44 million participants reported that increasing levels of PA were associated with lower risks of 13 types of cancer after a median of 11 years follow-up,[7] including esophageal adenocarcinoma, lung cancer, and breast cancer, etc. after adjustment for age, gender, smoking status, alcohol consumption, education, and race/ethnicity. However, the associations between PA and some site-specific cancers remain unclear, especially for prostate cancer.[7]

In addition to the common risk factors mentioned above, hormone replacement treatment (HRT) and marital status have been demonstrated as risk factors for breast cancer and prostate cancer respectively.[8,9] A study including more than 1 million UK women reported a relative risk of 1.66 for breast cancer incidence among current HRT users compared with the never users.[8] Another study showed that unmarried men had a higher prostate cancer-specific mortality compared with married men of similar age, race, tumor stage, and grade among 115 922 prostate cancer patients who were followed up from 1988 to 2003.[9]

## 1.3 Cardiorespiratory fitness (CRF)

Cardiorespiratory fitness (CRF) is an expression of maximal oxygen uptake.[10] It reflects the ability to transport oxygen from the atmosphere to the body cells during PA. As oxygen delivery in the body involves numerous organs, CRF also represents the integral work capacity between body systems, such as gas exchange function of the respiratory system,

blood circulation of the cardiovascular system, and metabolic function of the muscular system.[10] In other words, CRF is a reflection of the general health status of the body.

Although more than half of the CRF is determined by genetics, lifestyle factors, and personal parameters such as age and sex, habitual PA remains the primary way of improving fitness.[11] Thus, CRF is considered as an objective surrogate of PA in many studies because it is less prone to misclassification and more consistent from time to time than self-reported PA.

In addition, numerous studies have addressed that CRF is an independent risk factor for many chronic diseases, especially for cardiovascular disease (CVD).[10-13] For example, a prospective cohort study indicated that there was an inverse association between CRF and CVD events after an average 10-year follow-up among 20 728 men and 5909 women.[12] Men with moderate and high CRF tertile groups had an 18% and 39% lower CVD risk than men with low CRF, while women with moderate and high CRF had a 26% and 37% lower risk of CVD events than women with low CRF after adjustment for age, examination year, smoking, alcohol intake, exercise ECG responses, and family history of CVD.

Furthermore, in the recent decade, CRF has been recognized as a more powerful predictor than traditional risk factors to predict health outcomes.[10] Many studies have suggested that CRF in combination with traditional risk factors can significantly improve the risk classification for adverse CVD outcomes.[10,12,13] For instance, the Cooper Center Longitudinal Study used two Cox regression models to estimate the risk of CVD death among 66 371 asymptomatic subjects.[13] One model only included traditional risk factors (age, sex, systolic blood pressure, diabetes mellitus, total cholesterol, and smoking), and the other model included both CRF and traditional risk factors. After a median of 16 years follow-up, they found that the model with the addition of CRF to the traditional risk factors resulted in a net reclassification improvement of 0.121 and 0.041 at 10 years and 25 years, respectively.

Although the underlining mechanisms for the inverse association between CRF and CVD risk are not well understood, higher CRF is reported to be associated with lower blood pressure, improved insulin sensitivity and glucose intolerance, lower levels of inflammation, favorable lipid concentration, and integrated function of oxidative pathways in the mitochondria.[10,14]

### 1.4 CRF in relation to cancer

Since cancer and CVD share similar risk factors, such as smoking habits, high cholesterol, and physical inactivity, it is reasonable to assume that there may be a relationship between cancer and CRF.

To our knowledge, several studies have demonstrated that a higher level of CRF was associated with lower cancer mortality,[15-18] whereas the evidence is limited with respect to the relationship between cancer incidence and CRF. Among the limited existing literature on CRF and overall cancer incidence, most studies were conducted among men or in a specific group (veterans) and the sample size was usually small.[16,19-22] There was only one study that investigated the relationship between CRF and cancer incidence in 184 women participants.[15] Besides, it is worth noting that only participants who could perform the CRF measurement test were included in the above studies,[15-22] which may cause selection bias to some extent.

Regarding the relationships of CRF with site-specific cancer incidences, the studies remain sparse and the findings are inconsistent between studies. For example, only one study was conducted to investigate the relationship between CRF and breast cancer mortality, which showed that higher CRF was associated with reduced breast cancer mortality.[23] For the incidence of prostate cancer, one meta-analysis claimed no association with CRF,[24] while a prospective study suggested a protective role of CRF,[25] and another study showed a positive association.[26]

### 1.5 Estimated cardiorespiratory fitness (eCRF)

The gold standard measurement of CRF is laboratory exercise test by analyzing the ventilatory gas exchange during maximal effort exercise on a treadmill or a bicycle ergometer.[10] An accurate CRF test requires subjects to exert both maximal physical and mental effort, which is not applicable to everyone, such as the elderly, people with mental disorders, or exercise vulnerable patients. Moreover, the CRF test is time-consuming and costly, and it requires specialized equipment and trained workers. This makes it impractical to measure CRF in large populations. Thus, the non-exercise algorithms have been developed to

calculate the estimated CRF (eCRF) based on health indicators that can be easily obtained.

In recent years, several non-exercise eCRF algorithms have been generated to estimate CRF from different studies.[27,28] The variables often included in the algorithms are age, waist circumference (WC), resting heart rate (rHR), and PA, which can be easily measured at the clinical examination or obtained through questionnaires. However, it is noteworthy that most of the eCRF algorithms were derived from the population or race-based sub-samples. Thus, caution is needed when it is generalized to the whole population. In addition, to avoid the heterogeneity that may exist between the algorithms, the best way is to apply an eCRF algorithm that was derived from the same population.[29] As an example, a study showed that the eCRF was a useful predictor for stroke incidence among the whites but not among the blacks using the same eCRF algorithm generated from predominant whites.[30]

### 1.6 eCRF in relation to other diseases and cancer

Several large population-based cohort studies have demonstrated an inverse association of eCRF with risk of depression, all-cause mortality, and CVD mortality.[29-32] For instance, the NHANES III (1988-1994) study,[32] is a national study conducted on the US population. They used a non-exercise approach to estimate the association between eCRF and all-cause and CVD mortality among 12 834 subjects. After a median of 19.2 follow-up years, they found both the middle and upper eCRF tertile groups were associated with at least 20% lower all-cause mortality and 16% lower CVD mortality compared with the lower eCRF tertile group after adjustment for many other risk factors.

To date, two studies have reported an association between eCRF and overall cancer mortality,[33,34] but they were only conducted among the US population. One of these studies found higher eCRF was independently associated with lower cancer mortality in both men and women,[33] while the other one only showed an inverse association in women.[34] To the best of our knowledge, no studies have investigated the eCRF in relation to the incidence of cancer overall, breast or prostate cancer. A few studies have used eCRF as an approach to investigate eCRF and various health outcomes in the Norwegian population,[29,31,35,36] such as with all cause and CVD mortality, depression, and atrial fibrillation, but none of them have

evaluated the association between eCRF and cancer incidence.

Thus, the aim of this study was to investigate the associations between eCRF, estimated from the non-exercise algorithms, and incidence of cancer overall as well as of breast and prostate cancer in a prospective cohort of the Norwegian population. The applied eCRF algorithm was derived from the same Norwegian population.

## 2. Methods

### 2.1 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 150 000 Norwegian participants aged over 19 years old in four different surveys: HUNT1 (1984-1986), HUNT2 (1995-1997) and HUNT3 (2006-2008), and HUNT4 (2017-19).[37] HUNT data were collected with clinical measures, questionnaires, interviews, and biological samples. The clinical measures included height, weight, WC, rHR), etc. The questionnaire provided information about PA, smoking habits, education, etc. Participants may be followed up by linking the HUNT surveys and national health registers or other registers that cover the total population in Norway.[37]

In our study, we included all participants who joined in HUNT2 (n=65 226) at baseline from 1995-1997. Participants with incomplete data (missing information of WC, rHR, or PA) were excluded from this study because these variables were necessary for the estimation of CRF. We further excluded participants who were diagnosed with cancer before the participation date in HUNT2 as we aimed to study the first incidence of cancer during the follow-up. The analysis dataset included a total of 46 968 participants (23 375 men and 23 593 women). The flow chart (Figure 1) below shows detailed information about how the analysis dataset was derived.

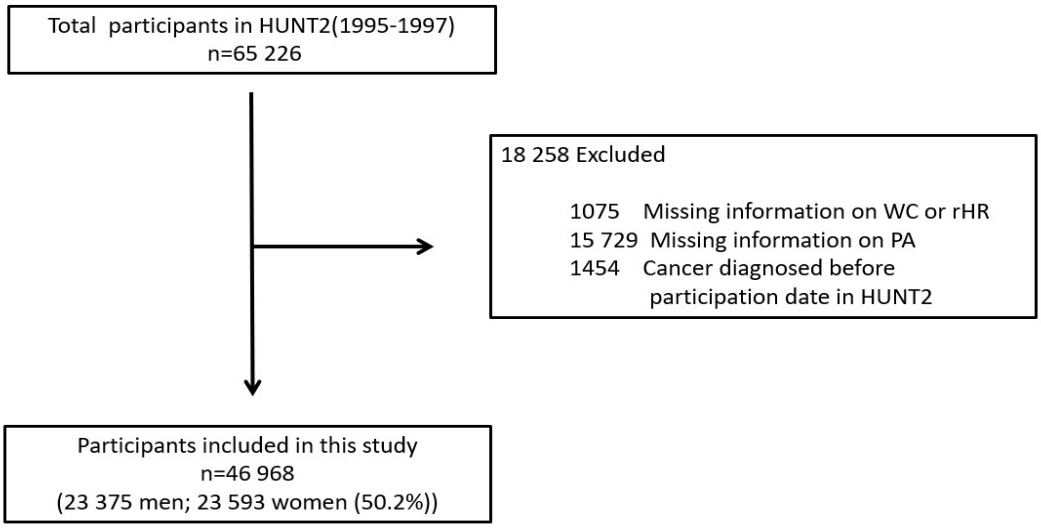


**Figure 1.** The selection process of participants in Trøndelag Health Study 2 (HUNT2). Participants with complete data on WC, rHR, or PA, with no history of diagnosed cancer before participation data of HUNT2 were included for analysis.

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

Two non-exercise sex-specific algorithms were used in this study to estimate CRF.[29] These algorithms were derived from the HUNT study and showed high comparability with other studies.[27,38] The algorithms for predicting eCRF in peak oxygen consumption (ml/kg/min) were as follows:

For women ($R^2$=0.52, standard error of estimate=5.37):

78.00-(0.297·Age)-(0.270·WC)-(0.110·rHR)+(2.674·PA)

For men ($R^2$=0.58, standard error of estimate=5.88):

105.91-(0.334·Age)-(0.402·WC)-(0.144·rHR)+(3.102·PA)

WC and rHR were measured at clinical examinations.[37] WC was measured horizontally at the height of the umbilicus to the nearest 1.0 cm when the participant standing with the arms hanging relaxed. Dinamap 845XT (Critikon Inc) was used to measure rHR by trained nurses or technicians after the participant had been seated for two minutes, the mean of rHR of three measurements was recorded.

The information on PA and age were retrieved from self-administered questionnaires. We classified PA into two categories according to the response to the PA questions (frequency, duration, and intensity). PA=1 if the participant met the American College of Sports Medicine (ACSM) recommendation[39] : moderate-intensity cardiorespiratory exercise training for ≥30 minutes (min) a day on ≥5 days a week for a total of ≥150 min a week or vigorous-intensity cardiorespiratory exercise training for ≥20 min a day on ≥3 days a week for a total of ≥75 min a week, PA=0 if not.

eCRF was treated as a continuous and a categorical variable in our study. As a continuous variable, eCRF was converted to metabolic equivalent (MET) by using eCRF divided by 3.5 ml/kg/min. In our study, per 4 METs was used to estimate the potential effect of eCRF since many daily life activities equal a value of 4 METs, such as a brisk walk (3-4 miles/h),[40] climbing stairs, gardening, or bicycling (<10 miles/h).[41] As a categorical variable, the eCRF was classified into sex and age-specific tertiles (as low, medium, and high levels) within each 10 years of age interval.

### 2.3 Cancer incidence as the outcome variable

The HUNT population data was linked to the data from The Cancer Registry of Norway. The unique 11-digit Norwegian personal identification number was used for the linkage that allowed accurate matching of outcomes. The participants were followed up from the baseline participation date in HUNT2 until the following circumstances happened whichever came first: 1) the first diagnosis of any cancer/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 code for the types of cancer in the Cancer Registry. In this study, we focused on the incidence of cancer overall as well as breast and prostate cancer specifically.

## 2.4 Covariates

Age, sex, body mass index (BMI), PA level, sitting hours/day, smoking status, alcohol consumption, education, economic difficulties, severe disease, and family history of cancer were identified as potential confounders in the association between the exposure (eCRF) and outcome variable such as cancer overall. A directed acyclic graph (DAG) presents an explicit illustration of the possible confounding situation in the relationship between eCRF and the incidence of cancer overall (Figure 2).

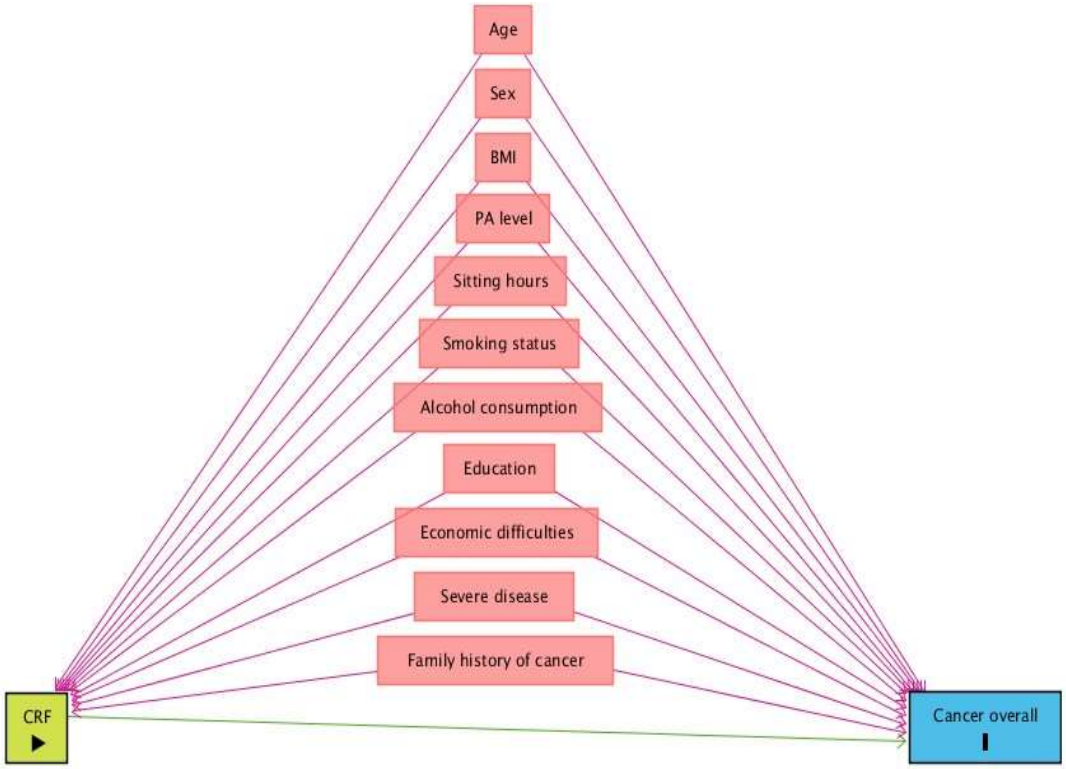


**Figure 2.** Directed acyclic graph (DAG) described possible confounding in the association between eCRF and incidence of cancer overall.

Information of the mentioned covariates was obtained from the clinical examination or self-administered questionnaires. Height and weight were measured with participants wearing light clothes without shoes. BMI was calculated as body weight divided by height squared (kg/m²) and 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) according to the WHO nutritional status.[42]

The classification of PA level (inactive, low, moderate, and high) was based on the previous HUNT studies.[43,44] Participants were asked about "Average of hours of light or hard physical activity per week in the last year?" with 4 options such as "none, ≤ 1 hour, 1-2 hours, ≥3 hours" in the HUNT2 survey. Light activity referred to no sweating or not out of breath, hard physical activity referred to sweating or out of breath. A moderate or high level of PA was assumed to be comparable to the ACSM PA recommendation. Sitting hours/day was categorized as ≤4, 5-7, and ≥8. Smoking status (pack-years) was classified as never smoked, former smoker <10 pack-years (pyr), former smoker 10-20, former smoker >20, current smoker <10, current smoker 10-20, and current smoker >20 pyr. Alcohol consumption was categorized as never, 1-4 times/month, and ≥ 5 times/month.

The categorizations of educational years in our study were <10, 10–12, and ≥13. Economic difficulties was defined as yes or no by asking participants "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 into yes/no categories: yes, if participants experienced either myocardial infarction (heart attack), angina pectoris (chest pain), stroke/brain hemorrhage, diabetes, or cancer before; no, if participants had never experienced these diseases. Family history of cancer was classified as yes/no by using the following question "Do the relatives (mother, father, brother, sister, child) that have or have had cancer?".

To study breast cancer as the outcome in females, we added HRT as an additional confounder according to a previous study[7]. The HRT (not for birth control) question was asked "Have you taken estrogen in any form?" and it was classified as never and ever use. To study prostate cancer as the outcome in males, marital status was added as an additional covariate since research had demonstrated a relationship of marital status with prostate cancer risk[8]. Marital status was categorized as single, widow/divorced/separated, and married/registered partner. A separate "unknown" category was defined for the missing information in the variables of BMI, PA level, sitting hours/day, smoking status, alcohol consumption, education, economic difficulties, severe disease, HRT, and marital status. The "unknown" categories were included in the analysis. The categorizations of covariates in the present study were commonly used in the previous HUNT publications.[43,44]

## 2.5 Statistical analysis

Baseline characteristics of participants were presented by the sex and age-specific tertiles of eCRF (as low, medium, and high levels). They were presented as mean ± SD for continuous variables and as percentages (%) for categorical variables. Comparisons of the baseline characteristics among the eCRF tertile groups were performed using one-way variance (ANOVA) for continuous variables and the Pearson Chi-square test for categorical variables.

Cox proportional hazards models were used to evaluate the possible associations between eCRF and cancer overall, as well as with breast cancer, and prostate cancer respectively. Crude and adjusted hazard ratios (HRs) and 95% confidence intervals (CI) were presented. Age was used as the time scale in the Cox models, with entry and exit time defined as the participation age in HUNT2 and age at any cancer diagnosis for the first time or censoring, respectively. Potential confounding factors included in the adjusted Cox models for cancer overall were sex, BMI, PA level, sitting hours/day, smoking status, alcohol consumption, education, economic difficulties, severe disease, and family history of cancer for cancer overall. For breast cancer in women, HRT was additionally taken into the adjusted Cox model. For prostate cancer in men, marital status was additionally adjusted.

Global test with Lowess curves was used to test the proportional hazards assumption for both the exposure variable and all the potential confounding factors. The *tvc* function in STATA was added in the Cox model if a covariate did not satisfy the proportional hazards assumption. The possible effect modification by sex regarding the association between eCRF and incidence of cancer overall was evaluated by the likelihood ratio test (LRT). To reduce the possibility of reverse causality due to existing but undiagnosed cancer at the early years of follow-up, sensitivity analyses were performed; We excluded the first three years of follow-up to assess the associations between eCRF and incidence of cancer overall, breast and prostate cancer. All statistical analyses are performed with STATA, release 16 (StataCorp LP, College Station, Texas).

## 2.6 Research ethics

Participation in the HUNT study was voluntary for every participant and written informed consent was obtained from all participants prior to the HUNT study. The data had already been collected at the HUNT Research Center. All names and personal ID numbers were removed when we received the data from the HUNT Research Center. Therefore, all information was de-identified. No person was contacted for the gathering of new data for the current master project. This master project was conducted as a sub-study under the approval of the Regional Committees for Medical Research Ethics – REK (2019/337 REK sør-østA).

## 3 Results

### 3.1 Baseline characteristics of the study population

In total, 46 968 participants were included in this study who were followed up for a median of 22.1 years. The study consisted of 49.8% men and 50.2% women, with a similar distribution of sex among the eCRF tertile groups (Table 1). Participants with low eCRF level had a higher prevalence for most of the potential risk factors for cancer at baseline compared with the other two eCRF tertile groups. For example, participants with low eCRF were more likely to be obese (39.1% vs 8.0% vs 1.2% in women; 34.1% vs 6.6% vs 0.9% in men), physically inactive (52.2% vs 33.0% vs 11.1% in women; 43.0% vs 23.2% vs 7.8% in men), former or current smokers (49.8% vs 48.4% vs 44.8% in women; 56.1% vs 53.7% vs 46.7% in men), less educated (27.3% vs 35.4% vs 43.4% in women; 25.4% vs 30.5% vs 35.8% in men) and to have more economic difficulties (29.6% vs 24.5% vs 21.5% in women; 23.4% vs 21.2% vs 19.3% in men) when compared with the participants with medium and high eCRF levels. However, there seemed no major difference regarding the sitting hours, severe disease, or family history of cancer among the eCRF tertiles groups (Table 1). The distribution of HRT or marital status was similar in these three eCRF tertile groups in women and men, respectively.

**Table 1. Baseline characteristics of 46 968 participants from the HUNT2 Study, stratified by sex and by eCRF in tertiles**

| | Women (n=23 593) | | | | Men (n=23 275) | | | |
|---|---|---|---|---|---|---|---|---|
| | **Low eCRF level** | **Medium eCRF level** | **High eCRF level** | p-value | **Low eCRF level** | **Medium eCRF level** | **High eCRF level** | p-value |
| **N** | 7866 | 7864 | 7863 | | 7793 | 7793 | 7789 | |
| **Age (y) at baseline** | 47.4 (16.7) | 46.5 (16.4) | 45.2 (16.2) | <0.001 | 48.2 (16.2) | 47.3 (15.9) | 46.3 (15.9) | <0.001 |
| **WC (cm)** | 90.2 (10.9) | 78.7 (7.4) | 72.2 (6.1) | <0.001 | 99.5 (8.5) | 90.7 (5.8) | 84.2 (5.9) | <0.001 |
| **rHR (bpm)** | 79.8 (13.2) | 74.2 (10.9) | 68.3 (9.7) | <0.001 | 77.1 (12.9) | 69.5 (10.5) | 62.9 (9.6) | <0.001 |
| **eCRF(ml/kg/min)** | 31.5 (6.7) | 36.2 (6.1) | 39.8 (5.8) | <0.001 | 39.7 (7.3) | 45.5 (6.5) | 50.2 (6.5) | <0.001 |
| **CRF(METs)** | 9.0 (1.9) | 10.3 (1.7) | 11.4 (1.7) | <0.001 | 11.3 (2.1) | 13.0 (1.9) | 14.3 (1.9) | <0.001 |
| **BMI** | | | | <0.001 | | | | <0.001 |
| 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** | 2114 (26.9%) | 4046 (51.5%) | 6584 (83.7%) | <0.001 | 2435 (31.3%) | 4635 (59.5%) | 6642 (85.3%) | <0.001 |
| **PA level** | | | | <0.001 | | | | <0.001 |
| 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 (per 24 hours)** | | | | <0.001 | | | | <0.001 |
| ≤ 4 hours | 1978 (25.2%) | 2111 (26.8%) | 2091 (26.6%) | | 1440 (18.5%) | 1747 (22.4%) | 1862 (23.9%) | |
| 5-7 hours | 2068 (26.3%) | 2031 (25.8%) | 2089 (26.6%) | | 1819 (23.3%) | 1873 (24.0%) | 1954 (25.1%) | |
| ≥8 hours | 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)** | | | | <0.001 | | | | <0.001 |
| 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** | | | | <0.001 | | | | <0.001 |
| 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)** | | | | <0.001 | | | | <0.001 |
| < 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** | | | | <0.001 | | | | <0.001 |
| 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** | | | | <0.001 | | | | <0.001 |
| 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%) | | 921 (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** | | | | 0.06 | | | | 0.09 |
| 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%) | |
| **Hormone replacement treatment** | | | | <0.001 | | | | |
| Never | 4988 (63.4%) | 5012 (63.7%) | 5088 (64.7%) | | | | | |
| Ever | 1112 (14.1%) | 1227 (15.6%) | 1276 (16.2%) | | | | | |
| Unknown | 1766 (22.5%) | 1625 (20.7%) | 1499 (29.1%) | | | | | |
| **Marital status** | | | | <0.001 | | | | <0.001 |
| 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%) | |

BMI, body mass index; bpm, beats per minute; eCRF, estimated cardiorespiratory fitness; PA, physical activity; rHR, resting heart rate; WC, waist circumference.
Data presented as mean (standard deviation) for continuous variables or number of participants (%) for categorical variables.
p-values reported using ANOVA for continuous covariates and Pearson Chi-square tests for categorical covariates.

### 3.2 eCRF and cancer overall incidence

7752 participants were diagnosed with any type of cancer during a median of 22.1 years follow-up of the 46 968 participants. Among them, 3387 were women (43.7%) and 4365 were men (56.3%).

The global test and Lowess curves revealed that only sex (p<0.001) did not satisfy the proportional hazards assumption in the adjusted Cox model for the incidence of cancer overall (Figure 3). The Schoenfeld residuals for sex deviated from the y=0 line after the 60 years old. Thus, the *tvc* function in STATA was applied for sex in the adjusted Cox model.


**Figure 3.** Schoenfeld residuals for sex in the adjusted Cox model for the incidence of cancer overall, using eCRF as the exposure variable.

Hazard ratios for cancer overall incidence by tertiles of eCRF and per 4 METs increase in eCRF are presented in Table 2. Among all the participants, the group with the medium eCRF level had a HR of 0.96 (95% CI 0.90-1.01), and the group with the high eCRF level had a HR of 0.85 (95% CI 0.79-0.91), p for trend <0.001. Among women, only the high eCRF level appeared to be inversely associated with the incidence of cancer overall (p for trend =0.087). Among men, both the medium and high eCRF levels were inversely associated with the incidence of cancer overall (P for trend <0.001). The risk reductions of cancer overall associated with the high eCRF level were 19% (HR 0.81, 95% CI 0.74-0.89) in men and 9%

in women (HR 0.91, 95% CI 0.81-1.02). However, the LRT test showed that there was no obvious effect modification by sex for cancer overall incidence (p=0.086).

Per 4 METs increase in eCRF did not seem to be associated with the incidence of cancer overall in all the population or in women (Table 2), whereas there appeared to be a reduced HR (0.94, 95% CI 0.84-1.05) for the incidence of cancer overall in men although the 95% CI was wide. In the sensitivity analysis after excluding the first 3 years' follow-up, the estimates of the association of eCRF with cancer overall incidence in all the population and in women and men respectively were similar to the original results (Supplementary Table 1).

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

| eCRF | Cases | IR (per 1000 person-years) | Crude HR[a] | 95% CI | Adjusted HR[b] | 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 for trend | | | <0.001 | | <0.001 | |
| Per 4 METs | | | 0.94[c] | 0.88-1.00 | 0.99 | 0.97-1.01 |
| 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 for trend | | | 0.018 | | 0.087 | |
| Per 4 METs | | | 0.96 | 0.86-1.07 | 1.00 | 0.86-1.18 |
| 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 for trend | | | <0.001 | | <0.001 | |
| Per 4 METs | | | 0.93 | 0.86-1.01 | 0.94 | 0.84-1.05 |

CI, Confidence interval; HR, Hazard ratio; IR, Incidence rate.

[a] Age was used as the time scale.

[b] Age was used as the time scale and adjusted for sex, BMI, PA level, sitting hours, smoking (pack-years), alcohol consumption, education, economic difficulties, severe disease, family history of cancer.

[C] Age was used as the time scale and adjusted for sex.

Per 4 METs=(eCRF/3.5)/4.

### 3.3 eCRF in relation to breast and prostate cancer incidence

Table 3 presents the association of eCRF with the incidence of breast cancer and prostate cancer, respectively. No association was observed between eCRF and breast cancer incidence. Nevertheless, high eCRF level only seemed to be associated with a reduced HR for the incidence of prostate cancer (prostate cancer: HR 0.85, 95% CI 0.71-1.02). Per 4 METs increase in eCRF was not associated with the incidence of breast cancer or prostate cancer (Table 3). After exclusion of the first 3 years of follow-up in the sensitivity analysis (Supplementary Table 2), the associations between eCRF and breast, prostate cancer incidence were not altered.

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

| eCRF | Cases | IR (per 1000 person-years) | Crude HR[a] | 95% CI | Adjusted HR[b] | 95% CI |
|---|---|---|---|---|---|---|
| Breast cancer | | | | | | |
| Low | 265 | 1.74 | 1.00 | Reference | 1.00 | Reference |
| Medium | 320 | 2.06 | 1.20 | 1.02-1.42 | 1.16 | 0.96-1.40 |
| High | 273 | 1.72 | 1.03 | 0.87-1.22 | 0.95 | 0.76-1.19 |
| Per 4 METs | | | 1.20 | 0.97-1.49 | 1.03 | 0.75-1.42 |
| 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 | 0.71-1.02 |
| Per 4 METs | | | 1.19 | 1.03-1.36 | 1.05 | 0.86-1.28 |

CI, Confidence interval; HR, Hazard ratio; IR, Incidence rate.

[a] Age was used as the time scale.

[b] Age was used as the time scale and adjusted for sex, BMI, PA level, sitting hours, smoking (pack-years), alcohol consumption, education, economic difficulties, severe disease, family history of cancer.

Hormone replacement treatment was additionally adjusted in the model for breast cancer.

Marital status was additionally adjusted in the model for prostate cancer.

Per 4 METs=(eCRF/3.5)/4.

**Supplementary table 1. The association between eCRF and incidence of cancer overall in the HUNT study after excluding the first 3 years of follow-up**

| eCRF | Cases | IR (per 1000 person-years) | Crude HR[a] | 95% CI | Adjusted HR[b] | 95% CI |
|---|---|---|---|---|---|---|
| All (n=45 674) | | | | | | |
| Low | 2408 | 9.65 | 1.00 | Reference | 1.00 | Reference |
| Medium | 2386 | 9.29 | 0.96 | 0.91-1.01 | 0.96 | 0.90-1.03 |
| High | 2228 | 8.45 | 0.88 | 0.83-0.93 | 0.86 | 0.80-0.93 |
| p for trend | | | <0.001 | | <0.001 | |
| Per 4 METs | | | 0.90[c] | 0.84-0.97 | 0.93 | 0.84-1.02 |
| Women (n=23 065) | | | | | | |
| Low | 1045 | 8.11 | 1.00 | Reference | 1.00 | Reference |
| Medium | 1040 | 7.88 | 0.97 | 0.89-1.06 | 1.00 | 0.90-1.10 |
| High | 990 | 7.33 | 0.92 | 0.84-1.00 | 0.94 | 0.83-1.06 |
| p for trend | | | 0.064 | | 0.278 | |
| Per 4 METs | | | 0.92 | 0.82-1.03 | 0.97 | 0.82-1.15 |
| Men (n=22 609) | | | | | | |
| Low | 1363 | 11.29 | 1.00 | Reference | 1.00 | Reference |
| Medium | 1346 | 10.78 | 0.95 | 0.88-1.02 | 0.94 | 0.86-1.02 |
| High | 1238 | 9.63 | 0.84 | 0.78-0.91 | 0.81 | 0.73-0.89 |
| p for trend | | | <0.001 | | <0.001 | |
| Per 4 METs | | | 0.89 | 0.82-0.97 | 0.90 | 0.80-1.02 |

CI, Confidence interval; HR, Hazard ratio; IR, Incidence rate.

[a] Age was used as the time scale.

[b] Age was used as the time scale and adjusted for sex, BMI, PA level, sitting hours, smoking (pack-years), alcohol consumption, education, economic difficulties, severe disease, family history of cancer.

[C] Age was used as the time scale and adjusted for sex.

Per 4 METs=(eCRF/3.5)/4.

**Supplementary table 2. The associations between eCRF and incidence of breast cancer in women as well as prostate cancer in men in the HUNT study after excluding the first three years of follow-up**

| eCRF | Cases | IR (per 1000 person-years) | Crude HR[a] | 95% CI | Adjusted HR[b] | 95% CI |
|---|---|---|---|---|---|---|
| Breast cancer | | | | | | |
| Low | 236 | 1.83 | 1.00 | Reference | 1.00 | Reference |
| Medium | 289 | 2.19 | 1.21 | 1.02-1.44 | 1.18 | 0.97-1.43 |
| High | 252 | 1.87 | 1.06 | 0.89-1.27 | 0.99 | 0.78-1.26 |
| Per 4 METs | | | 1.17 | 0.93-1.48 | 1.00 | 0.71-1.43 |
| Prostate cancer | | | | | | |
| Low | 382 | 3.16 | 1.00 | Reference | 1.00 | Reference |
| Medium | 444 | 3.56 | 1.12 | 0.98-1.29 | 1.02 | 0.88-1.18 |
| High | 425 | 3.31 | 1.04 | 0.91-1.20 | 0.87 | 0.72-1.04 |
| Per 4 METs | | | 1.15 | 0.99-1.34 | 1.03 | 0.83-1.27 |

CI, Confidence interval; HR, Hazard ratio; IR, Incidence rate.

[a] Age was used as the time scale.

[b] Age was used as the time scale and adjusted for sex, BMI, PA level, sitting hours, smoking (pack-years), alcohol consumption, education, economic difficulties, severe disease, family history of cancer.

Hormone replacement treatment was additionally adjusted in the model for breast cancer.

Marital status was additionally adjusted in the model for prostate cancer.

Per 4 METs=(eCRF/3.5)/4.

**Supplementary table 3. Comparison of key baseline characteristics between the participants who were included in the study and those who were excluded among the HUNT2 population**

| Variables | HUNT2 participants included | HUNT2 participants excluded |
|---|---|---|
| Number of subjects | 46 968 | 18 258 |
| Age (years), mean (SD) | 46.8 (16.2) | 58.7 (16.8) |
| BMI | 26.1 (4.0) | 26.9 (4.3) |
| Sex | | |
| Female | 23 593 (50.2%) | 11 063 (60.6%) |
| Male | 23 375 (49.8%) | 7095 (39.4%) |
| Sitting hours (per 24 hours) ≥8 | 23 905 (50.9%) | 9816 (53.8%) |
| Ever smoker | 25 916 (55.2%) | 10 130 (55.5%) |
| Alcohol consumption ≥1 (times/month) | 29 515 (62.9%) | 6988 (38.3%) |
| Education <10 (years) | 14 089 (30.0%) | 8596 (47.1%) |
| Having economic difficulties | 10 923 (23.3%) | 2852 (15.6%) |
| Having severe disease ever | 4103 (8.7%) | 4584 (25.1%) |
| Having family history of cancer | 11 510 (24.5%) | 5230 (28.6%) |

BMI, body mass index

Data presented as mean (standard deviation) for continuous variables or number of participants (%) for categorical variables.

# 4 Discussion

## 4.1 Main findings

Our present study found that there was an inverse dose-response association between eCRF and the incidence of cancer overall in the whole population and in men. In women, only the high eCRF level was inversely associated with the incidence of cancer overall. The risk reductions of cancer overall associated with the high eCRF level were 19% in men and 9% in women. Per 4 METs increase in eCRF was not associated with the incidence of cancer overall in women, whereas there was a 6% risk reduction for the incidence of cancer overall in men. But there was no clear evidence showing an effect modification by sex. No association was observed between eCRF and breast cancer incidence, nevertheless, high eCRF level seemed to be inversely associated with the incidence of prostate cancer.

## 4.2 Comparison with previous studies

### 4.2.1 eCRF as an independent risk factor for cancer overall incidence

To our best knowledge, this is the first prospective cohort study to investigate the association between eCRF based on non-exercise algorithms and cancer overall incidence. Previous studies examined the relationship between eCRF and cancer mortality in the US population and the results were inconsistent.[33,34] Vainshelboim et al. demonstrated higher eCRF was independently associated with lower risks of cancer mortality across eCRF quintiles in men and women.[33] For each 1-MET increase in eCRF, there was an 11% reduction in cancer mortality among both men and women. In contrast, Wang et al. did not observe a statistically significant association between eCRF quintiles and cancer mortality in men.[34] The different findings of these two studies might be due to the different score systems of PA in the

algorithms for estimation of eCRF. In Wang et al.[34] study, they used 0 to 4 to score PA based on the intensity and frequency from the questionnaire, whereas in the study by Vainshelboim et al. they used scores 0 to 7 of PA based on the frequency only.

Several population-based cohort studies have investigated the relationship of exercise measured CRF and cancer overall incidence in men and demonstrated an inverse association.[16,19,20,21,22] Our results support these findings. Besides, our study adds to the existing literature. We used per 4 METs to estimate the potential effect of eCRF since many daily life activities with a moderate intensity equal to a value of 4 METs. We found there was a 6% risk reduction for the incidence of cancer overall in men with every 4 METs increase. Thus, this finding has public health implications in terms of promoting moderate PA in everyday life. Among women participants in our study, we observed that only high eCRF level seemed to be protective against cancer overall, whereas Vainshelboim et al. found an inverse association between both the medium and high CRF tertile groups and the incidence of cancer in veteran women participants.[15] The small sample size and the small number of cancer events in the Vainshelboim et al. study might lead to a random finding. Besides, veterans are a unique population, which may limit the generalizability of their findings. To our knowledge, this referred study is the only study conducted among women participants to evaluate the association between CRF and cancer incidence.

### 4.2.2 eCRF as an independent risk factor for breast and prostate incidence

Scientific evidence regarding the relationship between eCRF and breast, prostate cancer incidence remains unexplored. In our study, we did not find a statistically significant association between eCRF and breast cancer. Contrastingly, Peel et al. showed an inverse association between exercise measured CRF and breast cancer mortality among 14 811 US women.[23] However, no adjustment for PA was made in this study, and the participants included in the analysis were limited to married, well-

educated women. Our study extends previous studies by including more participants and adjusting more potential confounders such as PA, sitting hours, education, and economic difficulties to investigate the association of eCRF and breast cancer incidence. Nevertheless, the risk factors for breast cancer mortality might not be the risk factors for breast cancer incidence. Thus, more research is needed to investigate the relationship between CRF and breast cancer incidence.

We found the high level of eCRF only seemed to be associated with a lower prostate cancer incidence compared with the low level of eCRF. Our results were inconsistent with several prospective cohort studies in which no association was found between CRF and prostate cancer incidence.[20-22] However, a positive association between CRF and prostate cancer incidence was observed in a study by Byun et al. They viewed this unexpected result as a non-causal association most likely due to a screening/detection bias in men who were fitter.[26] In addition, prostate cancer was self-reported through mail-back health surveys in this cited study. Moreover, the follow-up duration (9.3 years) was shorter when compared with our study (22.1 years), during which the events might have not fully occurred.

### 4.3 Potential biological mechanisms

The underlying mechanisms on how high levels of CRF reduces cancer incidence have not been fully understood. Some potential biological explanations have been proposed. For incidence, an animal study demonstrated that exercise-induced humoral factors (myokines) inhibited mammary cancer cell proliferation and induced apoptosis of these cells.[45] A clinical prevention study randomized 400 inactive, healthy, and postmenopausal women into high (300 min/week) or moderate (150 min/week) aerobic exercise training programs.[46] Although they did not find differential effects on inflammatory biomarkers related to breast cancer risk after one-year training, they proposed that exercise, which accompanied with improved CRF, might be effective in

reducing levels of inflammatory markers, such as CRP, IL6, and TNFa.[46] These inflammatory markers have a positive correlation with cancer incidence and development.[47] Additionally, as we mentioned before, CRF reflects the general health status of the body. Good CRF may help to improve the integral function of body systems, such as increased cardiovascular blood circulation, and increased muscle protein synthesis.[10] Vainshelboim et al. pointed that good CRF may decrease the interaction time of potential carcinogens in the airway by enhancing pulmonary ventilation, lung perfusion to decrease the development of lung cancer.[48] However, cancer is a broad and complex disease, the mechanisms for the association between CRF and cancer may vary between different cancer sites among different individuals. With this regard, future research addressing the biological roles of CRF in the prevention of specific cancer is warranted.

### 4.4 Strengths and limitations

Scientific evidence regarding eCRF in relation to cancer incidence is scarce. To our knowledge, this prospective cohort study is the first to provide an insight into the potential associations between eCRF and cancer overall incidence as well as breast and prostate cancer incidence. The follow-up duration (22.1 years) in our study was long enough to observe rare disease outcomes such as cancer incidence, and the sample size was sufficient to study site-specific cancer events. Moreover, we included many important sociodemographic and lifestyle confounders in the adjustment, which strengthened the validity of our results. The ascertainment of cancer outcomes was highly accurate based on registration in the Cancer Registry of Norway. We also excluded participants with cancer at baseline in our main analysis and excluded the first 3 years of follow-up in the sensitivity analysis. Therefore, potential reverse causations because of pre-existing but undiagnosed cancer may not be a major issue in our study.

However, our study has several limitations. First, although the distribution of most key baseline characteristics was similar (supplementary table 3) between the participants who were included in the analysis and those who were excluded due to missing information among the HUNT2 population, it differed in age, sex, education, and ever severe disease. Thus, we should be cautious when interpreting our results as selection bias cannot be excluded. Second, misclassification of PA due to self-reporting and measurement error of WC and resting HR were possible, which may lead to misclassification of eCRF. However, this misclassification can be regarded as non-differential misclassification. In addition, misclassification was also present for lifestyle factors and social-economic variables due to self-reporting. Nevertheless, the self-reported variables have been used in all previous CRF related studies[12,15,16,18-23,25,26,29-36] and regarded as an established way to measure lifestyle factors. Third, participants' information was collected at baseline only prior to a diagnosis of any cancer, meaning that we were unable to evaluate how changes in eCRF level or lifestyle over time would affect the cancer incidence. Fourth, information on dietary habits was not collected in the HUNT2 questionnaire, which may result in residual confounding since diets high in red meat and low in fruits and vegetables have been linked to increased risk of cancer.[48] However, socioeconomic status can reasonably be used as a proxy variable for dietary habits.[49] Fifth, although non-exercise eCRF was significantly correlated with the directly measured CRF, variations were observed between different algorithms.[50] In the present study, we used the algorithms derived from the same population to predict CRF, which may have provided more valid and accurate estimations of CRF. Finally, participants in our study were mainly Caucasian, which limits the generalizability of our results to other ethnic populations. Indeed, the genetic susceptibility for CRF and cancer may differ between populations.

## 4.5 Conclusion

In summary, this is the first prospective cohort study to investigate the associations between eCRF and incidence of cancer overall as well as breast and prostate cancer. We found that eCRF had an inverse dose-response association with the cancer overall incidence in the whole population. No significant associations were found between eCRF and breast cancer. However, only the high level of eCRF appeared to be associated with a lower prostate cancer incidence. The results suggest eCRF may be a practical and cost-effective means in studying the association between CRF and cancer incidence. Possible mechanisms driving the association deserve further investigation.

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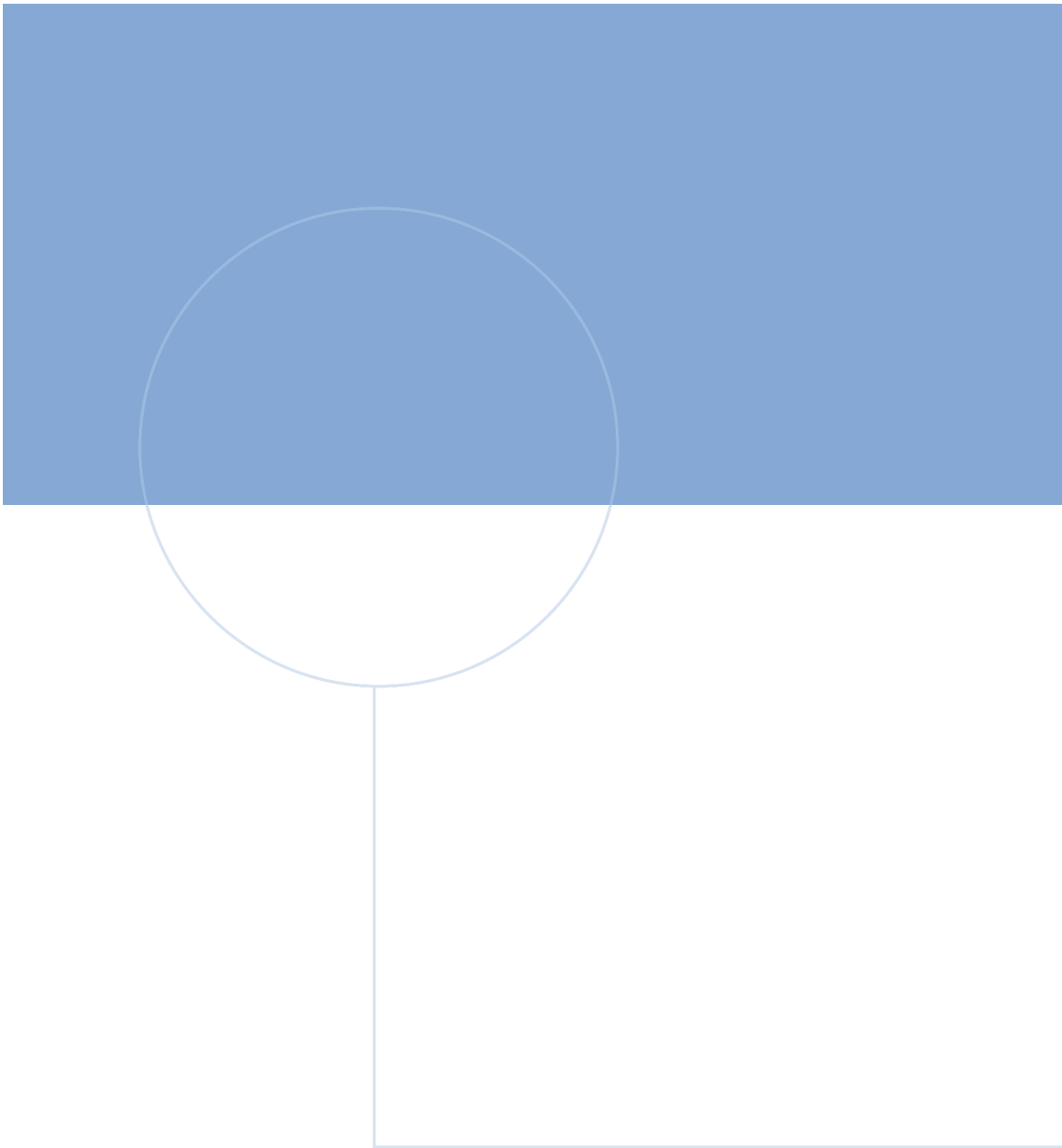

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