EUROPEAN JOURNAL OF CANCER 46 (2010) 355–363

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# Cardiorespiratory fitness, lifestyle factors and cancer risk and mortality in Finnish men

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ARTICLE INFO

*Article history:*
Received 5 May 2009
Received in revised form 10 July 2009
Accepted 17 July 2009
Available online 13 August 2009

*Keywords:*
Cancer risk
Physical activity
Maximal oxygen uptake
Lifestyle
Lung cancer

ABSTRACT

*Background:* Physical fitness along with lifestyle factors may have important roles in the prevention of cancer. We examined the relationship between common lifestyle factors such as energy expenditure, physical activity and maximal oxygen uptake ($VO_{2max}$), nutrition and smoking habits and the risk of cancer.

*Methods:* A population-based cohort study was carried out in 2268 men from Eastern Finland with no history of cancer. They were followed up for an average of 16.7 years. The outcome measures were cancer incidence ($n = 387$) and cancer mortality ($n = 159$).

*Results:* Men with $VO_{2max}$ of more than 33.2 mL/kg/min (highest tertile) had 27% (95% confidence interval (CI) 0.56–0.97) decreased cancer incidence and 37% (95% CI 0.40–0.97) reduced cancer mortality than men with $VO_{2max}$ of less than 26.9 mL/kg/min (lowest tertile) after adjustment for age, examination year, alcohol, smoking, socioeconomic status, waist-to-hip ratio and energy, fibre and fat intake. The risk reduction was mainly due to decreased risk of lung cancer in fit men. The adjusted risk of cancer was 0.73 (95% CI 0.55–0.98) among fit ($VO_{2max} \geqslant 26.9$ mL/kg/min) men with the total energy expenditure of physical activity over 2500 kcal/week. A total of 290 active (energy expenditure >2500 kcal and at least 2 h of physical activity per week) men with a favourable lifestyle (good fitness, balanced diet and non-smoking) had an adjusted relative risk of 0.63 (95% CI 0.46–0.87) for cancer.

*Conclusion:* Favourable lifestyle including good cardiorespiratory fitness and healthy dietary habits with active and non-smoking lifestyle considerably reduces the risk of cancer.



## 1. Introduction

Weight gain is one of the most important factors contributing to the increased risk for certain cancers, but the role of physical fitness, activity level and dietary energy intake in the prevention of cancer is not well defined.[1] Some studies have found that physical activity may reduce the risk of cancer at all sites[2–8] including the risk of colon,[9–14] lung,[3,10,12,15–17] pros-

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0959-8049/$ - see front matter 
doi:10.1016/j.ejca.2009.07.013

tate[3,18–20] and breast cancers[21–23] whereas other epidemiologic studies have observed only a weak or borderline significant association between physical activity and cancer risk.[23–28] It has been reported that total energy expenditure is more important than the type of exercise for reducing overall mortality.[29–31] However, little is known about the duration, intensity and energy expenditure of physical activity needed to reduce the risk of cancer when initial fitness level is taken into account. In general, the dose–response relationship between self-reported physical activity and cancer risk is uncertain but using objective and reliable measure of exercise capacity may help in achieving additional valuable information for its prognostic value.[7,8,28,32]

The latest recommendation suggest that should perform every adult 30 min of moderate-intensity physical activity on 5 d of the week helps to promote health and maintain health.[31] Only few prospective studies have reported the quantity and intensity of physical activity needed to reduce overall mortality.[28,29] Some studies indicate that reduced total mortality among fit men is largely due to reduced mortality from non-cardiovascular causes,[4,33,34] but there are no studies on the relationship between physical fitness and cancer morbidity or mortality.

The aim of the present study was to study the amount of modifiable lifestyle factors such as diet, smoking, physical activity and the level of cardiorespiratory fitness, as measured by maximal oxygen uptake ($VO_{2max}$), necessary to reduce the risk of morbidity and mortality from common cancers in a population-based sample of men.

## 2. Methods

### 2.1. Subjects

The present study is based on Kuopio Ischemic Heart Disease Risk Factor Study which is an ongoing population-based study to investigate various risk factors including physical fitness for atherosclerotic CVD and cancers.[35] The study population is a representative random sample of 2682 men who were 42–60 years of age at baseline examination and exercise data were available for 2361 men. Of these, men who had a history of cancer (93 men) were excluded, and thus, complete data on $VO_{2max}$, energy expenditure, duration, mean intensity and frequency of physical activity were available for 2268 men. Baseline examinations were conducted between March 1984 and December 1989. The study was approved by the Research Ethics Committee of the University of Kuopio, Kuopio, Finland. Each participant gave written informed consent.

### 2.2. Measurements

#### 2.2.1. Cardiorespiratory fitness

A maximal symptom-limited exercise tolerance test was performed between 8:00 a.m. and 10:00 a.m. using an electrically braked cycle ergometer. The standardised testing protocol comprised an increase in the workload of 20 W/min. The tests were supervised by an experienced physician with the assistance of an experienced nurse. The electrocardiogram (ECG), blood pressure and heart rate were registered during the exercise stress test.

A detailed description of the measurement of $VO_{2max}$ has been given elsewhere.[36] In short, respiratory-gas exchange was measured for the first 581 men by the mixing-chamber method, and for the other 1687 men by a breath-by-breath method. $VO_{2max}$ was defined as the highest value for or the plateau of oxygen uptake. The MET is the ratio of the metabolic rate during exercise to the metabolic rate at rest. One metabolic equivalent corresponds to oxygen uptake of 3.5 mL/kg/min.

#### 2.2.2. Physical activity

Physical activity was assessed using the 12-month physical activity questionnaire.[37,38] The checklist included the most common physical activities of middle-aged Finnish men, selected on the basis of a previous population-based study in Finland.[39] For each activity performed, the subjects were asked to record the frequency (number of sessions per month), average duration (hours and minutes per session) and intensity (scored as 0 for recreational activity, 1 for conditioning activity, 2 for brisk conditioning activity and 3 for competitive, strenuous exercise). A trained nurse checked and completed the questionnaire in an interview.

The intensity of physical activity was expressed in metabolic units (MET or metabolic equivalents of oxygen consumption). The four categories of intensity of activity were assigned their own metabolic unit values, and revised on the basis of a synthesis of available empirical data.[39] One metabolic unit corresponds to an energy expenditure of approximately 1 kcal/kg of body weight per hour, or an oxygen uptake of 3.5 mL/kg/min.

Physical activity was categorised according to type: (1) conditioning physical activity – walking (mean intensity, 4.2 MET), jogging (10.1 MET), skiing (9.6 MET), bicycling (5.8 MET), swimming (5.4 MET), rowing (5.4 MET), ball games (6.7 MET), and gymnastics, dancing, or weight lifting (5.0 MET); (2) non-conditioning physical activity – crafts, repairs, or building (2.7 MET), yard work, gardening, farming, or snow shovelling (4.3 MET), hunting, picking berries, or gathering mushrooms (3.6 MET), fishing (2.4 MET), and forestry (7.6 MET); and (3) walking (3.5 MET) or bicycling (5.1 MET) to work.

#### 2.2.3. Diet and smoking

Dietary energy intake was assessed using 4-d food recording.[40] Instructions were given and completed food records were checked by a nutritionist. Intake of nutrients was estimated using the NUTRICA software. The data bank of NUTRICA is complied using mainly Finnish value nutrient compositions that take into account possible food preparation losses.

Lifelong exposure to smoking (cigarette pack-years) was estimated as the product of years spent smoking and the number of cigarettes smoked daily at the time of examination.[41] Energy expenditure >2500 kcal/week, physical activity duration >2 h/week (men with healthy lifestyle), $VO_{2max} \geqslant 26.9$ mL/kg/min, energy intake >108.6 kJ/kg/week, lowest tertile and non-smoking were considered as criteria for protective lifestyle factors.

#### 2.2.4. Body mass, other lifestyle factors and biochemical variables

Body mass index (BMI) was computed as weight in kilograms divided by the square of height in metres, and waist-to-hip ratio was computed as the ratio of the circumference of the waist to the hip. Alcohol consumption was assessed using the Nordic Alcohol Consumption Inventory.[12] Socioeconomic status (SES) is as described previously.[42] Blood specimens were collected at baseline and serum lipids and glucose were measured as described elsewhere.[35,41]

### 2.3. *Outcome events*

Cancer deaths and overall mortality were ascertained by linkage to the National Death Registry using the Finnish personal identification code. There were no losses to follow-up. Incident cancer cases were derived from the population-based Finnish Cancer Registry. Follow-up was started at the date of baseline measurement and ended at death or on 31st December 2005, whichever was first. Follow-up for cancer incidence was done in an automatic record linkage (based on personal identifier, PID) with the files of the population-based countrywide Finnish Cancer Registry. All residents of Finland have a unique PID which is used in all main registers in Finland.

### 2.4. *Statistical analysis*

For the descriptive purposes, the associations of $VO_{2max}$ with the possible risk factors for cancer were examined using covariate analysis. Risk factors for cancer were analysed using multivariate Cox model. The levels of $VO_{2max}$ were entered as dummy variables into forced SPSS Cox proportional hazards models. In these models, $VO_{2max}$ was categorised according to tertiles. If possible, covariates were entered uncategorised into the Cox models. Two different sets of covariates were used: (1) age and examination year and (2) age, examination year, smoking, alcohol consumption, waist-to-hip ratio, SES and total caloric, fibre and fat intake.

In additional Cox models, fit ($VO_{2max} \geqslant 26.9$ mL/kg/min, lowest tertile) and unfit ($VO_{2max} < 26.9$ mL/kg/min) men were categorised according to physical activity; energy intake and smoking as reference group consisted of unfit men with other risk predictors of interest. On the basis of previous results,[43,44,48,49] the protective factors were combined to find out the optimal levels of factors that help in the reduction of cancer risk. Relative hazards, adjusted for risk factors, were estimated as antilogarithms of coefficients from multivariable models. Tests for statistical significance were two-sided. Statistical analyses were performed using the SPSS 14.0 for Windows (SPSS, Inc., Chicago, Illinois).

## 3. Results

### 3.1. *Baseline characteristics*

At the beginning of the follow-up, the median $VO_{2max}$ was 30.0 mL/kg/min (range 16.0–65.4 mL/kg/min). The distribu-

**Table 1 – Means (and standard deviations) of 2268 men in Eastern Finland according to tertiles of maximal oxygen uptake.**

| | Tertiles of maximal oxygen uptake | | | | |
|---|---|---|---|---|---|
| | All men Mean (SD) | Lowest (1) Mean (SD) | Middle (2) Mean (SD) | Highest (3) Mean (SD) | P-value |
| *Age* | 52.8 (5.1) | 55.0 (4.1) | 52.7 (4.8) | 50.6 (5.3) | <0.001 |
| Total physical activity | | | | | |
| Energy expenditure (kcal/week) | 2603 (2343) | 2473 (2517) | 2573 (2325) | 2764 (2169) | 0.049 |
| Mean intensity (METs)[a] | 4.53 (1.18) | 4.28 (1.05) | 4.41 (1.06) | 4.90 (1.32) | <0.001 |
| Duration (h/week) | 2.15 (2.65) | 2.24 (2.99) | 1.92 (2.45) | 2.28 (2.48) | 0.01 |
| Diet | | | | | |
| Total energy intake (kJ/day) | 9969 (2602) | 9372 (2497) | 9854 (2404) | 10681 (2727) | <0.001 |
| Total fat intake (g) | 102.6 (33.8) | 97.6 (33.7) | 101.9 (31.4) | 108.3 (35.4) | <0.001 |
| Total fibre intake (g) | 25.1 (8.3) | 23.6 (7.7) | 24.5 (8.2) | 27.1 (8.7) | <0.001 |
| | 161.7 (83.8) | 166.7 (87.8) | 163.7 (85.0) | 154.8 (78.1) | <0.001 |
| Fruits and vegetable intake (sum g) intake (g/day) | 121.2 (136.5) | 121.9 (151.9) | 114.7 (124.1) | 126.9 (132.0) | 0.218 |
| Cigarette smoking (pack-years[b]) | 8.1 (16.2) | 11.1 (19.6) | 8.3 (15.2) | 5.0 (12.4) | <0.001 |
| Alcohol consumption (g/week) | 73.8 (121.2) | 80.6 (144.5) | 77.4 (120.9) | 63.3 (91.7) | 0.01 |
| Body mass index (kg/m$^2$) | 26.8 (3.4) | 28.2 (3.9) | 26.9 (3.2) | 25.5 (2.7) | <0.001 |
| Waist-to-hip ratio | 0.95 (0.06) | 0.97 (0.06) | 0.95 (0.06) | 0.92 (0.06) | 0.001 |
| Blood glucose (mmol/L) | 4.8 (1.2) | 5.0 (1.5) | 4.8 (1.2) | 4.6 (0.8) | <0.001 |
| Serum polyunsaturated to saturated fatty acid ratio | 1.19 (0.23) | 1.13 (0.25) | 1.19 (0.22) | 1.24 (0.21) | <0.001 |
| Serum total cholesterol (mmol/L) | 5.91 (1.07) | 5.98 (1.08) | 5.95 (1.06) | 5.79 (1.04) | 0.001 |
| Serum insulin level (mmol/L) | 11.56 (6.91) | 13.99 (8.8) | 11.30 (6.0) | 9.40 (4.3) | <0.001 |
| Cancer in family (%) | 25.0 | 26.3 | 26.7 | 21.8 | 0.051 |
| Use of PG-inhibitors (%)[c] | 10.9 | 15.0 | 9.5 | 7.7 | <0.001 |

Tertile 1 $\leqslant$ 26.9 mL/kg/min, tertile 2 = 26.9–33.2 mL/kg/min, and tertile 3 $\geqslant$ 33.2 mL/kg/min.

a MET denotes metabolic equivalents of oxygen consumption. The metabolic unit is the ratio of metabolic rate during exercise to the metabolic rate at rest. One MET corresponds to approximately 1 kcal/kg of body weight per hour and an oxygen uptake of 3.5 mL/kg/min.

b Pack-years denotes the lifelong exposure to smoking which was estimated as the product of years smoked and the number of cigarette smoked daily at the time of examination.[42]

c Regular use of prostaglandin inhibitors.

**Table 2 – Risk factors for lung, GI-tract and prostate cancers in 2268 men without cancer diagnosed at baseline.**

| Risk factor | Lung cancer risk (52 cases) | | GI-tract cancer risk (92 cases) | | Prostate cancer risk (127 cases) | |
|---|---|---|---|---|---|---|
| | Relative risk[b] (95% CI) | P-value | Relative risk[b] (95% CI) | P-value | Relative risk[b] (95% CI) | P-value |
| Age (years) | 1.07 (0.99–1.15) | 0.781 | 1.04 (0.99–1.10) | 0.130 | 1.11 (1.05–1.16) | <0.001 |
| Smoking (cigarette pack-years per 10 years)[a] | 1.36 (1.24–1.48) | <0.001 | 1.08 (0.95–1.23) | 0.245 | 0.94 (0.82–1.09) | 0.425 |
| Body mass index (per 5 kg/m$^2$ increment) | 0.62 (0.39–0.93) | 0.045 | 1.04 (0.76–1.43) | 0.816 | 0.96 (0.71–1.23) | 0.766 |
| Physical fitness (per 1 MET increase) | 0.80 (0.69–0.93) | 0.001 | 0.88 (0.79–0.99) | 0.032 | 1.03 (0.94–1.12) | 0.599 |
| Alcohol consumption (per 10 g/week)[c] | 1.01 (1.00–1.02) | 0.029 | 1.01 (0.99–1.02) | 0.086 | 1.01 (0.99–1.03) | 0.277 |

CI = confidence interval and MET = metabolic equivalent of oxygen consumption.
a Pack-years is divided by 10, and cigarette pack-years denotes the lifelong exposure to smoking which was estimated as the product of years spent smoking and the number of cigarettes smoked daily at the time of examination.[42]
b Relative risks are adjusted for all other risk factors shown in the table in addition to fat, fibre and energy intake.
c Risk factor is expressed as a one standard deviation increment in the value.

tions of the energy expenditure, duration and mean intensity of total physical activity and other baseline characteristics according to tertiles of $VO_{2max}$ are shown in Table 1.

### 3.2. *Outcomes events*

A total of 593 deaths occurred during an average follow-up of 16.7 years (range 0.4–21.8 years), and 159 deaths were due to cancers. There were 387 cancer events during the follow-up. Most common types of incident cancers were cancers of the prostate ($n$ = 127), lung ($n$ = 52), colo-rectum ($n$ = 49), urinary bladder or kidney ($n$ = 36), skin ($n$ = 27), cerebrum ($n$ = 15), upper gastro-intestinal (GI) tract ($n$ = 19), liver ($n$ = 7), pancreas ($n$ = 18) and lymphoid tissues ($n$ = 9).

### 3.3. *Risk factors for cancer*

The significant risk factors were smoking, body mass index, $VO_{2max}$ and alcohol consumption for lung cancer, $VO_{2max}$ for GI-tract cancers and age for prostate cancer. Alcohol consumption was a significant predictor of prostate cancer when not adjusted for serum fatty acid and dietary factors. One MET increase in $VO_{2max}$ (3.5 mL/kg/min) amounted to a 20% decrease in lung cancer risk and 12% decrease in GI-tract cancer risk (Table 2a). Physical fitness was not independently related to prostate cancer risk but the interaction between age and $VO_{2max}$ was almost statistically significant ($p$ = 0.07).

In the multivariate analysis, the significant risk factors for overall cancer incidence were age, smoking, $VO_{2max}$ and alcohol consumption and the risk predictors for cancer mortality were age, smoking, $VO_{2max}$, dietary energy intake and socioeconomic status. One MET increase in physical fitness was related to 6% decreased risk of cancer incidence (relative risk, RR 0.94, 95% confidence interval (CI) 0.89–0.99, $p$ = 0.026) and cancer mortality by 12% (0.88(0.80–0.96), $p$ = 0.002).

Smoking was one of the most significant predictors for cancer mortality and morbidity for lung cancer. The RR of fit non-smokers compared with that of unfit smokers was 0.43 (95% CI 0.31–0.59) for cancer incidence and 0.37 (95% CI 0.23–0.60) for cancer mortality, after adjustment for age, examination year and confounders. The adjusted risk of cancer incidence was lower (RR = 0.68, 95% CI 0.49–0.94) in fit smokers than in unfit smokers. No statistically significant interaction existed between smoking or non-smoking and the predictive power of physical fitness. $VO_{2max}$ was related to the risk of cancer among both smokers and non-smokers.

### 3.4. *Physical fitness and cancer risk*

Men with $VO_{2max}$ of more than 33.2 mL/kg/min (highest tertile) had 28% decreased cancer incidence and 45% reduced cancer mortality than men in the lowest tertile after adjustment for age and examination year (Table 3). The respective risk reductions were 27% and 37% after further adjustment for smoking, alcohol consumption, waist-to-hip ratio, SES and total caloric, fibre and fat intake. The results did not change substantially although fruits, vegetables and meat intake, family history of cancer and the regular use of prostaglandin inhibitors were controlled with the tertiles of $VO_{2max}$. The adjusted RR of overall death was 0.42 (95% CI

**Table 3 – Relative risks of cancer according to physical fitness in 2268 men with no history of cancer at baseline.**

| | Cancer incidence | | | Cancer mortality | | | Overall mortality | | |
|---|---|---|---|---|---|---|---|---|---|
| | Relative risk (95% CI) | P-value | No. of events | Relative risk (95% CI) | P-value | No. of deaths | Relative risk (95% CI) | P-value | No. of deaths |
| Maximal oxygen uptake (mL/kg/min) | 387 Events | | | 159 Deaths | | | 593 Deaths | | |
| *Follow-up time from baseline to outcome events* | | | | | | | | | |
| <26.9, <8.3 METs (*n* = 756) | 1.00 (reference) | | 150 | 1.00 (reference) | | 58 | 1.00 (reference) | | 306 |
| 26.9–33.2, 8.3–9.5 METs (*n* = 756) | 0.87 (0.67–1.11)[a] | 0.249 | 133 | 0.79 (0.55–1.12)[a] | 0.030 | 55 | 0.58 (0.49–0.70)[a] | <0.001 | 183 |
| | 0.87 (0.68–1.10)[b] | 0.292 | | 0.84 (0.56–1.21)[b] | 0.340 | | 0.64 (0.53–0.77)[b] | <0.001 | |
| >33.2, >9.5 METs (*n* = 756) | 0.72 (0.56–0.94)[a] | 0.015 | 104 | 0.55 (0.36–0.83)[a] | 0.005 | 36 | 0.34 (0.27–0.43)[a] | <0.001 | 104 |
| | 0.73 (0.56–0.97)[b] | 0.028 | | 0.63 (0.40–0.97)[b] | 0.037 | | 0.42 (0.33–0.54)[b] | <0.001 | |
| | P = 0.0016 for linear trend | | | P < 0.001 for linear trend | | | P < 0.001 for linear trend | | |
| | P = 0.012 for linear trend[c] | | | P = 0.014 for linear trend[c] | | | P < 0.001 for linear trend[c] | | |
| | | 363 Events | | | 137 Deaths | | | 489 Deaths | |
| *Follow-up time from 5 years after baseline to outcome events* | | | | | | | | | |
| <26.9, <8.3 METs | 1.00 (reference) | | 62 | 1.00 (reference) | | 35 | 1.00 (reference) | | 240 |
| 26.9–33.2, 8.3–9.5 METs | 0.90 (0.71–1.16)[a] | 0.421 | 45 | 0.83 (0.56–1.23)[a] | 0.354 | 19 | 0.62 (0.51–0.76)[a] | <0.001 | 156 |
| | 0.90 (0.70–1.16)[b] | 0.415 | | 0.88 (0.59–1.31)[b] | 0.524 | | 0.67 (0.54–0.82)[b] | <0.001 | |
| >33.2, >9.5 METs | 0.77 (0.59–1.00)[a] | 0.053 | 35 | 0.62 (0.40–0.96)[a] | 0.033 | 13 | 0.38 (0.30–0.49)[a] | <0.001 | 93 |
| | 0.79 (0.59–1.05)[b] | 0.100 | | 0.72 (0.45–1.15)[b] | 0.165 | | 0.46 (0.35–0.59)[b] | <0.001 | |
| | P = 0.029 for linear trend | | | P = 0.007 for linear trend | | | P < 0.001 for linear trend | | |
| | P = 0.092 for linear trend[c] | | | P = 0.043 for linear trend[c] | | | P < 0.001 for linear trend[c] | | |

a Model 1: RRs are adjusted for age and examination year.
b Model 2: RRs are further adjusted for age and examination year, cigarette smoking, alcohol consumption, waist-to-hip ratio, SES and total caloric, fibre and fat intake.
c P for linear trend across the tertiles of maximal oxygen uptake from adjusted Cox model.

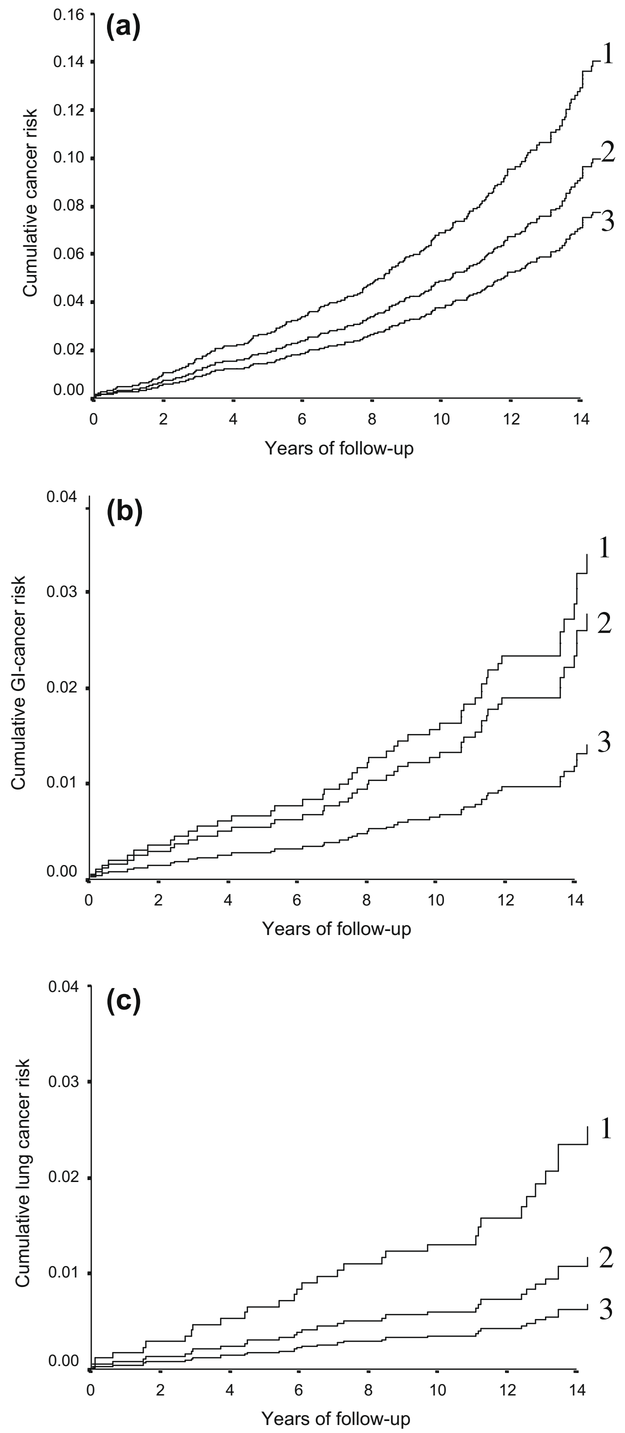


**Fig. 1 – Multivariable-adjusted cumulative overall cancer (a), GI-cancer (b) and lung cancer (c) incidence during an average follow-up of 12 years in men according to tertiles of maximal oxygen uptake (1st group < 26.9 mL/kg/min, 2nd group = 26.9–33.2 mL/kg/min and 3rd group > 33.2 mL/kg/min).**

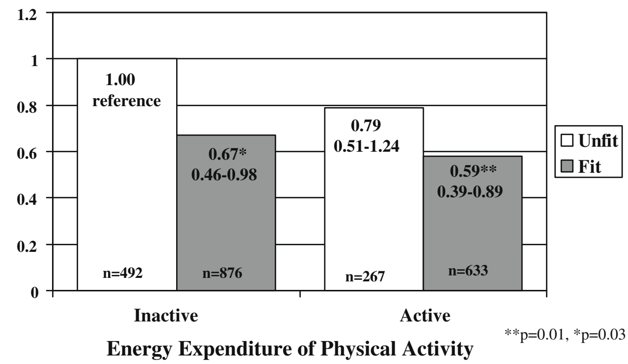


**Fig. 2 – The multivariate-adjusted (age, examination year, cigarette smoking, alcohol consumption, waist-to-hip ratio, SES and total caloric, fibre and fat intake) relative risks of cancer during an average of 12 years of follow-up in 2268 men classified according to maximal oxygen uptake and the energy expenditure of total physical activity. Unfit men included those with maximal oxygen uptake less than 26.9 mL/kg/min and fit men included those with maximal oxygen uptake of at least 26.9 mL/kg/min. Active = energy expenditure of physical activity over 2500 kcal/week and inactive = energy expenditure of physical activity over 2500 kcal/week.**

0.33–0.54, $p < 0.001$) among men with the highest $VO_{2max}$ (>33.2 mL/kg/min). Some of the relative risks presented in Table 3 are not significant after full adjustment.

In order to reduce selection bias due to ill health the association between $VO_{2max}$ and cancer risk was estimated excluding cancer cases that occurred during the first 5 years of follow-up (Table 3). In this restricted analysis, $VO_{2max}$ was related to a decreased age-adjusted risk of cancer and overall mortality after exclusion. Cumulative curves for the incidence of GI-tract, lung and overall cancers according to three groups of $VO_{2max}$ are presented in Fig. 1.

### 3.5. *Physical fitness, physical activity, and cancer risk*

The total energy expenditure of physical activity of over 2500 kcal/week among fit men was related to an additional risk reduction. The multivariate-adjusted risks were 0.82 (95% CI 0.67–1.03) for any cancer, 0.51 (95% CI 0.26–0.99) for lung cancer, 0.61 (95% CI 0.39–0.96) for GI-tract cancers and 0.61 (95% CI 0.43–0.86) for cancer death in fit men ($VO_{2max} \geqslant 26.9$ mL/kg/min) with moderate intensity (>4 METs) of physical activity ($n = 1026$) than in all other counterparts. Fig. 2 shows the multivariate-adjusted relative risks of cancer during an average of 12 years of follow-up in 2268 men classified according to maximal oxygen uptake and the energy expenditure of total physical activity. Fit men who accumulated over 2 h of physical activities weekly also had a 16% and a 26% reduced risk of non-fatal and fatal cancer events, after adjustment for age and examination year and confounders. The frequency of physical activity was not independently related to the risk of cancer showing that frequency was a less important component of physical activity for reducing cancer risk.

### 3.6. *The combination of protective lifestyle factors and cancer risk*

A total of 290 (12.8%) active (energy expenditure >2500 kcal/week and physical activity duration >2 h/week) men with a healthy lifestyle ($VO_{2max} \geqslant 26.9$ mL/kg/min, energy intake

>108.6 kJ/kg/week; lowest tertile, non-smoking) had markedly reduced (RR = 0.63, 95% CI 0.46–0.87) risk of cancer incidence than all other study participants, after adjustment for age examination year, alcohol consumption, SES, waist-to-hip ratio and fibre and fat intake. Among men with a combination of favourable lifestyle factors no lung cancer occurred and only one rectal cancer event occurred. A total of 362 (16.0%) men with the above-mentioned protective lifestyle factors combined with moderate-intensity physical activity expending of over 2500 kcal/week had a decreased (RR = 0.71, 95% CI 0.52–0.96) risk of cancer incidence, after adjustment for confounders.

## 4. Discussion

This prospective population-based study shows that good cardiorespiratory fitness including active lifestyle and reasonable high dietary energy intake may be vital modifiable factors that help in decreasing cancer risk in middle-aged men. The combination of the favourable lifestyle factors provides maximal protection against the risk of cancer. In our study, $VO_{2max}$ has an inverse dose-response association with cancer incidence and death through its whole range.

On the basis of previous studies energy expenditure from physical activity has been inversely associated with overall incidence of cancer and cancer mortality.[14] It is suggested that the total energy expenditure of physical activity is more important than the type, duration, frequency or intensity of physical activity with respect to reduced mortality.[31] In the Multiple Risk Factor Intervention Trial[30] moderate amounts of total leisure-time physical activity (energy expenditure of 1000–2300 kcal/week) were sufficient to reduce overall mortality, but there was no further risk reduction at higher amounts of physical activity. In the Harvard Alumni Health Study,[29] subjects spending 500–3500 kcal in total leisure-time physical activity per week had decreased overall mortality but above this level the all-cause death rates became relatively stable. The risk reduction in active men is not only due to reduced risk of CVDs,[29,30,40] but it may also be partly due to decreased risk of death from cancer. Consistent with our previous study,[34] the strong risk reduction for overall morality among fit men is likely due to reduced risk for both cancer and CVD mortality. Our finding that 1-MET increase in exercise capacity was related to a 6–20% decreased risk of overall, GI-tract and lung cancers is similar to that reported in previous studies.[33,46]

There was an inverse association between cardiorespiratory fitness and lung and GI-cancers, although no independent relation between fitness and prostate cancer was observed in our study. Advancing age and serum fatty acids were related to the increased prostate cancer risk, and they may be important contributing factors in the association between fitness and prostate cancer.[1,18,19] Our results show that fit men expending $\geqslant$1000 kcal and spending $\geqslant$2 h by performing moderate-intensity physical activity weekly have a slightly reduced cancer risk, but a higher amount of energy expenditure may provide further risk reduction. In few previous studies, moderate to high amounts of physical activity have been related to decreased risk of the lung,[15–17] breast[22] and colon[11,12,14,47] cancers and some other site-specific cancers such as prostate[8,19] and kidney[48] cancers. However, rather convincing evidence exists only for an association between physical activity and colon and breast cancers with the relationship to other site-specific cancers being not clear.[8,28] Cardiorespiratory fitness has been related inversely to mortality from cancer of combined sites,[33] both smoking- and non-smoking-related cancers and prostate cancer incidence.[20] In Aerobics Center Longitudinal Study, on the other hand, there was no independent association between physical activity and prostate cancer incidence or mortality in the US physician,[49] Harvard Alumni[50] and Health professional[51] studies, which is consistent with our recent findings based on cardiorespiratory fitness and prostate cancer. We did not take into account professional energy expenditure in the present study.

Some underlying non-specific mechanisms during the initiation or later stages of cancer development have been proposed. First, physical activity and good cardiorespiratory fitness may help to block initiators of cancer if exercise has been performed regularly at a relatively young age.[7,43] Second, physical activity may counter promoters of cancer cell replication, so that regular exercise and good cardiorespiratory fitness when combined with optimal diet during later stages of the neoplastic process may be vital in decreasing or preventing the development of clinically significant disease.[43,44] Therefore, physical inactivity during the lifespan may be a key factor in the initiation of cancer development. It is possible that exercise training can improve functioning of the immune system including monocytes, macrophages and natural killer (NK) cells that are thought to be the primary line of defence against the development of malignancies. Some studies have shown high NK cell activity at rest after a period of exercise training.[52–54] Regular physical exercise has been found to improve the decreased antioxidant defence that occurs normally with ageing. Our results show that reasonable energy intake among fit men who had active lifestyle may have decreased GI-cancers risk. This indicates that energy balance, which includes body mass, energy intake and energy expenditure, is importantly related to GI-tract cancers, especially to colon cancer.[14,59] Exercise increases gut motility and prostaglandins levels that decrease the gastro-intestinal transit time thereby reducing the contact time between faecal carcinogenesis and the colonic mucosa and hence allow less opportunity for initiation of carcinogenesis, colonic cell division and proliferation.[7,11–14,43,45,60] Additionally, it has been observed that exercise may decrease the risk of colon and prostate cancers through its impact on insulin metabolism.[58,61] Insulin is a growth factor for tumour cells. Factors such as sedentary lifestyle, abdominal obesity and diets rich in refined sugar increase insulin resistance and decrease production of insulin-like growth factor binding globulins which may increase the risk of colon and prostate cancers.[28,55–57] Furthermore, high intake of saturated fat has been associated with increased prostate and colon cancers,[58] thus, it is possible that aerobic exercise alters the metabolism of fat by increasing the utilisation of free fatty acids and by decreasing hyperinsulinaemia.

Protection against lung cancer related to cardiorespiratory fitness is likely to be due to non-smoking lifestyle because smoking is also related to reduced physical fitness.[17] Good cardiorespiratory fitness may be related to lung function and may also help in the prevention of lung cancer through an independent pathway. On the other hand, cardiorespiratory fitness and exercise increase the functional capacity of the lungs and their antioxidant enzyme activities and decrease concentrations of possible carcinogenesis, and may thereby decrease the risk of lung cancer.[8,15,16] Furthermore, smoking is inter-related with unfavourable lifestyle such as increased alcohol consumption, unhealthy diet and sedentary lifestyle.[7,8] Therefore, one explanation for our main results is that fit men also have a good dietary habit with non-smoking lifestyle. Cardiorespiratory fitness has been related to several factors, such as age, gender, heredity, prevalent cardiovascular disease, use of medications, quantity and quality of physical activity, cigarette smoking, obesity and nutrition.[62] One of the possible explanations for the differences between unfit and fit men may be genetic predisposition.[63] Furthermore, maximal oxygen uptake ($VO_{2max}$) is an accurate measurement of the functional capacity of the cardiovascular system.

To our knowledge, this is the first population-based study on physical fitness with reliable measure of $VO_{2max}$ and cancer risk. Strengths of the study include the measurement of $VO_{2max}$ which is not dependent on the type of exercise. Second, we have reliable data on mortality because deaths were ascertained by Finnish National Death and Cancer Registry using personal identification codes, supplemented with reliable data on health status, physical activity, nutritional measurements and alcohol consumption. It is impossible to know whether cardiorespiratory fitness decreased or increased during follow-up because of the probable changes in the exercise and other health habits of the subjects. It is difficult to distinguish an increased risk of cancer or death due to a low level of cardiorespiratory fitness from an increased risk because of prevalent asymptomatic or preexisting heart or lung disease. The exclusion of the first 5 years of follow-up did not substantially change the results.

In conclusion, the present study supports the latest recommendations on physical activity and health outcomes that moderate amount of physical activity and good cardiorespiratory fitness decrease the risk of cancer. A healthy lifestyle including good dietary habits with an active lifestyle considerably reduces the risk of cancer in middle-aged men.

## Financial disclosures

None reported.

## Conflict of interest statement

None declared.

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