Introduction

Cancers are among the leading causes of morbidity and mortality worldwide, with approximately 14 million new cases and 8.2 million cancer-related deaths in 2012 [1]. The number of new cases is expected to rise by about 70% over the next two decades [1] and prevention of cancers is an important health issue.

Physical activity influences several biologic mechanisms (hormonal, immunologic, and mechanical), and may reduce the risk of several cancers [2–5]. In a large number of epidemiologic studies, the relationship between physical activity and cancer risk has been investigated. However, evidence of a beneficial effect in men is only found for colon cancer [6, 7]. The unclarified relationship between physical activity and cancer development may be due to difficulties in obtaining reliable data on physical activity habits. Self-reported physical activity, typically used in epidemiological research, may underestimate the association between physical activity and health outcomes [8, 9].

Physical fitness, a set of physiologic attributes that are enhanced through regular physical activity, is less prone to misclassification and may better capture health consequences of an active versus sedentary lifestyle than self-reported activity. Most common in use in health studies is the measurement of cardiorespiratory fitness (CRF), which reflects the ability of the body’s circulatory and respiratory systems to supply oxygen during sustained physical activity. CRF thus constitutes an objective measure of aerobic activity performed over time [10], although it cannot capture all physical activity (e.g., strength,
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between CRF and cancer than found for self-reported physical activity. This provides an expectation of a stronger association between CRF and cancer than found for self-reported physical activity and it may add knowledge about the preventive value of physical activity level.

Several studies have reported an inverse relationship between CRF and cancer mortality in men [12–22], whereas with regard to cancer risk, very few studies are based on measured CRF [19, 23–25]. The results, however, indicate an inverse association between CRF and risk of total cancer [19, 24, 26], lung cancer [19, 24], colon cancer [24], and cancers of the gastrointestinal tract [19], while for prostate cancer, the results are inconclusive [19, 23–25]. These findings provide further support and more studies are requested to reveal the level of CRF necessary to influence risk of site-specific cancer [24]. There is also a need to examine whether CRF is related to risk of cancer at other sites, than those previously focused on.

Based on a male cohort of 1997 initially healthy middle-aged men, we aimed to assess relationships between CRF levels and risk of site-specific cancers.

Material and Methods

The study is based on the Oslo Ischemia Cohort [27], linked to data from the Cancer Registry of Norway.

Data sources

The Oslo Ischemia Study is a comprehensive health survey established in 1972, aimed to examine the prevalence and development of coronary heart disease and other cardiovascular diseases in a healthy male population [27]. In total, 2341 employed men in the age-group 40–59 years were invited, of whom 2014 (86%) apparently healthy men participated by completing the study protocol. Men were defined as healthy as determined by a thorough screening of health records and by medical examinations. Inclusion required absence of Cardiovascular Diseases (CVD), diabetes, cancer or other advanced disease (pulmonary, renal, and liver), or disorders that made it impossible to undertake a symptom-limited exercise test. Men who regularly were taking medications that might affect the exercise test or heart rate response were excluded. Details about the selection criteria are presented elsewhere [27–29]. At baseline, after 12 h of fasting and 8 h non-smoking, a comprehensive clinical examination was conducted, including measurements of height, weight, blood pressure, and a panel of blood tests [27]. CRF was assessed by an incremental bicycle exercise test, with a duration of 6 min on each step, starting at 100 W. The load was incremented by 50 W per step until volitional exhaustion [27]. Based on this cohort, two studies have reported results on cancer—one studying the relation between cholesterol and prostate cancer [30], another investigating associations between CRF and overall cancer risk and death, and correlations between CRF and self-reported physical activity [31].

The Cancer Registry of Norway has, since the establishment in 1953, registered data on all malignancies diagnosed in the total Norwegian population. Mandatory reporting from several independent sources ensures completeness and high data quality [32]. The Oslo Ischemia study was linked to the Cancer Registry and the Cause of Death Registry, using the unique 11-digit personal identification number, assigned to all Norwegians in 1960 and thereafter to all newborns and persons residing in Norway. The linkage gave information on cancer and vital status. Permission to link the data was provided by the Regional Committees for Medical and Health Research Ethics.

Exposure variables

Cardiovascular fitness was measured as total work (sum of work performed in the bicycle test) divided by body weight, kJ/kg, in tertiles, giving the tertile limits: 1: <118.9 (mean 91.9); 2: 119–161.4 (mean 139.1); 3: >161.5 (mean 207.9). Age at inclusion was divided into four groups (<45, 45–49, 50–54, 55 + years). Individual body mass index (BMI) was calculated based on the objective measurements of height and weight (body weight/height², kg/m²), divided into two categories: low/normal weight (BMI < 25) and overweight/obese (BMI ≥ 25). Based on self-reported information on smoking, the men were categorized as ever and never smokers.

Of the 2014 men, two were excluded due to missing vital status data and 15 were excluded due to a cancer diagnosis prior to date of the first examination, leaving 1997 men for analyses.

Information on diet and alcohol consumption, which are factors associated with risk of cancers in men, in particular of the gastrointestinal tract [6, 7] was not available. Nor were we able to consider the role of socioeconomic factors.

Statistical analyses

The study cohort was followed from the date of health examination (inclusion) to the date of cancer diagnosis, date of death, emigration, or end of follow-up, at December 31, 2012, whichever occurred first. Descriptive analyses were conducted for baseline characteristics, presented as means (with SD, standard deviations) and percentages.
Cancer cases were categorized into cancer sites, using ICD-10 codes for each cancer diagnosis.

Cox regression models were conducted to evaluate the relationship between CRF and risk of specific cancers. Time to event was calculated as time from date of inclusion to date of primary diagnosis for each cancer-site. Effect estimates are presented as hazard ratios (HRs) with 95% confidence intervals (CI). Potential confounding factors included in the final Cox model were age, BMI, and smoking. In each model we verified that the proportional-hazards assumption was met based on analyzing Schoenfeld residuals. P-values for trend were estimated by increasing CRF tertile, for each cancer site.

The relationship between CRF and cancer was assessed for cancer sites that have been of main focus in relation to physical activity [6]: colon, rectum, lung, pancreas, kidney, bladder, prostate, skin, lymphoma and leukemia, and cancers of the central nervous system. In addition, we assessed the relationship for mouth/pharynx, esophagus/stomach, liver/gallbladder/bile duct, as suggested cancer prevention mechanisms of physical activity also may apply for these cancer sites.

Colonic subsites are suggested to be differently associated with lifestyle variables such as physical activity, smoking, alcohol, hormones, and BMI [31]; therefore, separate analyses were conducted for cancer risk of the proximal and distal parts of the colon. For prostate cancer, the analyses were stratified by stage of disease, due to potential different diagnostic intensities of prostate cancer in physically active and inactive men [3]. For skin cancer, separate analyses were conducted by anatomic site, to allow taking excess exposure from ultraviolet radiation (UVR) into account [33]. Finally, a corresponding Cox model was used for sensitivity analyses. To eliminate the possibility that a low score CRF resulted from an ongoing cancer disease (reverse causality), this analysis was restricted to men still alive and cancer-free 10 years after baseline.

All statistical analyses were performed using Stata 14 [34]. The statistical significance level was set at 5%.

**Results**

Table 1 shows the characteristics of the study cohort at baseline. For all men together, mean age at baseline was 49.8 years (SD: 5.5). With increasing age category, the percentage of men in the lowest fit tertile increased, while the percentage of men in the highest fit tertile decreased. For those youngest at baseline (<45 years), the majority were in CRF tertile 3 (57.8%), while for the oldest (≥55 years), the majority were in CRF tertile 1 (59.7%).

| Characteristics | CRF tertiles [kJ/kg] |  |
|-----------------|---------------------|--|
|                 | 1                   | 2                   | 3                   |
|                 | [<118.9]            | [119-161.4]         | ≥[161.5]            |
|                 | n = 667             | n = 665             | n = 665             |
| Age years, mean (SD) | 52.4 (5.2) | 49.9 (5.0) | 46.9 (4.8) |
| <45, n (%) | 66 (14.1) | 132 (28.1) | 271 (57.8) |
| 45–49, n (%) | 139 (24.5) | 206 (36.3) | 223 (39.2) |
| 50–54, n (%) | 218 (39.6) | 209 (38.0) | 123 (22.4) |
| ≥55, n (%) | 245 (59.7) | 118 (28.8) | 47 (11.5) |
| CRF kJ/kg, mean (SD) | 91.9 (19.9) | 139.1 (12.3) | 207.9 (50.7) |
| Weight kg, mean (SD) | 76.8 (11.1) | 77.2 (9.5) | 76.5 (9.0) |
| Height cm, mean (SD) | 175.3 (6.1) | 176.8 (5.9) | 178.1 (6.2) |
| BMI kg/m², mean (SD) | 24.9 (3.1) | 24.7 (2.7) | 24.1 (2.3) |
| <25, n (%) | 365 (30.0) | 386 (31.7) | 467 (38.3) |
| ≥25, n (%) | 312 (39.6) | 279 (35.4) | 197 (25.0) |
| Smoking ever, n (%) | 521 (78.1) | 509 (76.5) | 465 (69.9) |
| Cholesterol mmol/L, mean (SD) | 6.8 (1.2) | 6.7 (1.1) | 6.5 (1.2) |
| Blood pressure, mmHg, mean (SD) | 135.3 (19.8) | 129.9 (16.8) | 125.1 (15.0) |
| Systolic | 135.3 (19.8) | 129.9 (16.8) | 125.1 (15.0) |
| Diastolic | 89.3 (10.8) | 87.1 (10.0) | 84.9 (9.8) |

SD, standard deviation; BMI, body mass index.
758 men, where 84% had one diagnosis, 14% had two diagnoses, and 2.5% had three or several diagnoses. Table 2 presents the number of cancer diagnoses by site, illustrating that prostate was the most frequent site, followed by lung and colon. The table also shows the number of site-specific cancer diagnoses according to CRF tertiles. When comparing the cancer occurrence in the study cohort with the general male population in the area the men were recruited from, no major differences were revealed [30].

Results from the Cox analyses are presented in Table 3, showing the HR for cancer risk by site (with 95% CIs) for CRF tertiles 2 and 3 relative to tertile 1, adjusted for age, BMI, and smoking. For colon, men in the second and third CRF tertile had noticeably lower HRs compared to men in tertile 1, although the differences were not statistically significant. When separating colonic subsites, the number of cases was near equally distributed at the proximal and distal part. For the proximal colon, a significantly reduced cancer risk was found for men in the second CRF tertile, compared to tertile 1, while no significant relationship was found between CRF and cancer of the distal colon and neither for cancer of the rectum (Table 3). Relative to CRF tertile 1, men in CRF tertile 3 had significantly lower risk of lung cancer, pancreatic cancer, and bladder cancer. Furthermore, a significant trend for lower risk by increasing CRF tertile was found for cancers of proximal colon, lung, and bladder (P-value for trend <0.05).

No significant relation was found between CRF and kidney cancer (Table 3). Neither was the risk of prostate cancer related to CRF nor in analyses stratified by stage at diagnosis (results not shown).

For melanoma skin cancer, the association tends to go in the opposite direction, although not statistically significant. Subanalyses by anatomic site of the melanoma revealed that the risk increase was valid for head and trunk only (results not shown).

For cancer located at mouth/pharynx, the relation tended to be inverse, although not statistically significant (Table 3). For other cancer sites, no significant relations with CRF were found (Table 3).

### Discussion

Based on the present cohort, of initially healthy middle-aged men, we previously have found that high CRF was associated with lower overall cancer risk, cancer mortality, and cancer case fatality, compared to men with low CRF [26]. In this study, we found that high midlife CRF was associated with decreased risk of cancers of lung, pancreas, and bladder, and that medium CRF was associated with decreased risk of proximal colon cancer, when compared to low CRF. For other cancer sites, no significant associations were found.

| Cancer site | ICD-10 | Total | CRF tertiles |
|-------------|--------|-------|--------------|
| All sites   | C00-96 | 898   | 278 313 307 |
| Mouth, pharynx | C00-14 | 24    | 10  8  6 |
| Esophagus, stomach | C15, C16 | 43    | 13  14 16 |
| Colon | C18 | 87    | 35  23 29 |
| Proximal | C18.0-18.5 | 46    | 21  7  18 |
| Distal | C18.6-18.7 | 41    | 14  16 11 |
| Rectum, anus | C19-21 | 44    | 10  19 15 |
| Liver, gallbladder/bile ducts | C22, C23-24 | 13    | 4   6  3 |
| Pancreas | C25 | 29    | 14  11  4 |
| Lung, trachea | C33-34 | 109   | 46  41 22 |
| Prostate | C61 | 213   | 52  71 90 |
| Kidney, renal pelvis | C64, C65 | 34    | 11  12 11 |
| Bladder, ureter, urethra | C66-68 | 76    | 32  26 18 |
| Skin, melanoma | C43 | 49    | 9   15 25 |
| Skin, nonmelanoma | C44 | 47    | 12  14 21 |
| Lymphoma | C81-90 | 30    | 5   13 12 |
| Leukemia | C91-95 | 37    | 9   16 12 |
| Central nervous system | C70-72/D42-43 | 19    | 5   6  8 |
| Unspecified | C39, C76, C80 | 23    | 8   9  6 |
| Other sites\(^1\) | C39, C76, C80 | 21    | 3   9  9 |

\(^1\)Nose (C30-31), Larynx (C32), Other digestive organs (C26), Other male genitals (C60, C63), Eye (C69), Endocrine glands (C37/C73-75), Soft tissue (C48-49).
A recently published pooled analysis, based on 1.4 million participants and about 180,000 cancer cases during 11 years of follow-up [35], reports that higher levels of self-reported leisure time activity were associated with lower risk of nine cancer sites in men. In this study, based on CRF measurement, we found the same relationship for several cancer sites, with an even larger magnitude, although the number of cancer cases was small.

Colon cancer has received much research attention with respect to the role of physical activity, and is the only site with sufficient evidence for a beneficial role of physical activity in men [6, 7]. In general, the risk reduction reported is approximately 20-25% [3]. In this study, based on CRF measurements, men with the lowest CRF seem to have the highest risk of colon cancer, compared to men having higher CRF, but the difference was not statistically significant. To our knowledge, only one study had previously examined the relationship between CRF and colon cancer risk, and the results show an inverse graded relationship [24]. This study was conducted with a similar design and methods as we included men only and in corresponding age groups. An important difference, however, is that it was a substantially larger study, including 181 colon cancers [24]. Moreover, biological differences between colonic segments [36, 37] have raised questions on whether lifestyle factors affect the cancer risk of colon subsites differently. Nevertheless, two meta-analyses report that physical activity was inversely associated with cancer of the proximal and distal colon, with the same magnitude for both subsites [31, 38]. To our knowledge, no studies have examined the relation between CRF and site-specific colon cancer. Our analyses revealed decreased risk of proximal colon cancer for men in CRF tertile 2, compared to men in tertile 1, and the P-value for trend was 0.03. For distal colon, no significant association was found. Our findings may indicate a subsite difference between the colonic segments, although it has to be kept in mind that we were not able to take alcohol consumption or dietary factors into account.

There is no epidemiologic evidence for a relationship between physical activity and rectum cancer [6, 7]. Nor did we, in this study, observe any relation between CRF and rectum cancer. To our knowledge, this is the first study based on CRF that reports a site-specific result for rectum. The study by Laukkanen et al. [19], however, found an inverse association between CRF and all gastrointestinal tract cancers (n = 92), including the rectum, but the number of rectum cancers was not given.

For lung cancer, we found an evident inverse relationship between CRF and risk. Compared to men in CRF

| Cancer site                      | CRF tertiles [kJ/kg, tertile limits, mean per tertile] | Trend | P-value |
|---------------------------------|------------------------------------------------------|-------|---------|
| Mouth/pharynx                   | 1 (<118, 91.9)                                      | 2 [119–161, 139.1] | 3 [>161, 207.9] | 0.25         |
| Esophagus/stomach               | 1.00                                               | 0.64 (0.25,1.65) | 0.41 (0.14,1.19) | 0.86         |
| Colon                           | 1.00                                               | 1.09 (0.50,2.36) | 1.24 (0.56,2.77) | 0.15         |
| Proximal                        | 1.00                                               | 0.60 (0.35,1.01) | 0.69 (0.40,1.17) | 0.03         |
| Distal                          | 1.00                                               | 0.30 (0.13,0.73) | 0.69 (0.34,1.29) | 0.49         |
| Rectum, anus                    | 1.00                                               | 1.00 (0.48,2.08) | 0.65 (0.28,1.50) | 0.38         |
| Liver/gallbladder/bile duct     | 1.00                                               | 1.65 (0.76,3.61) | 1.16 (0.49,2.73) | 0.57         |
| Pancreas                        | 1.00                                               | 1.62 (0.44,5.97) | 0.81 (0.16,4.01) | 0.15         |
| Lung, trachea                   | 1.00                                               | 0.80 (0.35,1.80) | 0.32 (0.10,1.00) | 0.02         |
| Prostate                        | 1.00                                               | 0.78 (0.50,1.19) | 0.39 (0.23,0.66) | 0.002        |
| Kidney, renal pelvis            | 1.00                                               | 1.17 (0.81,1.69) | 1.20 (0.83,1.74) | 0.59         |
| Bladder, ureter, urethra        | 1.00                                               | 0.86 (0.37,1.99) | 0.65 (0.27,1.58) | 0.63         |
| Skin cancer                     | 1.00                                               | 0.69 (0.41,1.18) | 0.40 (0.21,0.74) | 0.01         |
| Melanoma                        | 1.00                                               | 1.31 (0.73,2.35) | 1.70 (0.96,3.00) | 0.18         |
| Nonmelanoma                     | 1.00                                               | 1.48 (0.63,3.42) | 2.19 (0.99,4.96) | 0.14         |
| Lymphoma                        | 1.00                                               | 1.06 (0.48,2.35) | 1.20 (0.55,2.60) | 0.88         |
| Leukemia                        | 1.00                                               | 2.44 (0.85,6.99) | 1.89 (0.62,5.78) | 0.25         |
| Central nervous system          | 1.00                                               | 1.86 (0.80,4.30) | 1.26 (0.49,3.21) | 0.30         |
| Unspecified                     | 1.00                                               | 1.03 (0.31,3.44) | 1.27 (0.38,4.18) | 0.90         |
| Other sites†                    | 1.00                                               | 0.97 (0.37,2.58) | 0.59 (0.19,1.82) | 0.59         |

†Nose (C30-31), Larynx (C32), Other digestive organs (C26), Other male genitals (C60, C63), Eye (C69), Endocrine glands (C37/C73-75), Soft tissue (C48-49).
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A large number of studies have investigated the relationship between self-reported physical activity and prostate cancer, showing inconsistent results [3, 6]. Further, in the recently published pooled analysis, men who reported the highest physically active level were found to have a slightly elevated risk of prostate cancer [35]. No studies based on measured CRF have been able to clarify this relation. To our knowledge, five studies report risk estimates for the relation between CRF and risk of prostate cancer—two report no association [19, 24], two report a positive association [25, 30], while one reports an inverse association for men aged <60 years [23]. In this study, no significant relation between CRF and prostate cancer was found. An issue often discussed in studies on prostate cancer is the possible selection bias of higher diagnostic intensity of small tumors in physically active men, as they may belong to a higher socioeconomic level and are more concerned about health. In this study, information on socioeconomic variables (i.e., education, income) was not available. An approach to overcome this limitation, sensitive analyses by stage of disease, was conducted, expecting a positive association for local stage disease at diagnosis, but not for advanced stage disease. This analysis revealed no significant findings and no differences between the stage groups.

For melanoma skin cancer, we observed elevated HR for men in CRF tertile 3, compared to those in tertile 1, indicating a positive relationship. Also, studies based on self-reported physical activity report a positive relation to skin cancer [35]. Physically active people may spend more time outdoor than inactive individuals and may therefore have higher exposure to UVR from the sun, the main risk factor for skin cancer [40]. Additional analyses, stratified by anatomic site, showed that the elevated risk was restricted to tumors located at the head and the trunk, giving support for this explanation.

Studies examining relations between physical activity and lympho-hematopoietic cancers indicate an inverse association for non-Hodgkin’s lymphoma and leukemia [3, 35, 43]. To our knowledge, this study is the first that investigated the association between CRF and these cancers, revealing no significant associations. Prevention of obesity is one mechanism of physical activity suggested to explain the inverse relationship to hematologic cancers [43]. BMI, measured at baseline, was taken into account in our analyses, but did not significantly influence the association between CRF and cancer risk. However, we cannot exclude a possible impact of weight gain after baseline. Another beneficial effect of physical activity suggested to play a role is improved immune function [39, 43, 44]. On the other hand, regularly intense exercise is related to immune suppression [45, 46] and increased susceptibility to infections associated with lymphoid cancers [47]. Unfortunately, information on immunologic factors or prevalence of infections was not available and, thus, not taken into account in our analyses.
For other cancer forms, no significant relation to CRF was found, but of interest might be the lower HRs of mouth and pharynx cancers in CRF tertiles 2 and 3, compared to tertile 1, although not statistically significant. In general, physical activity has not been related to cancer at these sites [6]. The main risk factors for mouth and pharynx cancers are tobacco, alcohol, and human papillomavirus (HPV) [40]. In this study, we adjusted for smoking, but were not able to adjust for alcohol intake and HPV infections, as we had no information about these factors.

The study has several strengths. Primarily this entails complete information on CRF in 1997 men, who were prospectively followed up for cancer outcomes over a 40-year period. The midlife CRF measurements is a reliable measure of aerobic activity over time, which is a key factor that has to be emphasized, although we are aware that a CRF test not capture all kind of activity (i.e., light activity that does not impact the aerobic capacity). From the Cancer Registry of Norway we have complete and valid information on cancer diagnoses and cause of death during the time-span covered, and we have individual-level information on several potential confounding variables. Lastly, the cohort is shown to be representative of this age group of men, with regard to cancer occurrence in the counties were recruited from (Oslo and Akershus), within the given time-period [30]. On the other hand, the study has limitations that need to be considered when interpreting the results. First, the study has a relatively small sample size, resulting in few cases of each cancer site and thus low power in cancer-specific analyses. Second, all variables were assessed at baseline, which make us unable to account for changes over the life course, that may have influenced the observed associations and, with regard to the smoking variable, lack of information on pack-years is a weakness. Third, although one main criterion for cohort inclusion was good health, a low-score CRF test may result from an ongoing undiagnosed disease. To overcome this, we conducted analyses excluding the first 10 years after enrollment. This analysis, however, gave similar results and thus rejects such an explanation. Fourth, we lack information on dietary factors and alcohol intake, factors that are associated with cancers of the gastrointestinal tract. Nor were we able to consider socioeconomic factors (i.e., education, income), which is a limitation as health concerns vary between socioeconomic levels.

Conclusion

In men, a beneficial relation between physical activity and colon cancer is established, but for other cancers, the relationship is inconclusive. Little is known about the relations between CRF and cancer risks. This 40-year follow-up study of initially healthy middle-aged men reveals a potentially adverse effect of having low CRF, for risk of several cancers. Compared to men with low CRF, men with higher levels have reduced risk of cancers in the proximal colon, lung, pancreas, and bladder. Despite the fact that the study is small, our results are in line with previous findings, which strengthen the role of CRF as a potential cancer preventive factor.

Conflict of Interest

None declared.

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