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Combined Impact of Lifestyle Factors on Cancer Mortality in Men

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Abstract

PURPOSE—The impact of lifestyle factors on cancer mortality in the U.S. population has not been thoroughly explored. We examined the combined effects of cardiorespiratory fitness, never smoking, and normal waist girth on total cancer mortality in men.

METHODS—We followed a total of 24,731 men ages 20–82 years who participated in the Aerobics Center Longitudinal Study. A low-risk profile was defined as never smoking, moderate or high fitness, and normal waist girth, and they were further categorized as having 0, 1, 2, or 3 combined low-risk factors.

RESULTS—During an average of 14.5 years of follow-up, there were a total of 384 cancer deaths. After adjustment for age, examination year, and multiple risk factors, men who were physically fit, never smoked, and had a normal waist girth had a 62% lower risk of total cancer mortality (95% confidence interval [CI], 45%-73%) compared with men with zero low-risk factors. Men with all 3 low-risk factors had a 12-year (95% CI: 8.6–14.6) longer life expectancy compared with men with 0 low-risk factors. Approximately 37% (95% CI, 17%-52%) of total cancer deaths might have been avoided if the men had maintained all three low-risk factors.

CONCLUSIONS—Being physically fit, never smoking, and maintaining a normal waist girth is associated with lower risk of total cancer mortality in men.

Keywords

Cardiorespiratory Fitness; Smoking; Waist Girth; Cancer Mortality

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Conflict of Interest: none

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INTRODUCTION

Cancer is the leading cause of death in the United States (US) for people under age 80 years (1). The lifetime risk of developing cancer in US men and women are 45% and 38%, respectively (1). Approximately 1.5 million US adults are diagnosed with cancer each year (2). Of these, about 38% are fatal (2). Effective treatments for most common cancers that are detected based on clinical symptoms are limited; and estimated 5-year survival rates for these late-stage cancers are low (2,3). Therefore, primary prevention is imperative to reduce the burden of these diseases.

Maintaining healthy lifestyles is the most important primary prevention strategy for most cancers (2,3). Tobacco use, poor diet, and physical inactivity are the leading causes of mortality in US (4), and these lifestyle factors also account for about 70% of cancer incidence and mortality (5). In fact, cigarette smoking, physical inactivity, and obesity are key modifiable risk factors associated with most common cancers (5–8). Few studies have shown that healthy lifestyle factors are associated with a lower risk of total cancer mortality in European middle-aged and elderly populations (9–11), and there has been little research on the association between lifestyle factors and cancer mortality in US men. Notably, the prevalence of healthy lifestyle behaviors among US cancer survivors is low as 5% (12). To address cancer prevention strategies, it is important to investigate the magnitude of single and combined effects of lifestyle factors on cancer mortality. We therefore investigated the combined effects of cardiorespiratory fitness, never smoking, and normal waist girth on total cancer mortality in men from the Aerobics Center Longitudinal Study (ACLS).

METHODS

Study Population

The ACLS is a prospective cohort study to investigate factors influencing chronic disease morbidity and mortality. All participants came to the clinic for periodic preventive medical examinations (volunteers) and for counseling regarding health and lifestyle behaviors, including diet and physical activity. The clinic has a marketing department that does broad marketing of clinic services via mass media and among occupational groups. The Cooper Clinic serves anyone who elects to come for an examination and patients come from all 50 states. The current study population comprises 24,731 men, ages 20 to 82 years, who completed a baseline medical examination at the Cooper Clinic, Dallas, Texas, during 1972 to 2001. Participants were mostly non-Hispanic whites (>95%) of middle to high socioeconomic status. The study design and examination techniques have been reported previously (13,14). All participants completed a maximal treadmill exercise test and self-reported health habits at baseline and achieved at least 85% of their age-predicted maximal heart rate (220 minus age in years) during the treadmill test. We excluded those with a personal history of cancer, myocardial infarction, stroke, or an abnormal resting or exercise ECG at baseline; and those missing baseline waist girth or other covariate values. All participants gave their informed written consent for the medical evaluation and subsequent registration in the follow-up study. The study protocol was reviewed and approved annually by Institutional Review Board at The Cooper Institute.

Clinical Measurements

The medical evaluation, performed after an overnight fast of at least 12 hours, included a physical examination, anthropometry, electrocardiogram, blood chemistry analyses, blood pressure assessment, a maximal exercise treadmill test, self-report of health habits, and demographic characteristics. Body weight and height were measured with a standard physician’s scale and stadiometer, and body mass index (BMI) was calculated as weight in

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kilograms divided by height in meters squared (kg/m^2). Resting blood pressure was measured in a seated position by ausculatory methods with a mercury sphygmomanometer. Blood samples were drawn from an antecubital vein and were analyzed by automated bioassays at the Cooper Clinic Laboratory, which meets quality control standards of the US Centers for Disease Control and Prevention Lipid Standardization Program. Details of the clinical evaluation procedures have been published previously (14).

Assessment of Lifestyle Factors and Other Factors

Smoking habits, alcohol use, and family history of cancer (either parent died of cancer) were assessed with a self-report on a personal and family medical history questionnaire. Smoking status was classified as never, former, or current. Ever smokers included former or current smokers. Current smokers were further classified as smoking fewer than 20, 20 to fewer than 40, and 40 or more cigarettes per day. Alcohol consumption was classified as a continuous variable (ethanol intake, g/day) and further categorized as moderate (14 to <28 g/day) or non-moderate alcohol intake. Waist girth was measured at the level of the umbilicus with a plastic tape measure. A normal waist girth was defined as waist girth less than 94 cm (15). Cardiorespiratory fitness was measured by a maximal treadmill exercise test as described previously (13,14). Total treadmill endurance time (minutes) was used as an index of aerobic power, with time on treadmill in this protocol correlated highly ($r = 0.92$) with maximal oxygen uptake (VO_2max) (16). Age-specific distributions of treadmill exercise duration were created within the following age groups: 20 to 39 years, 40 to 49 years, 50 to 59 years, and 60 or older. All participants were classified into low, moderate, or high physical fitness groups based on age-specific treadmill time percentiles of the entire ACLS cohort (low = least-fit 20%; moderate = next 40%; high = most-fit 40%) to maintain consistency in our study methods and because a widely accepted clinical categorization of physical fitness does not exist. The detailed cutoff points have been published previously (17). We defined a low-risk profile as moderate or high fitness, never smoking, and normal waist girth. We combined these low-risk factors and categorized participants as having 0, 1, 2, or 3 low-risk factors.

Ascertainment of Cancer Mortality

We followed all participants from the baseline examination to the date of a cancer death or December 31, 2003 for censoring survivors. Cancer deaths were identified from the National Death Index and official death certificates. Causes of death were identified using International Classification of Diseases, 9^{th} Revision (ICD-9) codes before 1999, and International Statistical Classification of Diseases,10^{th} Revision (ICD-10) codes during 1999 to 2003 (in brackets) (cancer, 140–208 [C00-C97]).

Statistical Analysis

General linear models were used to test mean differences across categories representing the number of low-risk factors (i.e., 0, 1, 2, or 3) after adjustment for age. A χ^2 test was used to compare frequency differences across number of low-risk factors. Cox proportional hazards regression was used to examine the associations of single and combined number of low-risk factors with total cancer mortality in men (18). Hazard ratios (HRs) and 95% confidence intervals (CIs) in relation to low-risk factor groups for total cancer mortality were estimated after adjustment for age, examination year, alcohol intake, and family history of cancer. Men with zero low-risk factors constituted the reference category. Inspection of empirical cumulative hazards plots [log-log(survival function) versus log(time) across number of low-risk factors] indicated that the proportional hazards assumption was justified. We also estimated death rates per 10,000 person-years across the number of low-risk factors. Kaplan-Meier survival curves were constructed to compare probability of total cancer mortality across the number of low-risk factors. Population attributable fraction (PAF) was estimated

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for low cardiorespiratory fitness, ever smoking, and abdominal obesity (action level I) (15,19). PAF was computed as $1\text{-}\Sigma\ (pd_i/HR_i)$, where pd_i is the proportion of total cancers in the i^{th} exposure category (i = 0,1,2,3 low-risk factors) and HR_i is the hazard ratio (multivariable adjusted) for the i^{th} exposure category (19). Cancer survival differences between 0 compared with 3 combined low-risk factors were estimated using the risk advancement period approach (20). All statistical analyses were performed using Statistical Analysis Systems software (SAS Institute, Cary, North Carolina) and STATA statistical software (StataCorp, College Station, Texas).

RESULTS

As Table 1 shows, the mean scores of BMI, waist girth, ethanol intake, and fasting glucose level, and the prevalence of total cancer deaths and family history of cancer were progressively lower with increasing number of low-risk factors (all p <0.001). As expected, the mean score of aerobic power [METS: 1 MET = VO_2 (3.5 ml kg^{-1} min^{-1})] and the prevalence of never smoking were higher with increasing number of low-risk factors (all p <0.001) (Table 1).

We also estimated HRs of total cancer mortality by single low-risk factors. After adjustment for age, examination year, alcohol intake, and family history of cancer, the HRs (95% CI) of total cancer mortality for moderate or high fitness, never smoking, and normal waist girth were 0.73 (0.58–0.93), 0.67 (0.54–0.84), and 0.75 (0.61–0.93), respectively (all p <0.01). Table 2 shows the association between the number of low-risk factors and death rates per 10,000-person years, and total cancer mortality in men. After adjustment for age, examination year, and multiple risk factors, there was an inverse association between the number of low-risk factors and total cancer mortality (p for trend <0.001). Men who were physically fit, never smoked, and had a normal waist girth had a 62% lower risk of total cancer mortality (95% CI, 45%-73%) compared with men with zero low-risk factors. The Kaplan-Meier survival curves also indicate that men with 3 combined low-risk factors had greater cancer event-free time compared with men with 0 low-risk factors (Fig. 1).

The total cancer mortality in this population might have been reduced by 37% (95% CI, 17%-52%) if all men had been physically fit, never smoked, and had a normal waist girth (Table 3). Men with 0 versus 3 low-risk factors had 2.6 times (95% CI, 1.83–3.78) the risk of total cancer mortality, which was equivalent to a shorter life expectancy of 12 years (95% CI, 8.6–14.6) for total cancer mortality.

In supplemental analyses, we examined the association between lifestyle factors and most common cancer mortality (top 10 leading cancer deaths) in men (n = 244 deaths) (i.e., lung & bronchus, colon & rectum, prostate, stomach, liver, pancreas, urinary bladder, esophagus, leukemia, and kidney) (13). After adjustment for multiple risk factors, the relative risks (95% CI) across 0, 1, 2, and 3 combined low-risk factors were: 1.00 (reference), 0.70 (0.50, 0.98), 0.42 (0.30, 0.60), and 0.27 (0.17, 0.44) (p for trend <0.001). Men who were physically fit, never smoked, and with a normal waist girth had a 73% (95% CI, 56%-83%) lower risk of most common cancer mortality compared with men with zero low-risk factors. Approximately 51% (95% CI, 27%-65%) of the most common cancer deaths might have been avoided if the men had maintained these 3 low-risk factors.

DISCUSSION

The combined health benefits of moderate to high cardiorespiratory fitness, never smoking, and normal waist girth on cancer mortality in US men has not been thoroughly explored. Our major finding was that men who were physically fit, never smoked, and with a normal

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waist girth had a 62% lower risk of total cancer mortality, over 14.5 years, compared with men with none of these low-risk factors. This finding is consistent in direction with the European Prospective Investigation Into Cancer and Nutrition (EPIC)-Potsdam Study (9), the EPIC-Norfolk Prospective Population Study (10), and the Healthy Ageing Longitudinal Study (HALE) (11). According to the EPIC-Potsdam Study, German men and women who engaged in exercise (>3.5 h/wk), never smoked, had a healthy diet (high intake of fruits, vegetables, and whole-grain bread and low meat consumption), and maintained a BMI <30 kg/m^2 had a 36% lower risk of total cancer mortality compared with men and women without these lifestyle factors (9). The EPIC-Norfolk Prospective Population Study also showed that British men and women who maintained a healthy lifestyle (i.e., physically active, not smoking, moderate alcohol intake, and fruit and vegetable intake) had a 60% lower risk of total cancer mortality compared with their counterparts who did not maintain these behaviors (10). Another study with elderly participants also showed that Dutch men and women who engaged in healthy lifestyle choices (i.e., Mediterranean diet, moderate alcohol use, physically active, and nonsmoking) had a 69% lower risk of total cancer mortality compared with men and women without these lifestyle choices (11).

Our findings indicate a dose-response relationship between a greater number of low-risk factors and cancer mortality risks. Men with 1, 2, or 3 combined low-risk factors had a 29% (95% CI, 7%-46%), a 49% (95% CI, 33%-62%), or a 62% (95% CI, 45%-73%) lower risk of total cancer mortality, respectively, compared with men having 0 low-risk factors. There are several plausible ways by which an increasing number of low-risk factors might reduce carcinogenesis. Cigarette smoking contains at least 50 carcinogens, and a lifetime of not smoking would lead to substantially less exposure to tobacco carcinogens by reducing smoking-related cancers (i.e., lung & bronchus, esophagus, pancreas, bladder, kidney, trachea, larynx, oral cavity, etc) (5). Abdominal obesity is largely due to unhealthy diet and physical inactivity. Maintaining normal waist girth by healthy diet and physical activity may reduce adiposity-related cancers (i.e., colon & rectum, prostate, liver, pancreas, bladder, kidney, esophagus, breast, endothelium, etc) by lowering insulin level, insulin-like growth factor (IFG-1) level, steroid hormone level, and chronic inflammation (i.e., TNF-α, IL-6) that are believed to contribute to tumor formation and progression (21,22). Regular physical activity also enhances immune and antioxidant defense systems, natural killer and cytotoxic activity of T cells, DNA repair systems, and decreases leukocyte count and testosterone level and colonic exposure to carcinogens in the fecal stream, all of which may contribute to reducing inactivity-related cancers (i.e., lung & bronchus, colon & rectum, prostate, stomach, pancreas, esophagus, leukemia, breast, endothelium, ovary, testicle, etc)) (21,23–25). Overall, a combination of these lifestyle factors may contribute to reducing most common cancer and total cancer events.

In our study, approximately 37% of total cancer deaths might have been avoided if the men had maintained these 3 low-risk factors. The Dutch elderly study showed that about 60% of total cancer deaths might have been eliminated if their cohort had adhered to 4 healthy lifestyle choices including moderate alcohol intake, healthy diet, regular exercise, and not smoking (11). Interestingly, our data did not show statistical significance of moderate alcohol intake ($p = 0.78$) in the fully adjusted model. Thus, we did not include moderate alcohol intake as a low-risk factor in our study. It has been reported that moderate alcohol intake lowers coronary heart disease risk, but it still has a potential link to alcohol abuse which may elevate the risk of cancer mortality (26). Some investigators also have reported that alcohol intake is associated with carcinogenesis by activating the NF-κB proinflammatory pathway and generating free radicals when it is metabolized (27). Thus, any public health recommendations of moderate alcohol intake will require more careful consideration.

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Our findings also indicate that men with 3 low-risk factors had a 12-year longer life expectancy (total cancer mortality) compared with men with none of these low-risk factors. A strength of this study is the large, well-characterized cohort of men who had received an extensive clinical examination at baseline including objective laboratory data on several exposures and confounders. This study also used standardized maximal exercise testing to quantify an objective measurement of fitness. We believe this is the first study to estimate the combined health benefits of cardiorespiratory fitness, never smoking, and normal waist girth on total cancer mortality, PAF, and longevity. One of the limitations of our study is that we were not able to adjust for dietary habits due to insufficient data (e.g., anti-inflammatory or antioxidant foods). Also, our study is limited to white men at middle and upper socioeconomic levels. Moreover, we did not measure cancer incidence; thus, the casual relation of lifestyle factors and cancer events may be limited. Finally, we were unable to detect changes in the exposure measures during follow-up. Further studies are needed to confirm our findings across different race and sex groups and with more frequent follow-up.

Approximately 12 million people worldwide develop cancer each year. Of these, about 7.6 million are fatal (3). Western patterns of diet, tobacco use, and sedentary behaviors are significant risk factors for the most common cancers in developed countries and rates of these cancers are increasing rapidly in many developing countries (3,28). To address cancer prevention strategies, it is important to increase the proportion of people who are in the low-risk portion of high-risk populations. Doing so with respect to the three risk factors on which we have focused is a key to cancer prevention. In conclusion, we found that the combination of being fit, never smoking, and having a normal waist girth are associated with much lower risk of total cancer mortality in men. The effect of having these three low-risk factors to prevent cancer is impressive for both longevity and PAF. Public health agencies and clinicians should emphasize the importance of developing these healthy lifestyle factors across the lifespan.

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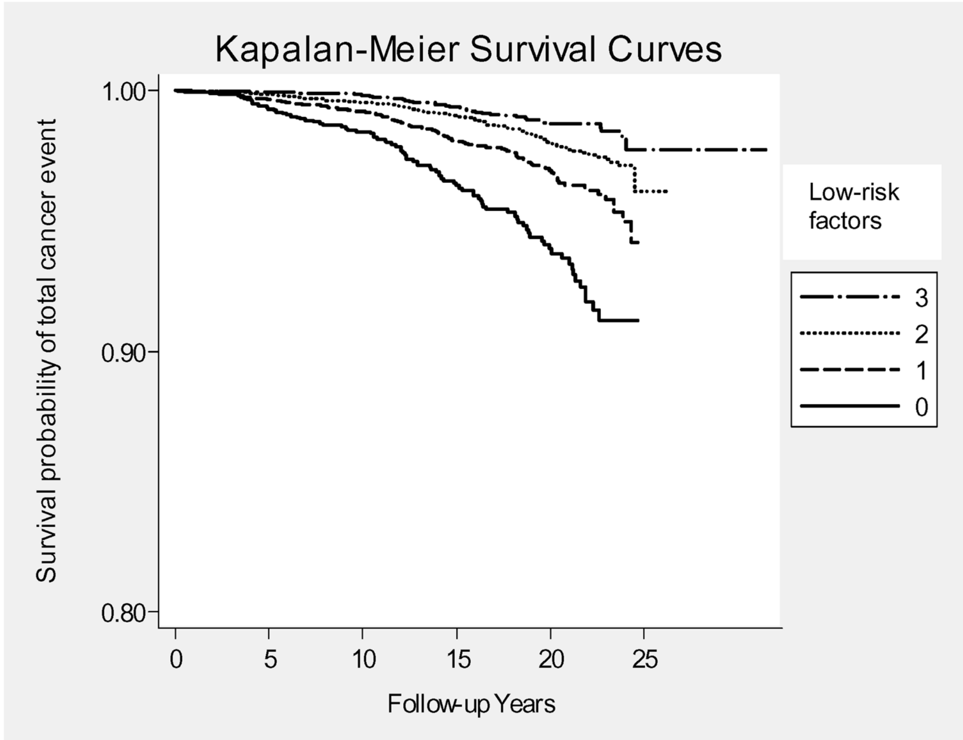

Figure 1.
Kaplan-Meier survival curves for total cancer mortality by number of low-risk factors. A low-risk profile was classified as moderate or high fitness, never smoking, and normal waist girth, and further categorized as 0, 1, 2, and 3 combined low-risk factors.