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Physical activity and sedentary behavior in relation to lung cancer incidence and mortality in older women: The Women's Health Initiative

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Abstract

Physical activity has been associated with lower lung cancer incidence and mortality in several populations. We investigated these relationships in the Women's Health Initiative Observational Study (WHI-OS) and Clinical Trial (WHI-CT) prospective cohort of postmenopausal women. The WHI study enrolled 161,808 women aged 50–79 years between 1993 and 1998 at 40 U.S. clinical centers; 129,401 were eligible for these analyses. Cox proportional hazards models were used to assess the association of baseline physical activity levels [metabolic equivalent (MET)-min/week: none <100 (reference), low 100 to <500, medium 500 to <1,200, high 1,200+] and sedentary behavior with total lung cancer incidence and mortality. Over 11.8 mean follow-up years, 2,148 incident lung cancer cases and 1,365 lung cancer deaths were identified. Compared with no activity, higher physical activity levels at study entry were associated with lower lung cancer incidence [$p = 0.009$; hazard ratios (95% confidence intervals) for each physical activity category: low, HR: 0.86 (0.76–0.96); medium, HR: 0.82 (0.73–0.93); and high, HR: 0.90 (0.79–1.03)], and mortality [$p < 0.0001$; low, HR: 0.80 (0.69–0.92); medium, HR: 0.68 (0.59–0.80); and high, HR: 0.78 (0.66–0.93)]. Body mass index (BMI) modified the association with lung cancer incidence ($p = 0.01$), with a stronger association in women with BMI < 30 kg/m^2. Significant associations with sedentary behavior were not observed. In analyses by lung cancer subtype, higher total physical activity levels were associated with lower lung cancer mortality for both overall NSCLC and adenocarcinoma. In conclusion, physical activity may be protective for lung cancer incidence and mortality in postmenopausal women, particularly in non-obese women.

Keywords

physical activity; lung cancer; mortality; incidence; sedentary behavior; exercise; Women's Health Initiative

Introduction

Lung cancer is currently the leading cause of cancer death in US women, responsible for more deaths than breast and gynecological cancers combined.[1] Smoking is the risk factor most strongly linked to all lung cancer subtypes, with 80% of cases in females linked to smoking in the United States (U.S.).[2] Passive smoking has also been linked with lung cancer, though the evidence is weaker than for active smoking.[3] Female never-smokers develop lung cancer at higher rates than male never-smokers.[4-6] As smoking rates decline, the incidence of lung cancer in never-smokers continues to rise in the U.S. and worldwide; therefore, a better understanding of risk factors for lung cancer other than smoking is needed, particularly for women.

Non-smoking-related risk factors for lung cancer include environmental toxins, pulmonary fibrosis, genetic history, physical activity, and dietary factors.[7] Evidence from literature suggests that physical activity may be associated with decreased risk and mortality of lung cancer and other pulmonary diseases.[8,9] Epidemiological studies have also suggested a possible link between physical activity and a decreased risk of developing lung cancer, though this relationship may exist at only high levels of physical activity.[9-11] Prior studies have also suggested protective effects of physical activity on the incidence and survival of other cancer types and diseases.[12-16]

The literature regarding the relationship of physical activity with lung cancer incidence and mortality is limited for women; therefore, we investigated this relationship prospectively in the large, multi-ethnic Women's Health Initiative (WHI) Observational Study (OS) and Clinical Trial (CT) cohort. The WHI contains detailed information on multiple measures of physical activity and sedentary behavior, other lifestyle factors, as well as incidence and survival of multiple lung cancer histological subtypes.

Methods

Design, setting, and participants

The large, multi-center WHI study was designed to study major causes of morbidity and mortality in older women. Postmenopausal women aged 50–79 years with a life expectancy of at least 3 years were recruited at 40 U.S. clinical centers between September 1, 1993 and December 31, 1998 to participate in randomized, controlled clinical trials of Hormone Therapy (HT) and/or Dietary Modification (DM), with a later opportunity to join a Calcium + Vitamin D (CaD) trial, or enroll in an Observational Study, as previously described.[17] Among the 161,808 women who participated in either the CT ($N = 68{,}132$) or OS ($N = 93{,}676$), we excluded women with a personal history of lung cancer and those with missing baseline physical activity, smoking, or covariates included as adjustors in the models, resulting in an analytic cohort of 129,401women (Supplementary material Figure 1). An analysis of sedentary behavior was also conducted within the WHI-OS cohort only due to data availability, which included 80,581 women after also excluding those with missing sedentary behavior data.

Measurement of exposures and confounders—WHI study implementation details have been previously published.[18] At study entry, participants completed questionnaires on demographics, reproductive, medical/family history, and various lifestyle factors including physical activity and smoking (OS + CT), and sedentary behavior (sitting hr/day in OS only). For smoking status, women were asked if they smoked fewer than 100 cigarettes in their lifetime (never smokers); for women smoking >100 cigarettes in their lifetime, they were asked if they smoked at study baseline (current smokers). Current and former smokers also reported duration of smoking in years and number of cigarettes/day.

As described previously,[19] women were asked in a baseline survey if they participated in strenuous or very hard exercise at least 3 times/week at ages 18, 35, and 50 years (self-recall of historical data). Women were then asked how often they currently (at study baseline) participate in strenuous exercise (never, 1, 2, 3, 4, or 5 days/week or more) and how long they exercised at each session (<20 min, 20–39 min, 40–59 min, 1+ hr). Participants were also asked similar questions about current participation in moderate- and low-intensity physical activities at study baseline. Examples of physical activity provided in the questionnaire included the following: strenuous—aerobics, aerobic dancing, jogging, tennis, swimming; moderate—biking, exercise machine, calisthenics, easy swimming, and popular/folk dancing; low-intensity—slow dancing, bowling, golf. Based on these responses, metabolic equivalent (MET) values were calculated by assigning strenuous-, moderate-, and low-intensity exercise as 7, 4, and 3 METs, respectively.[20] MET-min/week were computed by multiplying the MET level by the minutes exercised per week, and summing the total values for measures of physical activity (total, low-intensity, moderate-intensity, and strenuous-intensity). We defined four categories of MET-min/week based on prior WHI literature[21]: 0 to <100 (inactive), 100 to <500 (low), 500 to <1,200 (medium), 1,200+ (high). For sedentary behavior, we used previously defined categories of sitting time which was self-reported in hr/day: ≤5, 5.1 to 9.9, ≥ 10.

Clinical measurements

All participants had a baseline clinic visit during which trained clinical staff recorded body weight and height as measured with a calibrated balance beam or digital scale and a wall-mounted stadiometer, respectively, with participants wearing no shoes and having removed heavy clothing and pocket contents. Body mass index (BMI) was calculated as body weight (kg) divided by height in meters squared (m^2).

Classification of cases (follow-up and ascertainment)

Cancer cases were self-reported in questionnaires (annual in OS and semi-annual in CT) administered through 2009, with 93–96% completion rates. Physicians adjudicated lung cancer diagnoses through medical and pathology records review, according to guidelines from Surveillance Epidemiology and End Results (SEER). Tumors were histologically classified based on pathology reports according to International Classification of Disease for Oncology, second edition. Lung cancer subtypes included non-small cell lung cancer (NSCLC—squamous, adenocarcinoma, other NSCLC) and small cell lung cancer (SCLC), classified according to SEER, AJCC Cancer Staging Handbook, and WHO.[22]

The primary outcome of interest was time from the date of entry into trial (OS)/ randomization (CT) to onset of lung cancer (incidence) or to death from lung cancer (mortality). The follow-up period extended from study baseline to the end of Extension 1 on December 31, 2010. Women were censored at the last visit prior to the end of study period, at the last visit prior to loss to follow-up, or death due to other causes, whichever occurred first.

Statistical analysis

Multivariable-adjusted Cox proportional hazard models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the primary outcomes of lung cancer incidence and mortality in relation to physical activity. We first examined the primary outcomes in relation to past participation in 3×/week strenuous physical activity as recalled at ages 18, 35, and 50. We then assessed the relationship of the primary outcomes with self-reported total physical activity at study entry, as well as strenuous-, moderate-, and low-intensity physical activity separately using categories of MET-min/week as defined above.

We also investigated if the relationship between lung cancer incidence and mortality and total physical activity differed by smoking status [never smoker, former smoker <10 pack years, former smoker ≥ 10 pack years, and current smoker], BMI [(<24.9 (normal and underweight), 25.0–29.9 (overweight), ≥30.0 (obese)], and age (<50 to 59, 60–69, 70 to ≥79). Effect modification was investigated by adding an interaction between physical activity and the effect modifier to the model and testing whether the interaction term was statistically significant using Wald's test. This was done separately for each of the three potential effect modifiers.

Lung cancer subtypes were included as secondary outcomes: NSCLC, its subtypes (adenocarcinoma, squamous cell carcinoma, and other), and SCLC. We also analyzed the relationship between lung cancer incidence/mortality and sedentary behavior. Sedentary behavior analyses were conducted in OS only and adjusted for all of the covariates below except for OS/CT, hormone therapy trial arm, CaD, and DM trial arm.

Analyses were adjusted for the baseline covariates age, race/ethnicity, body mass index (BMI), family history of cancer, personal history of cancer (except lung), smoking, education, history of asthma, history of emphysema or chronic bronchitis, alcohol intake, vitamin D use, hormone therapy use, oral contraceptive use, NSAID use, hormone therapy trial arm, DM trial, CAD trial arm, OS/CT, hysterectomy status, servings of fruit, vegetables, and red meat. For smoking adjustment, we used seven categories: never, former smoker <10 pack years, former smoker 10 to <25 pack years, former smoker ≥25 pack years, current smoker <10 pack years, current smoker 10 to <25 pack years, current smoker ≥25 pack years.

A sensitivity analysis was performed to evaluate potential residual confounding due to our characterization of smoking. In the sensitivity analysis, we adjusted for pack-years smoked (included as a continuous variable) and whether someone was a current, former, or never smoker (in place of the seven-category smoking variable in the primary analysis). We performed the sensitivity analysis on our primary outcomes of lung cancer incidence and mortality in relation to different levels of physical activity.

Analyses were conducted by using SAS software, version 9.3 (SAS Institute, Cary, NC). Statistical tests were two-sided and considered statistically significant at the $\alpha = 0.05$ level.

Results

The baseline characteristics of the WHI OS + CT cohort, stratified by total physical activity at baseline, are shown in Table 1. Among 129,401 total participants, 21.9% reported 0 to <100 MET-min/week (inactive), 28.3% reported 100 to <500 MET-min/week (low), 28.0% reported 500 to <1,200 MET-min/week (medium), and 21.8% reported 1,200+ MET-min/week (high). Women reporting higher physical activity levels were more likely to be Caucasian, have lower BMI, higher education levels, to be in the WHI-OS, and less likely to be current smokers. Supplementary material Tables 1 and 2 displays the baseline characteristics for WHI-OS only for physical activity and sedentary behavior.

Over 11.8 mean years of follow-up for the WHI OS + CT cohort, 2,148 cases of lung cancer and 1,365 cases of lung cancer deaths were identified. For the OS-only cohort (used for sedentary behavior), the average follow-up was 11.5 years. The distribution of the 2,148 total incident lung cancer cases and 1,365 lung cancer deaths, by physical activity category, was as follows: 581 cases (27.0%) and 412 deaths (30.2%) in women reporting <100 MET-min/week, 588 cases (27.4%) and 382 deaths (28.0%) for 100 to <500 MET-min/week, 535 cases (24.9%) and 308 deaths (22.6%) for 500–1,200 MET-min/week, and 444 cases (20.7%) and 263 deaths (19.3%) for 1,200 + MET-min/week.

In our cohort, there were no significant associations between lung cancer incidence/mortality and past self-recalled participation in strenuous physical activity at ages 18, 35, or 50 years (Tables 2 and 3). However, higher total physical activity at study entry was associated with significantly lower lung cancer incidence ($p = 0.009$); compared with no physical activity, the hazard ratios and 95% confidence intervals by physical activity categories were as follows: low, HR: 0.86 (0.76–0.96); medium, HR: 0.82 (0.73–0.93); and high, HR: 0.90 (0.79–1.03). Higher total physical activity was also associated with significantly lower lung cancer mortality ($p < 0.0001$); compared with no physical activity, mortality was lower for low [HR: 0.80 (0.69–0.92)], medium [HR: 0.68 (0.59–0.80)], and high [HR: 0.78 (0.66–0.93)] physical activity. When total physical activity was further broken down by level of strenuousness, statistically significant associations were found only for moderate physical activity levels ($p = 0.01$ for incidence and $p = 0.001$ for mortality, Tables 4 and 5). Levels of sedentary behavior (sitting time/day) were not associated with significantly different risk of overall lung cancer incidence or mortality. The models from our primary analysis (Tables 4 and 5) were additionally refit in our sensitivity analysis using a different approach for adjusting for smoking history, and these results matched the conclusions in our primary analysis (Supplementary material Tables 3 and 4).

When examining effect modification, age was not a statistically significant effect modifier of the relationship between physical activity and either lung cancer incidence or mortality; however, BMI modified the relationship between total physical activity and lung cancer incidence ($p = 0.01$), with a stronger association found for higher physical activity levels in women with BMI <30 kg/m^2 (Table 6). BMI was not a statistically significant effect modifier for lung cancer mortality, though similar patterns were seen as with incidence (Table 7). There was insufficient evidence to conclude that smoking status modified the association between activity and outcome.

In lung cancer subtype analyses, higher physical activity levels were associated with lower mortality risk for NSCLC ($p = 0.02$) and adenocarcinoma ($p = 0.03$); however, there were no significant associations with lung cancer incidence (Tables 8 and 9).

Discussion

To our best knowledge, this is the first prospective study to investigate both lung cancer incidence and mortality in relation to physical exercise in older women. We found that higher physical activity at study baseline was associated with significantly lower lung cancer incidence and mortality. These protective associations were strongest for women who were not obese (BMI <30 kg/m^2). However, associations with reduced lung cancer incidence or mortality were not found for past participation in strenuous physical activity at ages 18, 35, or 50 years, nor for sedentary behavior. Though not significant for incidence, increased physical activity was also associated with significantly lower mortality from NSCLC, and specifically for adenocarcinoma within NSCLC.

Comparison with other studies

Prior studies have suggested that physical activity may be protective against incidence and mortality of pulmonary diseases and lung cancer.[8,9] Studies have found that the forced expiratory volume in one second adjusted for height (FEV1/ height) is positively related to strenuous physical activity and exercise duration;[8,23] one prospective study found a reduction in lung cancer risk among subjects with high FEV1.[24] It has also been theorized that pulmonary ventilation and perfusion from physical activity may reduce time and concentration of smoking-related carcinogens in the lungs.[11,25] In addition, physical activity may affect particle deposition location, as central deposition of carcinogens has been linked to increased risk of cancer induction.[26,27] Physical activity has also been hypothesized to affect sexual and metabolic hormone levels, growth factors, and immune function that may alter carcinogenesis.[28]

Multiple cohort studies have examined the effect of physical exercise (both leisure and occupational physical activity) on lung cancer risk, with some of these studies focusing on men only. Findings from six of these studies and another case–control study found protective effects of both leisure-time and occupational physical activity with a dose–dependent relationship; other studies found no statistically significant relationship between lung cancer and physical activity, and no studies found increased lung cancer risk with increasing physical activity.[10,11,29-39] In addition, some studies have suggested the possibility of residual confounding due to cigarette smoking, including the NIH-AARP Diet and Health Study (which found an inverse relationship between physical activity and lung cancer among former and current smokers but null results for never smokers).[37] Other studies have also reported an inverse association between lung cancer and physical activity for smokers but a null relationship for nonsmokers.[40-42] Studies that reported protective associations of physical activity on lung cancer incidence are similar to the findings in our prospective cohort study, which also includes extensive information on confounders.

Aside from these prospective cohort studies, one meta-analysis of studies from 1966 to 2003 found statistically significant protective effects for physical activity and lung cancer for both sexes and for moderate and high levels of physical activity; however, some studies included in the meta-analysis did not properly adjust for smoking status, which is by far the most established risk factor for lung cancer.[43] Our study confirms an inverse association of physical activity with lung cancer in women, and in addition to adjusting for smoking status, also finds that the association with lung cancer mortality differs by BMI.

Besides our findings on incidence, our study also found a similar inverse association between physical activity and lung cancer mortality, which is rarely measured in prospective cohort studies but has been suggested by prior literature. One retrospective study based on the beta-Carotene and Retinol Efficacy Trial found that increase of physical activity by one standard deviation was associated with significantly lower lung cancer mortality in women.[44] Another study among thirty-eight thousand men found that cardiorespiratory fitness was inversely correlated with lung cancer mortality among current and former smokers (similar to our study).[45]

Prior literature, including several WHI studies, has also suggested protective effects of physical activity on the incidence and survival of other cancer types and diseases, including breast cancer,[12,13] colorectal cancer,[14] and cardiovascular disease.[15,16] A study of 1.44 million adults found that leisure-time physical activity was associated with lower risk of many types of cancer, regardless of body size or smoking history.[46] Another study of 661,137 participants in pooled studies from the National Cancer Institute Cohort Consortium found a dose–response relationship between physical activity and survival from cardiovascular and cancer.[47] WHI studies on breast cancer and physical activity have found that increased physical activity is associated with decreased breast cancer risk and increased survival. In combination with our results, these studies suggest that physical activity may be protective for multiple disease types, though the protective mechanism may differ for lung cancer than breast cancer (through affecting carcinogen deposition and pulmonary function as described above, rather than affecting body fat and aromatization which has been hypothesized for breast cancer[19]).

Literature on physical activity and specific lung cancer subtypes is rare, although one study found decreased lung cancer risk for small cell carcinoma and adenocarcinoma for men who exercised at least 4 hr per week.[11] Our study found an association between physical activity and lung cancer mortality in the NSCLC and adenocarcinoma subtypes specifically. These cancer subtypes have been shown to be less strongly linked with smoking than SCLC or squamous cell carcinoma.[48,49] However, our study did not find the same association for incidence of these subtypes, suggesting that physical activity is associated with progression but not occurrence of these cancer subtypes in our cohort.

Our study also found that BMI was an effect modifier of the relationship between lung cancer incidence and physical activity, with a stronger association for women with BMI <30 kg/m^2. A meta-analysis found that obesity may be protective against lung cancer incidence,[50] though obesity has been linked to increased incidence of other cancers.[51,52] Multiple mechanisms have been proposed for how obesity may affect cancer incidence, including production of excess estrogen, higher hormone levels (including insulin, insulin-like growth factor-1, and adipokines), alteration of deposition of tobacco smoke carcinogens, and effects on the immune system.[51,53] In our cohort, we did observe a higher proportion of lung cancer cases among women with BMI <30, consistent with the meta-analysis. However, overall our findings suggest that physical activity is most strongly associated with decreased lung cancer incidence in this BMI group. The specific effect modification of BMI on lung cancer and physical activity warrants further investigation, as the mechanism is unclear and this effect modification has not been extensively studied in the literature.

Though prior WHI literature has suggested an association with prolonged sedentary behavior (sitting time) and cardiovascular disease independent of physical activity levels,[16] our study did not find an association with lung cancer incidence or mortality. In addition, past physical activity at earlier ages were not associated with decreases in lung cancer incidence or mortality. These findings suggest that recent physical activity (rather than avoiding sedentary behavior, or physical activity earlier in life) is linked to decreased lung cancer incidence and mortality.

Strengths and limitations

The strengths of this study include the prospective nature of the study, large size and geographic distribution of cohort, central adjudication of cancer cases and deaths, and detailed information on confounders and physical activity exposures. In particular, the availability of smoking data is crucial given the high percentage of lung cancer cases linked to smoking, as past studies have not always made this adjustment.

One limitation of the study is that residual confounding by cigarette smoking may contribute to the results, given the modest effect sizes. To further investigate this, we performed a sensitivity analysis which included a variable for smoking status (never/former/current) and the pack years smoked (continuous variable), rather than collapsing smoking status into seven categories as in our primary model). The sensitivity analysis found similar conclusions as the primary study, with no difference in which physical activity categories were found to be associated with mortality. Though residual confounding due to smoking cannot be excluded entirely, residual confounding would likely be least impactful among non-smokers or light smokers, a population among which lung cancer cases are on the rise.

Another limitation is that the ability to participate in physical activity may be related to lung health, which may be a confounding factor in terms of lung cancer incidence and progression. We adjusted for history of asthma, emphysema, and chronic bronchitis, though other measures of lung health may also be important to consider. Other limitations include the fact that physical activity baseline values were used and not continuously updated, physical activity levels and confounder data (including smoking) were self-reported, there was a high number of "other" subtypes, and the majority of the cohort was Caucasian, limiting generalizability of the analysis. Given that literature has suggested that self-report of smoking may be underestimated,[54] it is possible that residual smoking may be a larger than expected contributor to the findings (as residual confounding is likely to be more impactful among current and/or heavy smokers). However, yearly WHI reassessments indicated that 99% of non-smokers abstained from smoking, suggesting that the self-report of smoking status among non-smokers in WHI was fairly consistent over time. Past WHI analyses on physical activity and cancer have also used baseline physical activity information and found a high test-retest reliability for physical activity variables 10 weeks after baseline for a random sample of participants.[19]

Conclusions and Policy Recommendations

In conclusion, in a prospective cohort of postmenopausal women, our study is consistent with findings from several prior prospective studies in observing that physical activity prior to diagnosis is associated with lower lung cancer incidence and mortality. Our study found that women with BMI <30 may particularly benefit from physical activity. Given the high incidence and mortality of lung cancer, these findings are promising in highlighting a modifiable lifestyle risk factor that is associated with both the incidence and progression of the disease. However, further research is needed as residual confounding due to smoking may contribute to the findings. Future research directions include additional prospective research with continuously updated physical activity information, randomized controlled trials incorporating physical activity, inclusion of other markers of lung health to adjust for confounding, and investigation of this relationship in men and other ethnic populations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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What's new?

Physical activity is linked to a reduced risk of lung cancer, though studies have focused primarily on men. Here, lung cancer incidence and mortality were investigated in relation to physical activity in a prospective cohort of postmenopausal women ages 50–79. Lung cancer incidence and mortality were found to be significantly reduced among women whose levels of physical activity were relatively high at the time of study entry. Women who were not obese appeared to experience the greatest protective benefits of physical activity. No associations were found, however, for high physical activity at younger ages or for sedentary behavior.

Table 1

Baseline characteristics of the WHI OS + CT cohort by total physical activity at baseline

	Total physical activity in MET hours per week at baseline				
Variable	**0 to <100**	**100 to <500**	**500 to <1,200**	**1,200+**	***p* Values**
Total	28,332	36,596	36,278	28,195	
Age at baseline					<0.0001
<50 to 59	10,028	11,923	11,471	9,247	
	35.39	32.58	31.62	32.80	
60–69	12,475	16,468	16,640	12,996	
	44.03	45.00	45.87	46.09	
70 to 79+	5,829	8,205	8,167	5,952	
	20.57	22.42	22.51	21.11	
Age at baseline					<0.0001
Age in years	62.84	63.34	63.46	63.17	
(mean, SD)	7.21	7.24	7.17	7.14	
Race/ethnicity					<0.0001
American Indian or Alaskan Native	135	141	117	105	
	0.48	0.39	0.32	0.37	
Asian or Pacific Islander	760	1,000	1,026	823	
	2.67	2.73	2.83	2.92	
Black or African-American	3,221	3,207	2,256	1,548	
	11.37	8.76	6.22	5.49	
Hispanic/Latino	1,259	1,328	967	749	
	4.44	3.63	2.67	2.66	
White (not of Hispanic origin)	22,631	30,493	31,530	24,665	

Variable	Total physical activity in MET hours per week at baseline				
	0 to <100	100 to <500	500 to <1,200	1,200+	*p* Values
	79.88	83.32	86.91	87.48	
Other	326	427	382	305	
	1.15	1.17	1.05	1.08	
BMI at baseline					<0.0001
<25	6,456	11,418	14,679	13,842	
	22.79	31.20	40.46	49.09	
25 to <30	9,042	13,036	13,007	9,662	
	31.91	35.62	35.85	34.27	
30+	12,834	12,142	8,592	4,691	
	45.30	33.18	23.68	16.64	
BMI at baseline					<0.0001
BMI	30.21	28.39	27.05	25.99	
(mean, SD)	6.70	5.88	5.39	4.89	
Education					<0.0001
Primary	560	509	299	216	
	1.98	1.39	0.82	0.77	
Some HS	1,449	135,3	858	603	
	5.11	3.70	2.37	2.14	
HS	6,397	6,809	5,497	3,441	
	22.58	18.61	15.15	12.20	
Some college	11,239	14,256	13,367	9,939	
	39.67	38.96	36.85	35.25	
College	2,576	3,791	4,396	3,666	
	9.09	10.36	12.12	13.00	

Variable	Total physical activity in MET hours per week at baseline				*p* Values
	0 to <100	100 to <500	500 to <1,200	1,200+	
Graduate	6,111	9,878	11,861	10,330	
	21.57	26.99	32.69	36.64	
History of cancer					0.31
No history of cancer	25,821	33,258	32946	25,572	
	91.14	90.88	90.82	90.70	
History of cancer	2,511	3,338	3,332	2,623	
	8.86	9.12	9.18	9.30	
History of asthma					<0.0001
No history of asthma	25,739	33,788	33,595	26,202	
	90.85	92.33	92.60	92.93	
History of asthma	2,593	2,808	2,683	1,993	
	9.15	7.67	7.40	7.07	
History of emphysema or chronic bronchitis					<0.0001
No history of emphysema or chronic bronchitis	26,850	35,233	35,163	27,466	
	94.77	96.28	96.93	97.41	
History of emphysema or chronic bronchitis	1,482	1,363	1,115	729	
	5.23	3.72	3.07	2.59	
Vitamin D from diet and supplements at baseline					<0.0001
<400 IU	17,530	20,973	18,901	13,974	
	61.87	57.31	52.10	49.56	
> =400 IU	10,802	15,623	17,377	14,221	
	38.13	42.69	47.90	50.44	
Main occupation (missing N = 4216)					<0.0001

Variable	Total physical activity in MET hours per week at baseline				p Values
	0 to <100	100 to <500	500 to <1,200	1,200+	
Managerial/professional	9,808	14,469	16,094	13,330	
	35.98	40.86	45.73	48.78	
Technical/sales/admin	9,028	11,319	10,117	7,045	
	33.12	31.97	28.75	25.78	
Service/labor	5,629	6,166	5,452	4,232	
	20.65	17.41	15.49	15.49	
Homemaker only	2,794	3,453	3,527	2,722	
	10.25	9.75	10.02	9.96	
Alcohol consumption at baseline					<0.0001
Non drinker	3,926	4,360	3,514	2,135	
	13.86	11.91	9.69	7.57	
Past drinker	6,672	7,059	5,684	4,226	
	23.55	19.29	15.67	14.99	
<1 drink per month	4,480	4,846	4,271	2,803	
	15.81	13.24	11.77	9.94	
<1 drink per week	5,615	7,736	7,600	5,741	
	19.82	21.14	20.95	20.36	
1 to <7 drinks per week	5,224	8,904	10,450	8,885	
	18.44	24.33	28.81	31.51	
7 + drinks per week	2,415	3,691	4,759	4,405	
	8.52	10.09	13.12	15.62	
Smoking status					<0.0001
Never smoker	1,4842	19,691	18,812	13,984	
	52.39	53.81	51.86	49.60	

Variable	Total physical activity in MET hours per week at baseline				*p* Values
	0 to <100	100 to <500	500 to <1,200	1,200+	
Former smoker, <=3 cigarettes/day	5,434	7,760	8,637	7,276	
	19.18	21.20	23.81	25.81	
Former smoker, 4–7 cigarettes/day	5,175	6,308	6,845	5,668	
	18.27	17.24	18.87	20.10	
Current smoker	2,881	2,837	1,984	1,267	
	10.17	7.75	5.47	4.49	
Red meat consumption at baseline					<0.0001
Servings/day	0.82	0.73	0.64	0.56	
(mean, SD)	0.67	0.58	0.55	0.51	
Fruit consumption at baseline					<0.0001
Servings/day	1.51	1.79	2.01	2.25	
(mean, SD)	1.13	1.18	1.22	1.31	
Vegetable consumption at baseline					<0.0001
Servings/day	1.82	2.08	2.29	2.56	
(mean, SD)	1.13	1.20	1.28	1.41	
Hormone therapy use at baseline					<0.0001
Never used	13,224	16,397	14,873	11,178	
	46.68	44.81	41.00	39.65	
Past user	4,613	5,849	5,736	4,330	
	16.28	15.98	15.81	15.36	
Current user	10,495	14,350	15,669	12,687	
	37.04	39.21	43.19	45.00	
Oral contraceptive use ever at baseline					<0.0001

Variable	Total physical activity in MET hours per week at baseline				p Values
	0 to <100	100 to <500	500 to <1,200	1,200+	
No	16,537	21,561	20,961	15,923	
	58.37	58.92	57.78	56.47	
Yes	11,795	15,035	15,317	12,272	
	41.63	41.08	42.22	43.53	
Incident lung cancer during main trial					<0.0001
No	27,751	36,008	35,743	27,751	
	97.95	98.39	98.53	98.43	
Yes	581	588	535	444	
	2.05	1.61	1.47	1.57	
Death during main trial					<0.0001
No	24,407	32190	32,492	25,588	
	86.15	87.96	89.56	90.75	
Yes	3,925	4,406	3,786	2,607	
	13.85	12.04	10.44	9.25	
Death due to lung cancer after lung cancer diagnosis during main trial					<0.0001
No	27,920	36,214	35,970	27,932	
	98.55	98.96	99.15	99.07	
Yes	412	382	308	263	
	1.45	1.04	0.85	0.93	
HT trial arm					<0.0001
Not randomized to HRT	22,745	30,307	31,059	24,464	
	80.28	82.82	85.61	86.77	
E-alone intervention	1,203	1,237	930	579	
	4.25	3.38	2.56	2.05	

Variable	Total physical activity in MET hours per week at baseline				
	0 to <100	100 to <500	500 to <1,200	1,200+	*p* Values
E-alone control	1,168	1,296	950	616	
	4.12	3.54	2.62	2.18	
E+P intervention	1,646	1,874	1,694	1,264	
	5.81	5.12	4.67	4.48	
E+P control	1,570	1,882	1,645	1,272	
	5.54	5.14	4.53	4.51	
CaD trial arm					<0.0001
Not randomized to CaD	20,954	27,961	29,055	23,305	
	73.96	76.40	80.09	82.66	
Intervention	3,692	4,294	3,677	2,456	
	13.03	11.73	10.14	8.71	
Control	3,686	4,341	3,546	2,434	
	13.01	11.86	9.77	8.63	
DM trial arm					<0.0001
Not randomized to DM	18,277	25,014	26,766	22,240	
	64.51	68.35	73.78	78.88	
Intervention	4,020	4,645	3,812	2,390	
	14.19	12.69	10.51	8.48	
Control	6,035	6,937	5,700	3,565	
	21.30	18.96	15.71	12.64	
OS/CT					
CT	13,700	15,917	13,410	8,923	
	48.36	43.49	36.96	31.65	

Variable	Total physical activity in MET hours per week at baseline				
	0 to <100	**100 to <500**	**500 to <1,200**	**1,200+**	***p* Values**
OS	14,632	20,679	22,868	19,272	
	51.64	56.51	63.04	68.35	

Note: WHI Cohort $N = 161808 \rightarrow$ Has follow-up data $N = 161116 \rightarrow$ Has physical activity data at baseline $N \rightarrow$ 145659 meet inclusion criteria (no history of lung cancer and no missing covariates) $N =$ 129401.

Table 2

Cox proportional hazards model of time to lung cancer incidence according to past participation in 3×/week strenuous physical activity at ages 18, 35, and 50 years

	Past participation in strenuous physical activity	No of. cases	No. of non-cases	HR[1] (95% CI)	*p* Values
Age 18 yr	No	1,117	69,027	Ref.	0.23
	Yes	1,031	58,226	1.05 (0.97–1.15)	
Age 35 yr	No	1,219	70,727	Ref.	0.65
	Yes	929	56,526	0.98 (0.90–1.07)	
Age 50 yr	No	1,379	80,481	Ref.	0.72
	Yes	769	46,772	0.98 (0.90–1.08)	

[1] All physical activity models are adjusted for age, race/ethnicity, BMI, family history of cancer, personal history of cancer, history of asthma, history of emphysema or chronic bronchitis, smoking, education, alcohol intake, vitamin D use, hormone therapy, oral contraceptive use, NSAID use, hormone therapy trial arm, hysterectomy status, CAD trial arm, OS/CT, servings of fruit, vegetables, and red meat.

Table 3

Cox proportional hazards model of time to lung cancer mortality according to past participation in 3×/week strenuous physical activity at ages 18, 35, and 50 years

	Past participation in strenuous physical activity	No of. cases	No. of non-cases	HR[1] (95% CI)	*p* Values
Age 18 yr	No	707	69,437	Ref.	0.32
	Yes	658	58,599	1.06 (0.95–1.18)	
Age 35 yr	No	783	71,163	Ref.	0.50
	Yes	582	56,873	0.96 (0.87–1.07)	
Age 50 yr	No	883	80,977	Ref.	0.75
	Yes	482	47,059	0.98 (0.88–1.10)	

[1]All physical activity models are adjusted for age, race/ethnicity, BMI, family history of cancer, personal history of cancer, history of asthma, history of emphysema or chronic bronchitis, smoking, education, alcohol intake, vitamin D use, hormone therapy, oral contraceptive use, NSAID use, hormone therapy trial arm, hysterectomy status, CAD trial arm, OS/CT, servings of fruit, vegetables, and red meat.

Table 4

Cox proportional hazards model of time to lung cancer incidence according to amount of current (study entry) physical activity and sedentary behavior.

Incident lung cancer, current (study entry) total physical activity (MET-min/wk)					
		Unadjusted model		**Adjusted model[1]**	
MET minutes per week	**No. of cases**	**HR (95% CI)**	***p* Values**	**HR (95% CI)**	***p* Values**
0 to <100	581	Ref.	<0.0001	Ref.	0.009
100 to <500	588	0.76 (0.68–0.85)		0.86 (0.76–0.96)	
500 to <1,200	535	0.68 (0.60–0.76)		0.82 (0.73–0.93)	
1,200+	444	0.72 (0.63–0.81)		0.90 (0.79–1.03)	
Incident lung cancer, current (study entry) strenuous physical activity (MET-min/wk)					
		Unadjusted model		**Adjusted model[1]**	
MET minutes per week	**No. of cases**	**HR (95% CI)**	***p* Values**	**HR (95% CI)**	**Global *p* values**
0 to- <100	1675	Ref.	0.04	Ref.	0.27
100 to <500	155	0.83 (0.70–0.98)		1.03 (0.88–1.22)	
500 to <1,200	187	0.87 (0.75–1.02)		1.04 (0.89–1.21)	
1,200+	131	1.02 (0.86–1.22)		1.20 (1.00–1.43)	
Incident lung cancer, current (study entry) moderate physical activity (MET-min/wk)					
		Unadjusted model		**Adjusted model[1]**	
MET minutes per week	**No. of cases**	**HR (95% CI)**	***p* Values**	**HR (95% CI)**	**Global *p* values**
0 to <100	1,388	Ref.	<0.0001	Ref.	0.01
100 to <500	519	0.85 (0.77–0.94)		0.99 (0.89–1.09)	
500 to <1,200	185	0.76 (0.65–0.89)		0.82 (0.70–0.96)	
1,200+	56	1.18 (0.90–1.54)		1.28 (0.98–1.67)	

Incident lung cancer, current (study entry) total physical activity (MET-min/wk)

		Unadjusted model		Adjusted model[1]	
MET minutes per week	**No. of cases**	**HR (95% CI)**	***p* Values**	**HR (95% CI)**	***p* Values**

Incident lung cancer, current (study entry) mild physical activity (MET-min/wk)

		Unadjusted model		Adjusted model[1]	
MET minutes per week	**No. of cases**	**HR (95% CI)**	**Global *p* values**	**HR (95% CI)**	**Global *p* values**
0 to <100	1,702	Ref.	0.74	Ref.	0.65
100 to <500	348	0.96 (0.86–1.08)		0.94 (0.84–1.06)	
500 to <1,200	84	1.08 (0.86–1.34)		0.95 (0.76–1.18)	
1,200+	14	0.86 (0.51–1.45)		0.83 (0.49–1.41)	

Incident lung cancer, current (study entry) sedentary behavior (sitting hrs/day)

		Unadjusted model		Adjusted model[1]	
Sitting time (hrs/day)	**No. of cases**	**HR (95% CI)**	**Global *p* values**	**HR (95% CI)**	**Global *p* values**
≤5	399	Ref.	0.01	Ref.	0.37
6 to <10	571	1.17 (1.03–1.33)		1.08 (0.95–1.22)	
≥10	359	1.21 (1.05–1.39)		1.10 (0.95–1.28)	

[1] All sedentary behavior adjusted models are adjusted for age, race/ethnicity, BMI, family history of cancer, personal history of cancer, history of asthma, history of emphysema or chronic bronchitis, smoking, education, alcohol intake, vitamin D use, hormone therapy, oral contraceptive use, hysterectomy status, NSAID use, servings of fruit, vegetables, and red meat.

Table 5

Cox proportional hazards model of time to lung cancer mortality according to amount of current (study entry) physical activity and sedentary behavior

Lung cancer mortality, current (study entry) total physical activity (MET-min/wk)					
		Unadjusted model		**Adjusted model[1]**	
MET minutes per week	**No. of cases**	**HR (95% CI)**	**Global *p* values**	**HR (95% CI)**	**Global *p* values**
0 to <100	412	Ref.	<0.0001	Ref.	**<0.0001**
100 to <500	382	0.70 (0.61–0.80)		0.80 (0.69–0.92)	
500 to <1,200	308	0.55 (0.47–0.64)		0.68 (0.59–0.80)	
1,200+	263	0.60 (0.51–0.70)		0.78 (0.66–0.93)	
Lung cancer mortality, current (study entry) strenuous physical activity (MET-min/wk)					
		Unadjusted model		**Adjusted model[1]**	
MET minutes per week	**No. of cases**	**HR (95% CI)**	**Global *p* values**	**HR (95% CI)**	**Global *p* values**
0 to <100	1102	Ref.	<0.0001	Ref.	0.11
100 to <500	87	0.70 (0.57–0.88)		0.91 (0.73–1.14)	
500 to <1,200	95	0.67 (0.55–0.83)		0.83 (0.67–1.02)	
1,200+	81	0.96 (0.77–1.20)		1.17 (0.93–1.47)	
Lung cancer mortality, current (study entry) moderate physical activity (MET-min/wk)					
		Unadjusted model		**Adjusted model[1]**	
MET minutes per week	**No. of cases**	**HR (95% CI)**	**Global *p* values**	**HR (95% CI)**	**Global *p* values**
0 to <100	922	Ref.	<0.0001	Ref.	0.001
100 to <500	301	0.74 (0.65–0.85)		0.89 (0.78–1.01)	
500 to <1,200	105	0.65 (0.53–0.80)		0.72 (0.58–0.88)	
1,200+	37	1.17 (0.84–1.62)		1.30 (0.94–1.81)	

Lung cancer mortality, current (study entry) total physical activity (MET-min/wk)

		Unadjusted model		Adjusted model[1]	
MET minutes per week	**No. of cases**	**HR (95% CI)**	**Global *p* values**	**HR (95% CI)**	**Global *p* values**

Lung cancer mortality, current (study entry) mild physical activity (MET-min/wk)

		Unadjusted model		Adjusted model[1]	
MET minutes per week	**No. of cases**	**HR (95% CI)**	**Global *p* values**	**HR (95% CI)**	**Global *p* values**
0 to <100	1081	Ref.	0.95	Ref.	0.81
100 to <500	222	0.97 (0.84–1.12)		0.95 (0.82–1.09)	
500 to <1,200	51	1.03 (0.77–1.36)		0.91 (0.69–1.21)	
1,200+	11	1.06 (0.59–1.92)		1.05 (0.58–1.91)	

Lung cancer mortality, current (study entry) sedentary behavior (sitting hrs/day)

		Unadjusted model		Adjusted model[1]	
Sitting Time (hrs/day)	**No. of cases**	**HR (95% CI)**	**Global *p* values**	**HR (95% CI)**	**Global *p* values**
<5	234	Ref.	0.01	Ref.	0.23
6 to <10	357	1.25 (1.06–1.47)		1.13 (0.96–1.34)	
≥10	223	1.27 (1.06–1.53)		1.16 (0.96–1.40)	

[1]All sedentary behavior adjusted models are adjusted for age, race/ethnicity, BMI, family history of cancer, personal history of cancer, history of asthma, history of emphysema or chronic bronchitis, smoking, education, alcohol intake, vitamin D use, hormone therapy, oral contraceptive use, hysterectomy status, NSAID use, servings of fruit, vegetables, and red meat.

Table 6

Cox proportional hazards model of time to lung cancer incidence according to amount of current total physical activity (MET-min/wk) by BMI, smoking categories, and age groups

Total physical activity MET-min/wk	BMI					
	<25 kg/m^2		25 to <30 kg/m^2		≥30 kg/m^2	
	No. of cases	HR* (95% CI)	No. of cases	HR* (95% CI)	No. of cases	HR* (95% CI)
0 to <100	206	Ref.	192	Ref.	183	Ref.
100 to <500	203	0.68 (0.56–0.83)	207	0.86(0.71–1.05)	178	1.08 (0.88–1.33)
500 to <1,200	228	0.69 (0.57–0.84)	194	0.82 (0.67–1.00)	113	1.00 (0.79–1.26)
1,200+	237	0.81 (0.67–0.98)	129	0.77 (0.61–0.96)	78	1.25 (0.95–1.63)

p Values for interaction between physical activity and BMI **0.01.**

Total physical activity MET-min/wk	Smoking categories							
	Never smoker		Former smoker, <10 pack years		Former smoker, ≥10 pack years		Current smoker	
	No. of cases	HR* (95% CI)	No. of cases	HR* (95% CI)	No. of cases	HR (95% CI)	No. of cases	HR* (95% CI)
0 to <100	80	Ref.	24	Ref.	233	Ref.	244	Ref.
100 to <500	104	0.93 (0.69–1.25)	41	1.14 (0.69–1.89)	248	0.83 (0.69–0.99)	195	0.79 (0.65–0.95)
500 to <1,200	84	0.76 (0.56–1.04)	50	1.20 (0.74–1.96)	278	0.82 (0.69–0.98)	123	0.70 (0.57–0.88)
1,200+	79	0.97 (0.71–1.32)	51	1.44 (0.88–2.34)	237	0.85 (0.70–1.02)	77	0.70 (0.54–0.90)

p Values for interaction between physical activity and smoking 0.39.

Total physical activity MET-min/wk	Age groups					
	<50 to 59		60–69		70 to 79+	
	No. of cases	HR* (95% CI)	No. of cases	HR* (95% CI)	No. of cases	HR* (95% CI)
0 to <100	137	Ref.	295	Ref.	149	Ref.
100 to <500	115	0.82 (0.64–1.05)	310	0.87 (0.74–1.02)	163	0.86 (0.69–1.08)
500 to <1,200	94	0.76 (0.58–0.99)	294	0.87 (0.73–1.02)	147	0.79 (0.63–1.00)
1,200+	70	0.73 (0.55–0.98)	247	0.96 (0.81–1.15)	127	0.91 (0.71–1.16)

p Values for interaction between physical activity and age 0.80.

Table 7

Cox proportional hazards model of time to lung cancer mortality according to amount of current total physical activity (MET-min/wk) by BMI, smoking categories, and age groups

Total physical activity MET-min/wk	BMI					
	<25 kg/m^2		25 to <30 kg/m^2		≥30 kg/m^2	
	No. of cases	HR* (95% CI)	No. of cases	HR* (95% CI)	No. of cases	HR* (95% CI)
0 to <100	152	Ref.	127	Ref.	133	Ref.
100 to <500	135	0.63 (0.50–0.79)	127	0.82 (0.64–1.04)	120	1.03 (0.80–1.32)
500 to <1,200	146	0.63 (0.50–0.80)	106	0.70 (0.54– 20.90)	56	0.69 (0.51–0.95)
1,200+	142	0.71 (0.56–0.90)	77	0.73 (0.55–0.97)	44	0.99 (0.70–1.39)

p Values for interaction between physical activity and BMI 0.13.

Total physical activity MET-min/wk	Smoking categories							
	Never smoker		Former smoker, <10 pack years		Former smoker, ≥10 pack years		Current smoker	
	No. of cases	HR* (95% CI)	No. of cases	HR* (95% CI)	No. of cases	HR* (95% CI)	No. of cases	HR* (95% CI)
0 to <100	51	Ref.	16	Ref.	168	Ref.	177	Ref.
100 to <500	55	0.77 (0.52–1.13)	21	0.88 (0.46–1.69)	163	0.76 (0.61–0.94)	143	0.80 (0.64–0.99)
500 to <1,200	42	0.60 (0.40–0.90)	29	1.05 (0.57–1.94)	163	0.67 (0.54–0.83)	74	0.59 (0.45–0.77)
1,200+	42	0.81 (0.54–1.23)	22	0.93 (0.49–1.79)	145	0.73 (0.58–0.92)	54	0.69 (0.51–0.94)

p Values for interaction between physical activity and smoking 0.85.

Total physical activity MET-min/wk	Age groups					
	<50 to 59		60–69		70 to 791	
	No. of cases	HR* (95% CI)	No. of cases	HR* (95% CI)	No. of cases	HR* (95% CI)
0 to <100	88	Ref.	210	Ref.	114	Ref.
100 to <500	65	0.74 (0.54–1.02)	199	0.80 (0.66–0.97)	118	0.84 (0.65–1.08)
500 to <1,200	43	0.56 (0.39–0.81)	181	0.77 (0.63–0.95)	84	0.61 (0.46–0.81)
1,200+	36	0.62 (0.42–0.93)	141	0.81 (0.65–1.02)	86	0.83 (0.62–1.10)

p Values for interaction between physical activity and age 0.48.

Table 8

Cox proportional hazards model of time to lung cancer incidence according to amount of current (study entry) total physical activity (MET-min/wk) by lung cancer subtype

		Unadjusted model		Adjusted model*	
MET minutes per week	**No. of cases**	**HR (95% CI)**	**Global *p* values**	**HR (95% CI)**	**Global *p* values**
NSCLC subtype					
0 to <100	414	Ref.	0.49	Ref.	0.81
100 to <500	430	1.02 (0.89–1.17)		1.06 (0.92–1.22)	
500 to <1,200	421	0.93 (0.81–1.07)		1.06 (0.92–1.23)	
1,200+	345	0.94 (0.82–1.09)		1.03 (0.88–1.21)	
SCLC subtype					
0 to <100	61	Ref.	0.53	Ref.	0.53
100 to <500	52	1.07 (0.73–1.56)		1.45 (0.84–2.49)	
500 to <1,200	39	0.81 (0.54–1.22)		1.09 (0.63–1.89)	
1,200+	38	1.10 (0.73–1.67)		1.26 (0.73–2.15)	
NSCLC-squamous cell carcinoma					
0 to <100	73	Ref.	0.10	Ref.	0.16
100 to <500	75	0.87 (0.63–1.21)		0.79 (0.53–1.19)	
500 to <1,200	56	0.71 (0.50–1.01)		0.67 (0.43–1.05)	
1,200+	37	0.65 (0.43–0.97)		0.57 (0.33–0.97)	
NSCLC-adenocarcinoma					
0 to <100	202	Ref.	0.90	Ref.	0.68
100 to <500	221	1.02 (0.84–1.24)		1.13 (0.91–1.39)	

		Unadjusted model		Adjusted model*	
MET minutes per week	**No. of cases**	**HR (95% CI)**	**Global *p* values**	**HR (95% CI)**	**Global *p* values**
500 to <1,200	252	0.96 (0.80–1.16)		1.09 (0.88–1.34)	
1,200+	228	0.97 (0.80–1.17)		1.03 (0.83–1.28)	
NSCLC-other					
0 to <100	139	Ref.	0.74	Ref.	0.07
100 to <500	134	1.12 (0.88–1.42)		1.23 (0.95–1.60)	
500 to <1,200	113	1.03 (0.80–1.32)		1.43 (1.06–1.93)	
1,200+	80	1.13 (0.85–1.48)		1.46 (1.04–2.03)	

Table 9

Cox proportional hazards model of time to lung cancer mortality according to amount of current (study entry) total physical activity (MET-min/wk) by lung cancer subtype

		Unadjusted model		Adjusted model*	
MET minutes per week	**No. of cases**	**HR (95% CI)**	**Global *p* values**	**HR (95% CI)**	**Global *p* values**
NSCLC subtype					
0 to <100	269	Ref.	0.0001	Ref.	0.02
100 to <500	256	0.92 (0.77–1.09)		0.98 (0.82–1.16)	
500 to <1,200	217	0.72 (0.60–0.86)		0.80 (0.66–0.98)	
1,200+	179	0.70 (0.58–0.85)		0.76 (0.62–0.94)	
SCLC subtype					
0 to <100	51	Ref.	0.55	Ref.	0.46
100 to <500	38	0.93 (0.61–1.42)		1.10 (0.61–1.99)	
500 to <1,200	31	0.73 (0.47–1.15)		0.68 (0.38–1.25)	
1,200+	32	0.99 (0.63–1.54)		0.99 (0.56–1.76)	
NSCLC-squamous					
0 to <100	44	Ref.	0.15	Ref.	0.07
100 to <500	44	1.02 (0.67–1.55)		0.96 (0.56–1.64)	
500 to <1,200	26	0.61 (0.37–0.99)		0.57 (0.31–1.03)	
1,200+	22	0.81 (0.49–1.36)		0.52 (0.26–1.04)	
NSCLC-adenocarcinoma					
0 to <100	126	Ref.	0.0008	Ref.	0.02
100 to <500	108	0.75 (0.58–0.97)		0.81 (0.62–1.07)	

MET minutes per week	No. of cases	Unadjusted model		Adjusted model*	
		HR (95% CI)	Global *p* values	HR (95% CI)	Global *p* values
500 to <1,200	115	0.66 (0.52–0.86)		0.72 (0.54–0.96)	
1,200+	99	0.60 (0.46–0.79)		0.64 (0.48–0.87)	
NSCLC-other					
0 to <100	101	Ref.	0.42	Ref.	0.23
100 to <500	105	1.22 (0.92–1.60)		1.37 (1.01–1.85)	
500 to <1,200	78	0.98 (0.72–1.32)		1.15 (0.80–1.64)	
1,200+	60	1.10 (0.80–1.52)		1.13 (0.78–1.66)	