Journal of Science and Medicine in Sport 22 (2019) 403–407

Contents lists available at ScienceDirect

Journal of Science and Medicine in Sport

journal homepage: www.elsevier.com/locate/jsams

Original research

Cardiorespiratory fitness, incidence and mortality of lung cancer in men: A prospective cohort study

Baruch Vainshelboim [a,b,*,1], Ricardo M. Lima [b,c], Elisabeth Edvardsen [d], Jonathan Myers [b]

[a] Master of Cancer Care Program, School of Health Sciences, Saint Francis University, United States
[b] Cardiology Division, Veterans Affairs Palo Alto Health Care System/Stanford University, United States
[c] Faculty of Physical Education, University of Brasília, Brazil
[d] Department of Pulmonary Medicine, Oslo University Hospital/Department of Sports Medicine, Norwegian School of Sport Sciences, Norway

ARTICLE INFO

Article history:
Received 5 August 2018
Received in revised form 2 October 2018
Accepted 8 October 2018
Available online 19 October 2018

Keywords:
Exercise testing
Exercise capacity
Cancer incidence
Cancer mortality

ABSTRACT

Objectives: To evaluate the association between cardiorespiratory fitness (CRF), lung cancer incidence and cancer mortality in men.
Design: Prospective cohort study.
Methods: Maximal exercise testing was performed in 4920 men (59.2 ± 11.4 years) free from malignancy at baseline. Multivariate Cox hazard models adjusted for established cancer risk factors including smoking were analyzed for lung cancer incidence and cancer mortality among those who were diagnosed with lung cancer. Population attributable risks (PAR) of low CRF (<5 METs) were determined.
Results: During 12.7 ± 7.5 years follow-up, 105 (2.1%) participants were diagnosed with lung cancer and 83 (79%) of those died from cancer after 3.6 ± 4.6 years from diagnosis. CRF was inversely and independently associated with cancer outcomes. A 1-MET increase and categories of moderate and high CRF were associated with 10%, 47% and 65% reduction in lung cancer incidence ($p = 0.002$), and 13%, 58% and 76% reduction in cancer mortality ($p = 0.002$), respectively. Also, individuals who were diagnosed with lung cancer and were at moderate or high CRF categories at baseline exhibited longer survival time ($p < 0.001$). The PARs% for lung cancer incidence and cancer mortality were 8.7% and 18.5%, respectively.
Conclusions: Higher CRF is associated with lower lung cancer incidence in men. Among individuals who were diagnosed with lung cancer, higher CRF was associated with reduced cancer mortality and longer survival time. These results support the protective benefits of higher CRF in the prevention of lung cancer outcomes. Eliminating low CRF as a risk factor would potentially prevent considerable lung cancer morbidity and mortality.

1. Introduction

Worldwide, lung cancer remains the most frequent cancer with over 2 million new cases and 1.8 million lung cancer related deaths.[1,2] In the US, lung cancer is the second most common cancer in both men and women and a leading cause of cancer related death.[3] Lung cancer is one of the most aggressive cancers in humans, with a 5-year survival of only 10%-17%.[1,3] Tobacco use is the single most important risk factor for lung cancer and it's responsible for approximately 80% of lung cancer mortality and 22%-30% of total cancer mortality.[1–3] Despite the fact that smoking increases the risk for lung cancer about 25-fold, the majority of cigarette smokers do not develop lung cancer and thus there may be other factors besides smoking that modify the risk.[3,4]

Mounting evidence has firmly established that low cardiorespiratory fitness (CRF) is an important risk factor for the incidence of many chronic conditions as well as all-cause and cardiovascular mortality.[5,6] A recent meta-analysis demonstrated that higher CRF levels are associated with reduced risk for cancer-related mortality.[7] Several reports have also demonstrated the preventive role of CRF in lung cancer with an overall reduced incidence and mortality among individuals with comparatively higher CRF.[4,10,11] However, a significant gap exists with respect to the association between CRF at pre-lung cancer diagnosis and cancer mortality among those prospectively diagnosed with lung cancer. Given the low survival rate of patients with lung cancer,[3,14] investigation of the preventive value of CRF on lung cancer outcomes clearly has important public health implications. The current study aimed to evaluate the association between CRF, lung cancer incidence and

* Corresponding author.
E-mail address: baruch.v1981@gmail.com (B. Vainshelboim).
[1] Institution where the study was conducted.

https://doi.org/10.1016/j.jsams.2018.10.002
1440-2440/

cancer mortality among men diagnosed with lung cancer. An additional aim was to quantify the potential public health impact on lung cancer outcomes by removing low CRF as a risk factor.

2. Materials and methods

The Veterans Exercise Testing Study (VETS) has been previously described.[15,16] In brief, the VETS cohort is an ongoing, prospective evaluation of Veteran participants (aged 21-89 years) referred for exercise testing for clinical reasons, designed to address exercise test, clinical, and lifestyle factors and their association with health outcomes. The study was approved by the Institutional Review Board at Stanford University, CA, USA. All participants who underwent a maximal treadmill exercise test at the Veterans Affairs Palo Alto Health Care System between 1987 and 2012 were considered for inclusion. Clinical information on diagnoses, risk factors and health behaviors (smoking, alcohol and drug abuse) were collected at the time of the exercise test using the Veterans Affairs Computerized Patient Record System (CPRS) and self-report health history. Standard criteria to determine hypertension (The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure) and dyslipidemia (The Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults) were used.[17] The database of 5540 Veterans who completed the baseline treadmill test was screened and 620 participants were excluded; women (n = 352), those having history of malignancy at baseline (n = 76) and incomplete or prematurely terminated exercise tests (n = 192). A total of 4920 male veterans were included in the analysis; the mean follow-up was 12.7 ± 7.5 years. During the follow-up period, participants who were diagnosed with lung cancer were also followed for a mean of 3.6 ± 4.6 years from diagnosis.

Participants underwent maximal sign or symptom-limited exercise tests using an individualized ramp treadmill protocol according established guidelines.[17] The exercise protocol included continuous, individualized increments in treadmill speed and grade adjusted to achieve a targeted duration between 8 and 12 min as previously recommended. A 12-lead electrocardiogram, heart rate, blood pressure and Borg 6-20 perceived exertion rating were continuously recorded throughout the tests. Standard criteria for test termination were used. Participants were exercised to volitional fatigue in the absence of a clinical indication for stopping, and Borg scale >17 was used to verify maximal effort.[17] CRF [in Metabolic Equivalents (METs)] was calculated from peak treadmill speed and grade utilizing well-established metabolic equations from the American College of Sports Medicine.[17] CRF was analyzed as a continuous as well as a categorical variable divided into 3 categories (Low CRF < 5METs, Moderate CRF 5–10 METs and High CRF > 10 METs).[6,10]

The Veterans Affairs CPRS was used for capturing cancer outcomes; lung cancer diagnosis in the total cohort and cancer-related mortality in those who were diagnosed with lung cancer. Previous reports have demonstrated that the Veterans Affairs death records are relatively complete compared to those from other sources, such as the Social Security Administration.[18] The Veterans Affairs records also have excellent agreement (kappa = 0.82–0.91) with state death records[19] and high sensitivity for incidence of several chronic conditions.[20,21] Lung cancer diagnosis and cancer mortality were verified using pathology reports and International Classification of Diseases ninth and tenth edition codes. Medical records were carefully reviewed by qualified medical personal who were otherwise blinded to treadmill test results and other study information. Cancer diagnosis and vital status for each patient were ascertained as of August 2015.

SPSS (IBM, Chicago, IL, USA) version 23 was used for statistical analyses. The significance level was set at $p < 0.05$. Demographic, clinical and physiological data of the participants are presented as mean ± SD. Categorical variables are presented in percentages. Comparisons between participants who were diagnosed with lung cancer and those who were free from lung cancer were performed using independent sample t-tests for continuous variables and Chi-Square tests for categorical variables. The continuous and categorical Cox proportional hazard models were adjusted for age, smoking status (never smokers, previous smokers and current smokers) history of alcohol and drug abuse, presence of any pulmonary disease, body mass index and physical activity status (active or inactive). In order to address the potential reverse causality bias, a secondary analysis was performed after excluding participants who had less than two years follow up. Population attributable risk (PAR) was calculated for low CRF (<5 METs) according to the equation: $P(RR\text{-}1)/1 + P(RR\text{-}1)^{*}100$,[22] where P = prevalence of the risk factor (low CRF) and RR = relative risk calculated from the adjusted Cox models.[23,24] Kaplan–Meier curves were constructed for CRF categories, lung cancer incidence and cancer mortality and the log-rank test was utilized for calculating mean survival time in those who were diagnosed with lung cancer.

3. Results

The study sample included a total of 4290 men, aged 59.2 ± 11.4 years. Clinical, demographic and physiological characteristics of the sample are presented in Table 1. Approximately 58% were Caucasian, 20.6% African-American, 8.7% Hispanic and 8.3% Asian. Approximately 12% had a history of cardiovascular disease, 6.4% had pulmonary disease and 14.1% had diagnosis of diabetes at baseline. Twenty nine percent were smokers at baseline and 34.1% had history of smoking. Mean CRF was 8.3 ± 3.5 METs. Participants who were diagnosed with lung cancer were older, had higher prevalence of current smoking habit, and exhibited lower CRF at baseline (Table 1).

During a mean 12.7 ± 7.5 years follow-up, 105 (2.1%) participants were diagnosed with lung cancer, and 83 (79%) of them died from cancer (Tables 1 and 2). Among those who developed lung cancer, CRF was assessed at baseline (7 ± 5.3 years prior to the diagnosis) and followed for a mean of 3.6 ± 4.6 years after diagnosis. CRF was inversely and independently associated with lung cancer incidence and cancer mortality when examined as either continuous or categorical models. Each 1-MET increase was associated with 10% reduction in lung cancer incidence in the total cohort [Hazard Ratio (HR) = 0.9 95%Confidence Interval (CI) (0.84–0.96), p = 0.002] and 13% reduction in cancer mortality in those who were diagnosed with lung cancer [HR = 0.87 95%CI (0.8–0.9), p = 0.002]. Categories of moderate and high CRF were associated with 47% and 65% reduction in lung cancer incidence (p trend = 0.002) in the total cohort, and 58% and 76% reduction in cancer mortality (p trend = 0.002) in those who were diagnosed with lung cancer, respectively. In individuals who diagnosed with lung cancer, mean survival time was significantly longer among those who exhibited moderate and high CRF levels ($p < 0.001$), when compared to those with low CRF levels (Table 2). After the exclusion of those with less than two years follow up, CRF was still a significant predictor of lung cancer incidence [HR = 0.92, 95%CI (0.86–0.99), p = 0.032] and cancer mortality in those who diagnosed with lung cancer [HR = 0.88, 95%CI (0.79–0.98), p = 0.021]. The PAR% for lung cancer incidence was 8.7% 95% CI (4.7–11.6), p = 0.001 and for cancer mortality was 18.5% 95% CI (10–23.4), p = 0.001. Kaplan–Meier curves confirmed the positive association between lower CRF and higher lung cancer incidence and cancer mortality (Fig. 1).

Table 1
Demographic and clinical characteristics of the study sample (n = 4,920).

Clinical history and demographics	All (n = 4920)	Free from lung cancer (n = 4815)	Diagnosed with lung cancer (n = 105)	P value
Age (years)	59.2 ± 11.4	57.9 ± 17.2	67.1 ± 18.5	<.001
Body mass index (kg/m^2)	27.6 ± 5.5	28.4 ± 5.1	27.3 ± 4.3	.026
Race				
Caucasian	57.9%	57.4%	81%	
African-American	20.6%	21%	1%	
Hispanic	8.7%	8.8%	2.9%	<.001
Asian	8.3%	8.2%	12.4%	
Other	4.5%	5.6%	2.7%	
Clinical history				
Family history of coronary artery disease	22%	22.1%	23.8	.680
Hypertension	50.4%	50.4%	53.3%	.547
Dyslipidemia	35%	34.5%	42.9%	.075
Obesity (body mass index ≥ 30)	33%	31.6%	23.3%	.072
Any cardiac diseases	11.5%	11.5%	10.5%	.743
Any pulmonary diseases	6.4%	6.1%	22.9%	<.001
History of alcohol abuse	2.4%	2.4%	1.9%	.748
History of drugs abuse	1.6%	1.6%	2.9%	.302
Diabetes	14.1%	14%	13.6%	.884
Never smokers	36.5%	37.3%	3.9%	
Current smokers	29.3%	28.8%	51.5%	<.001
Previous smoker	34.1%	33.9%	44.7%	
Pack/years	42.7 ± 29	42.7 ± 27	22.5 ± 17.7	.289
Cardiorespiratory fitness (METs)	8.3 ± 3.5	8.3 ± 3.5	7 ± 3.4	<.001
Medications				
Anti-hypertensive drugs	20.3%	20.3%	21%	.872
Anti-hyperlipidemias drug	8.4%	8.5%	6.7%	.510

Data presented as means ± standard deviation or % of the group for categorical variables.

Table 2
Hazard ratios of cardiorespiratory fitness and lung cancer outcomes.

Outcomes/ CRF categories	Number of events (n/%)	Low <5 METs	Moderate 5 to10 METs	High >10 METs	P trend	1-MET increase	P value
Lung cancer incidence in the total cohort (n = 4920)	105/2.1	4.2%	2%	1.3%	N/A	N/A	<.001
HR 95% (CI) for lung cancer incidence		1 (Reference)	0.53 (0.33–0.83)	0.35 (0.19–0.65)	.002	0.9 (0.84–0.96)	.002
Cancer mortality among those who diagnosed with lung cancer (n = 105)	83/79	97%	73%	61%	N/A	N/A	.004
HR 95% (CI) for cancer mortality		1 (Reference)	0.42 (0.24–0.74)	0.24 (0.12–0.62)	.002	0.87 (0.8–0.95)	.002
Mean survival time from baseline among those who diagnosed with lung cancer (years) (n = 105)		4.6 (3.3–6)	9.4 (7.5–11.2)	11.5 (8–14.9)	N/A	N/A	<.001
Prevalence		16.6%	55.1%	28.3%			

CRF; cardiorespiratory fitness, CI; confidence interval, HR; hazard ratio, MET; metabolic equivalent. N/A: not applicable, all hazard models were adjusted for age, smoking status, history of drug and alcohol abuse, presence of pulmonary disease, body mass index and physical activity status.

4. Discussion

The current study aimed to evaluate the association between CRF and lung cancer incidence in the total cohort as well as the association between CRF and cancer mortality in men who were diagnosed with lung cancer. In addition, we sought to evaluate the potential public health implications of low CRF as a modifiable risk factor for the prevention of lung cancer-related outcomes. The salient findings indicate that CRF is inversely and independent of other cancer-related risk factors, associated with lung cancer incidence and cancer mortality. Participants diagnosed with lung cancer who had moderate or high CRF levels at baseline exhibited a longer survival time compared to those with low CRF. In addition, the results suggest that by eliminating the risk factor of low CRF, 8.7% of lung cancer incidence and 18.5% of cancer mortality in those diagnosed with lung cancer could potentially be prevented (Table 2). Given that lung cancer is one of the most prevalent cancers with a 5-year survival of only 10%–17%,[1,3] the current findings have important public health implication for primary and secondary prevention of lung cancer. In particular, screening, early detection and treating low CRF could be a potentially important strategy for prevention programs, which aligns with the recent recommendation of the American Heart Association to adopt CRF as a vital sign.[6] While these observations do not indicate causality, they suggest that by reducing the prevalence of low CRF, substantial lung cancer morbidity and mortality and its associated economic burden could potentially be lessened.

The current results are consistent with previous reports generally showing an inverse association between CRF, lung cancer incidence and cancer mortality.[8,9,12] Our findings strengthen these observations, and add relevant novel insights, particularly by demonstrating the protective benefits of higher pre-lung cancer diagnosis CRF for reduced cancer mortality risk among those who were diagnosed with lung cancer later in life. The results also show that mean survival time and five-year survival were significantly higher among those at moderate and high CRF levels compared to

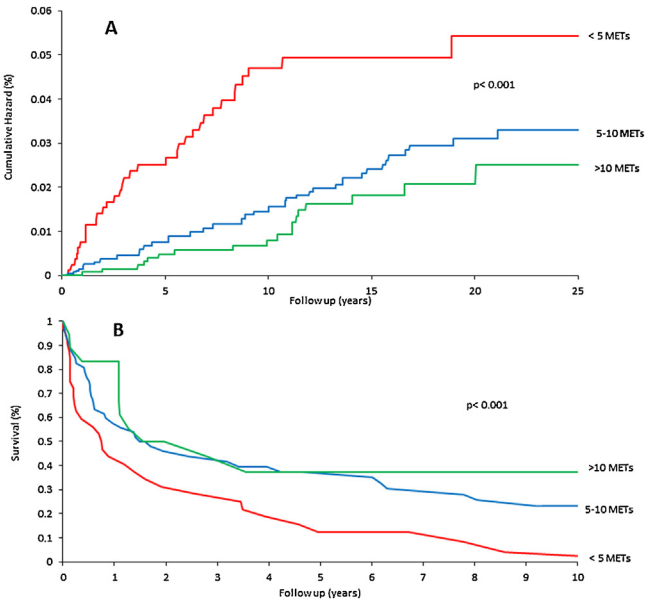

Fig. 1. (A) Cumulative hazard of cardiorespiratory fitness categories and lung cancer incidence in men. (B) Survival probability of cardiorespiratory fitness categories and cancer mortality among men diagnosed with lung cancer.
MET; metabolic equivalent.

individuals with low CRF levels (Table 2, Fig. 1). These novel findings suggest that higher CRF in pre-lung cancer diagnosis may play an important role in risk reduction and prevention of cancer mortality in those who diagnosed with lung cancer. However, the findings require further exploration and confirmation in large prospective studies. To our knowledge, the present study is the first to demonstrate the population attributable risk of low CRF for lung cancer outcomes. The latter results are important with respect to resource allocation and public-health decisions for lung cancer prevention strategies. Considering that lung cancer patients have >80% mortality over 5 years from the time of diagnosis; our observations potentially have important implications for primary and secondary preventions of lung cancer.[3,14,25] The current findings underscore the protective benefits of higher CRF against lung cancer outcomes both in general population, and in those who are diagnosed with lung cancer.

A variety of physiological mechanisms have been proposed in mediating CRF with lung cancer outcomes.[7,26] Potential protective mechanisms of higher CRF might include reduced chronic-systemic inflammation (particularly C-reactive protein) which has been suggested as promoter of carcinogenesis in a wide spectrum of cancers, including lung tissue.[4] Improved immune function through increasing the number of natural killer cells, an elevated antioxidant capacity, reduced oxidative stress and enhanced DNA repair, cell proliferation and apoptosis are all potential processes that could all interact in a complex manner by blocking cancer cell initiation and countering cancer cell replication among fit individuals.[26–28] In addition, fit individuals may have enhanced pulmonary ventilation, lung perfusion and cellular gas exchange which might decrease the interaction time of potential carcinogens in the airway and thus decrease the risk of lung cancer.[4,29] However, despite growing observational evidence supporting the concept that CRF has a role in lung cancer prevention,[4,8,10] prospective controlled studies addressing the protective mechanisms of CRF in lung cancer genesis are warranted.

The strengths of this study include its relatively large sample size (n = 4920), extended follow-up time (approximately 13 years), and prospective assessment of lung cancer outcomes. In addition, lung cancer diagnosis and cancer mortality were verified through the Veterans Affairs computerized medical records system, which has been demonstrated to be comparatively accurate and complete.[18,20,21] CRF was assessed from maximal treadmill exercise test utilizing an established technique.[17] This method has been widely used in epidemiologic studies and has been shown to be strongly predictive for incidence and mortality of many chronic diseases including lung cancer.[6,8,11] The additional analysis after excluding participants who had less than two years follow up further supports the strong association between CRF and lung cancer outcomes and suggests there was no bias due to reverse causality. The study also has several limitations. First, our multivariate hazard models, although adjusted for established covariates similar to those in previous studies, we did not collect data on dietary habits or the amount of alcohol consumption which may have an influence on cancer incidence; this is also consistent with previous studies.[10–12] Second, Veteran participants are a unique population with a rich mixture of co-morbidities that may have influenced the results by selection bias, although the findings are consistent with previous reports, showing similar lung cancer incidence (1.4%–3.1%) and hazard ratios.[10–12] Third, the study was limited to men, and the extent to which the findings apply to women needs to be examined in future studies. Finally, as in the case of all epidemiological studies, the findings provide an association between CRF and lung cancer outcomes, but they do not demonstrate a cause and effect relationship.

5. Conclusions

High CRF is associated with lower incidence of lung cancer and reduced cancer mortality among men diagnosed with lung cancer, independent from other cancer-related risk factors. In particular, individuals who exhibited moderate or high CRF at baseline showed longer survival after lung cancer diagnosis when compared to those with low CRF. Eliminating low CRF, a modifiable risk factor, would potentially prevent considerable lung cancer morbidity and mortality, and reduce the societal and economic burden associated with lung cancer. Future prospective studies should address the role of promoting CRF for primary and secondary prevention of lung cancer outcomes.

Practical implications

- CRF is an independent prognostic marker for lung cancer incidence and cancer mortality in those who were diagnosed with lung cancer.
- Achieving higher CRF provides preventive benefits against lung cancer outcomes.
- Screening, early detection and intervention for low CRF during middle-age may be an important public health strategy in prevention of lung cancer outcomes.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest

All authors declare there is no conflict of interest

Acknowledgement

The authors thank to the medical students who assisted with the study.

References

1. World Health Organization. World Cancer Report 2014. Lyon, 2014. http://www.eh-data.cn/yjbg/kxyj/201405/P020140527342097939887.pdf.
2. Bray F, Ferlay J, Soerjomataram I et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018 [Epub ahead of print].
3. American Cancer Society. *Cancer facts & figures 2018*, Atlanta, American Cancer Society, 2018.
4. Sui X, Lee DC, Matthews CE et al. Influence of cardiorespiratory fitness on lung cancer mortality. *Med Sci Sports Exerc* 2010; 42(5):872–878.
5. Bouchard C, Blair SN, Katzmarzyk PT. Less sitting more physical activity, or higher fitness? *Mayo Clin Proc* 2015; 90(11):1533–1540.
6. Ross R, Blair SN, Arena R et al. Importance of assessing cardiorespiratory fitness in clinical practice: a case for fitness as a clinical vital sign: a scientific statement from the American Heart Association. *Circulation* 2016; 134(24):e653–e699.
7. Schmid D, Leitzmann MF. Cardiorespiratory fitness as predictor of cancer mortality: a systematic review and meta-analysis. *Ann Oncol* 2015; 26(2):272–278.
8. Laukkanen JA, Pukkala E, Rauramaa R et al. Cardiorespiratory fitness, lifestyle factors and cancer risk and mortality in Finnish men. *Eur J Cancer* 2010; 46(2):355–363.
9. Robsahm TE, Falk RS, Heir T et al. Measured cardiorespiratory fitness and self-reported physical activity: associations with cancer risk and death in a long-term prospective cohort study. *Cancer Med* 2016; 5(8):2136–2144.
10. Lakoski SG, Willis BL, Barlow CE et al. Midlife cardiorespiratory fitness, incident cancer, and survival after cancer in men: the cooper center longitudinal study. *JAMA Oncol* 2015; 1(2):231–237.
11. Pletnikoff PP, Tuomainen TP, Laukkanen JA et al. Cardiorespiratory fitness and lung cancer risk: a prospective population-based cohort study. *J Sci Med Sport* 2016; 19(2):98–102.
12. Robsahm TE, Falk RS, Heir T et al. Cardiorespiratory fitness and risk of site-specific cancers: a long-term prospective cohort study. *Cancer Med* 2017.
14. American Cancer Society. *Cancer prevention & early detection facts & figs. 2015–2016*, Atlanta, American Cancer Society, 2015.
15. Myers J, Nead KT, Chang P et al. Improved reclassification of mortality risk by assessment of physical activity in patients referred for exercise testing. *Am J Med* 2015; 128(4):396–402.
16. Myers J, Prakash M, Froelicher V et al. Exercise capacity and mortality among men referred for exercise testing. *N Engl J Med* 2002; 346(11):793–801.
17. American College of Sports Medicine. *ACSM's guidelines for exercise testing and prescription*, 9th ed. Philadelphia, Wolters Kluwer/Lippincott Williams & Wilkins Health, 2014.
18. Page WF, Mahan CM, Kang HK. Vital status ascertainment through the files of the Department of Veterans Affairs and the Social Security Administration. *Annals Epidemiol* 1996; 6(2):102–109.
19. Dominitz JA, Maynard C, Boyko EJ. Assessment of vital status in Department of Veterans Affairs national databases. Comparison with state death certificates. *Annals Epidemiol* 2001; 11(5):286–291.
20. McCarron KK, Reinhard MJ, Bloeser KJ et al. PTSD diagnoses among Iraq and Afghanistan veterans: comparison of administrative data to chart review. *J Trauma Stress* 2014; 27(5):626–629.
21. Floyd JS, Blondon M, Moore KP et al. Validation of methods for assessing cardiovascular disease using electronic health data in a cohort of Veterans with diabetes. *Pharmacoepidemiol Drug Saf* 2016; 25(4):467–471.
22. Northridge ME. Public health methods–attributable risk as a link between causality and public health action. *Am J Public Health* 1995; 85(9):1202–1204.
23. Song M, Giovannucci E. Preventable incidence and mortality of carcinoma associated with lifestyle factors among white adults in the United States. *JAMA Oncol* 2016; 2(9):1154–1161.
24. Greenland S. Interval estimation by simulation as an alternative to and extension of confidence intervals. *Intl J Epidemiol* 2004; 33(6):1389–1397.
25. Leon ME, Peruga A, McNeill A et al. European code against cancer, 4th edition: tobacco and cancer. *Cancer Epidemiol* 2015; 39(Suppl 1):S20–S33.
26. Brown JC, Winters-Stone K, Lee A et al. Cancer, physical activity, and exercise. *Compr Physiol* 2012; 2(4):2775–2809.
27. Shephard RJ, Shek PN. Associations between physical activity and susceptibility to cancer: possible mechanisms. *Sports Med* 1998; 26(5):293–315.
28. Rundle A. Molecular epidemiology of physical activity and cancer. *Cancer Epidemiol Biomarkers Prev* 2005; 14(1):227–236.
29. Thune I, Lund E. The influence of physical activity on lung-cancer risk: a prospective study of 81,516 men and women. *Int J Cancer* 1997; 70(1):57–62.