20. Tan BH, Birdsell LA, Martin L, Baracos VE, Fearon KC. Sarcopenia in an overweight or obese patient is an adverse prognostic factor in pancreatic cancer. Clin Cancer Res 2009; 15: 6973–6979.
21. Ramos Chaves M, Boléo-Tomé C, Monteiro-Grillo I, Camilo M, Ravasco P. The diversity of nutritional status in cancer: new insights. Oncologist 2010; 15(5): 523–530.
22. Prado CM, Lieffers JR, McCargar LJ et al. Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. Lancet Oncol 2008; 9: 629–635.
23. Sinicrope FA, Foster NR, Yothers G et al. Body mass index at diagnosis and survival among colon cancer patients enrolled in clinical trials of adjuvant chemotherapy. Cancer 2013; 119(8): 1528–1536.
24. Basen-Engquist K, Scruggs S, Jhingran A et al. Physical activity and obesity in endometrial cancer survivors: associations with pain, fatigue, and physical functioning. Am J Obstet Gynecol 2009; 200(3): 288.e1–8.
25. Leibovitz E, Giryes S, Makhline R et al. Malnutrition risk in newly hospitalized overweight and obese individuals: Mr NOI. Eur J Clin Nutr 2013; 67(6): 620–624.
26. Correia Horvath JD, Dias de Castro ML, Kops N, Kruger Malinoski N, Friedman R. Obesity coexists with malnutrition? Adequacy of food consumption by severely obese patients to dietary reference intake recommendations. Nutr Hosp 2014; 29(2): 292–299.
27. Isenring EA, Banks M, Ferguson M, Bauer JD. Beyond malnutrition screening: appropriate methods to guide nutrition care for aged care residents. J Acad Nutr Diet 2012; 112(3): 376–381.
28. Must A, Spadano J, Coakley EH et al. The disease burden associated with overweight and obesity. JAMA 1999; 282: 1523–1529.
29. Gioulbasanis I, Kakalou D, Vassiliou Chr et al. Which nutritional assessment tool is related with musculature and functional status in patients with cachexia-related tumors? [abstract]. In Cancer Cachexia: Molecular Mechanisms and Therapeutic Approaches. Boston, USA, 21–23 September 2012 [Citation: J Sarcopenia, Cachexia and Muscle 2012; 3(4): 281–301].
30. Pischon T. Commentary: use of the body mass index to assess the risk of health outcomes: time to say goodbye? Int J Epidemiol 2010; 39: 528–529.
31. Gonzalez MC, Pastore CA, Orlandi SP, Heymsfield SB. Obesity paradox in cancer: new insights provided by body composition. Am J Clin Nutr 2014; 99: 999–1005.
32. Baracos VE, Prado CMM, Antoun S, Gioulbasanis I. 'Assessment of nutritional status'. In Del Fabbro E, Bruera E, Demark-Wahnefried W, Bowling T, Hopkinson JB, Baracos VE (eds), 'Nutrition and the Cancer Patient, 2010. New York: Oxford University Press, pp. 19–34.
33. Gagnon B, Murphy J, Eades M et al. A prospective evaluation of an interdisciplinary nutrition-rehabilitation program for patients with advanced cancer. Curr Oncol 2013; 20(6): 310–318.
34. Walzer S, Droeschel D, Nuijten M, Chevrou-Séverac H. Health economic analyses in medical nutrition: a systematic literature review. Clinicoecon Outcomes Res 2014; 6: 109–124.

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Active and passive smoking in relation to lung cancer incidence in the Women's Health Initiative Observational Study prospective cohort†

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Background: Lung cancer is the leading cause of worldwide cancer deaths. While smoking is its leading risk factor, few prospective cohort studies have reported on the association of lung cancer with both active and passive smoking. This study aimed to determine the relationship between lung cancer incidence with both active and passive smoking (childhood, adult at home, and at work).

Patients and methods: The Women's Health Initiative Observational Study (WHI-OS) was a prospective cohort study conducted at 40 US centers that enrolled postmenopausal women from 1993 to 1999. Among 93 676 multiethnic

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participants aged 50–79, 76 304 women with complete smoking and covariate data comprised the analytic cohort. Lung cancer incidence was calculated by Cox proportional hazards models, stratified by smoking status.

Results: Over 10.5 mean follow-up years, 901 lung cancer cases were identified. Compared with never smokers (NS), lung cancer incidence was much higher in current [hazard ratio (HR) 13.44, 95% confidence interval (CI) 10.80–16.75] and former smokers (FS; HR 4.20, 95% CI 3.48–5.08) in a dose-dependent manner. Current and FS had significantly increased risk for all lung cancer subtypes, particularly small-cell and squamous cell carcinoma. Among NS, any passive smoking exposure did not significantly increase lung cancer risk (HR 0.88, 95% CI 0.52–1.49). However, risk tended to be increased in NS with adult home passive smoking exposure ≥30 years, compared with NS with no adult home exposure (HR 1.61, 95% CI 1.00–2.58).

Conclusions: In this prospective cohort of postmenopausal women, active smoking significantly increased risk of all lung cancer subtypes; current smokers had significantly increased risk compared with FS. Among NS, prolonged passive adult home exposure tended to increase lung cancer risk. These data support continued need for smoking prevention and cessation interventions, passive smoking research, and further study of lung cancer risk factors in addition to smoking.

ClinicalTrials.gov: NCT00000611.

Key words: smoking, lung cancer, passive smokers, never smokers, lung cancer histology

introduction

Lung cancer is the leading cause of worldwide cancer deaths [1]. Smoking, the primary lung cancer risk factor, is linked to 80%–85% of female cases and 90% of male cases [2]. Studies have established that smokers have greatly increased lung cancer risk [3, 4] and that lung cancer incidence and mortality increase in a dose-dependent manner with smoking [4–6]. Smoking cessation reduces the risk of lung cancer incidence and mortality [3, 5, 7]. Among an estimated 16 000–24 000 lung cancer cases occurring annually in US never smokers (NS) [8], women have higher incidence rates than men [9].

Passive smoking is also an established risk factor for lung cancer [10]. However, evidence is mixed regarding which settings and durations of passive exposure are linked to increased lung cancer risk. Some studies report a positive association between lung cancer incidence and passive smoking during childhood [11, 12], adulthood home [13–15], and work [16, 17], including dose-dependent relationships [14, 15, 18]; other studies have found these correlations only at extensive exposure levels (≥40–80 pack-years) [19–22] or not at all for certain exposure categories [6, 11, 20, 23].

Despite extensive literature on smoking and lung cancer, few prospective cohort studies contain data on both active and passive smoking; most studies on this relationship in women have been conducted in case–control settings. Therefore, we studied relationships among active and passive smoking with lung cancer incidence using data from a large, multiethnic prospective cohort, the Women's Health Initiative Observational Study (WHI-OS). To our best knowledge, this is the first study to investigate the effect of both active and passive smoking on lung cancer risk in a complete prospective cohort of US women.

methods

design, setting, and participants

The WHI-OS is a multiethnic prospective cohort study designed to study morbidity and mortality in postmenopausal women; the study design has been previously described [24]. In brief, 93 676 postmenopausal women aged 50–79 were enrolled between 1993 and 1998 at 40 US clinical centers. Excluded from the original cohort were 1351 women due to incomplete data on smoking and 16 021 due to missing covariate data, resulting in 76 304 women for the study analysis.

measurement of exposures and confounders

This study aimed to determine the relationship between active/passive smoking and lung cancer incidence. All information on exposures and confounders was collected at baseline. NS were defined by questionnaire as having smoked <100 cigarettes in their lifetime ($N = 39\,771$: 36 135 with passive exposure, 3636 without). Former smokers (FS) were classified as having smoked ≥100 cigarettes but not smoking at study baseline ($N = 31\,804$). Current smokers (CS) reported smoking at baseline ($N = 4729$). CS and FS also reported age at smoking initiation, cigarettes/day, years of smoking, and age at quitting smoking (FS only).

We classified women who had only passive smoking exposure (i.e. no history of active smoking) as 'passive smokers'. Passive smoking data were self-reported in three categories in our analysis: childhood (<18 years), adult home (lived with smoker), and work (worked with smoker). For positive categories, women also reported exposure duration (childhood: <1, 1–4, 5–9, 10–18 years; adult home/work: <1, 1–4, 5–9, 10–19, 20–29, 30–39, ≥40 years).

The multivariable model adjusted for the following confounders (defined a priori, including established and hypothesized risk factors for lung cancer): age at enrollment, BMI, ethnicity, lung cancer history, family history of cancer, education, supplemental/dietary vitamin D, occupation, hormone therapy use, oral contraceptive use, alcohol use, physical activity, and servings/day of fruit, vegetables, and red meat.

classification of cases (follow-up and ascertainment)

Cancer cases were initially self-reported in annual questionnaires administered through 2009, with 93%–96% completion rates. Physicians adjudicated lung cancer diagnoses through medical records review, according to guidelines from Surveillance Epidemiology and End Results (SEER). When available through pathology reports, tumors were histologically classified according to International Classification of Disease for Oncology, second edition. Cases were further classified into non-small-cell lung cancer [NSCLC, subtypes: adenocarcinoma, squamous cell carcinoma (SqCC), large cell, neuroendocrine, other, unspecified], small-cell lung cancer (SCLC), and Other (carcinoid), according to SEER, AJCC Cancer Staging Handbook, and WHO [25].

Over 10.5 average years of follow-up through August 2009, $N = 901$ lung cancer cases were identified: CS $N = 531$ (58.9%), FS $N = 218$ (23.1%), NS with passive exposure $N = 136$ (15.1%), NS without passive exposure $N = 16$ (1.8%).

statistical analysis

The primary outcome of interest was time to development of lung cancer. We used Cox proportional hazards regression models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). Times were defined from enrollment into the WHI-OS to date of lung cancer diagnosis, death, loss to follow-up, or administrative censoring date (14 August 2009), whichever occurred first. We fit two models, age- and multivariable-adjusted. Participants missing information on any covariates in the model were excluded. For lung cancer subtypes, we used multinomial logistic regression models to calculate incidence because time of diagnosis was not available for subtype data. Kaplan–Meier method was used to graphically present results on lung cancer event-free survival by smoking status.

For the active smoking analysis, we estimated HRs for lung cancer development using the reference group of all NS. A secondary analysis on pack-years used 0–5 pack-years as the reference group and adjusted for age at smoking initiation. For the passive smoking analysis, we included only participants with no history of active smoking. We defined passive smoking categories a priori based on the methodology of Luo et al. [26] which investigated breast cancer incidence and active/passive smoking in the WHI-OS. Their predefined passive exposure categories included dichotomizing childhood exposure (<10 years, ≥10 years), adult home exposure (<20 years, ≥20 years), and work exposure (<10 years, ≥10 years). Due to literature suggesting dose-dependent associations between lung cancer incidence and passive smoking [14, 15, 18, 23], we further expanded the adult home ≥20 years category (20–<30 years, ≥30 years) and work ≥10 years category (10–<20 years, ≥20 years) a priori. We examined lung cancer incidence in relation to these predefined categories, as well as combinations where multiple exposures were summed in an un-weighted manner. Luo et al. defined an 'extensive exposure' category within the triple exposure category as childhood ≥10 years + adult home ≥20 years + work ≥10 years, which we further expanded as described above. We calculated HRs and Global Wald tests within passive smoking categories. All statistical analyses were completed using SAS 9.3 (SAS Institute, Cary, NC), and were two-sided at the 0.05 significance level.

results

The baseline characteristics of study participants, stratified by smoking status, are presented in Table 1. Among 76 304 women included in the study cohort, the vast majority had active and/or passive smoking exposure [$N = 3636$ NS-no passive (4.8%), $N = 36\,135$ NS-passive (47.4%), $N = 31\,804$ FS (41.7%), $N = 4729$ CS (6.2%)]. Approximately 85% of the participants were Caucasian. CS were more likely to be younger and have less education, lower physical exercise levels, lower BMIs, higher alcohol intake, higher use of oral contraceptives, and lower vitamin D intake. Additional characteristics of the cohort are presented in supplementary Tables S1–S4, available at *Annals of Oncology* online. There were not enough cases in each ethnic group to formally analyze incidence among NS.

The overall annualized lung cancer incidence rate was 112.3/100 000 person-years (CS 472.9, FS 158.1, NS 36.2, Table 2). When compared with NS, both CS (HR 13.44, 95% CI 10.80–16.75, $P < 0.0001$; multivariable-adjusted) and FS (HR 4.20, 95% CI 3.48–5.08, $P < 0.0001$) were significantly more likely to develop lung cancer, with CS also having a significantly higher risk than FS. For both CS and FS, the risk of developing lung cancer increased with pack-years (HR 1.58 for each 5-pack-year category, 95% CI 1.50–1.65, $P < 0.0001$); interaction term between CS and FS for the impact of increasing pack-years on risk was not significant ($P = 0.49$). The increased risk did not plateau up to ≥35 pack-years.

Among NS, lung cancer incidence did not differ between NS with passive exposure compared with NS without passive exposure (HR 0.88, 95% CI 0.52-1.49; Table 2), nor did it differ among predefined passive smoking subcategories (childhood, adult home, work, or combinations or durations of these passive exposures) compared with reference groups (NS without passive exposure, either overall or in a specific setting). However, borderline significant increased lung cancer risk was seen in NS with adult home exposure ≥30 years when compared with women with no adult home exposure (HR 1.61, 95% CI 1.00-2.58). In models exploring duration of childhood exposure, adult exposure, and exposure at work (Table 2), no significant interactions were seen among passive smoking categories, though the interaction between adult home and work approached significance (multivariable-adjusted $P = 0.06$). Global Wald P-values showed no significant differences in hazard within passive exposure categories.

The event-free survival for different smoking categories is displayed in a Kaplan–Meier plot in Figure 1A and B. CS had lower event-free survival rates than both FS and NS, while FS had lower event-free survival rates when compared with NS, log-rank test of equality over smoking categories $P < 0.001$. The event-free survival for NS with and without passive exposure did not appear to differ (Figure 1B).

NSCLC incidence was 97.9 per 100 000 person-years, and SCLC incidence was 9.9 (Table 3). Excluding unspecified cases, adenocarcinoma was the most common NSCLC subtype (incidence 55.0), followed by SqCC (14.8). CS were significantly more likely to develop NSCLC (OR 12.05, 95% CI 9.48–15.32) and particularly SCLC (OR 100.84, 95% CI 30.13–337.45) than NS ($P < 0.0001$); the same was true for FS, with lower ORs than CS. CS and FS had a higher rate of developing all NSCLC subtypes, when compared with NS ($P < 0.0001$), with the highest risk seen for SqCC and the lowest risk seen for adenocarcinoma.

discussion

Few prospective cohort studies contain data on passive smoking. To our knowledge, this is the first study to investigate the relationship between both active and passive smoking with lung cancer risk in a complete prospective cohort of US women. In this cohort of 76 304 postmenopausal women, we found a significant association between active smoking and lung cancer incidence, which was dose-dependent for both CS and FS. CS were over 13 times more likely to develop lung cancer compared with NS; FS were over 4 times more likely. Among NS, we did not find a significant association between any passive smoking and lung cancer incidence; however, adult home passive exposure ≥30 years was of borderline significance. Smoking increased risk of all lung cancer subtypes (particularly SCLC and SqCC), and smoking cessation decreased lung cancer risk.

comparison with other studies

Studies have estimated that active smokers have 5- to 30-fold increase in lung cancer incidence compared with NS [3, 4]. Our study confirms these findings in a prospective cohort of

Table 1. Baseline characteristics of participants in the Women's Health Initiative (WHI) Observational Study (OS) Cohort, stratified by smoking status

Covariate	Smoking exposure category (number, %)				Total	*P*-value (χ^2 test)
	Never, no passive	Never, passive	Former	Current		
Total	3636	36 135	31 804	4729	76 304	
	4.77%	47.36%	41.68%	6.20%		
Person-years of follow-up (per 100 000)	0.38	3.82	3.36	0.46		
Age group (at enrollment)						
<50–59	1059	11 321	10 219	1981	24 580	<0.0001
	29.13%	31.33%	32.13%	41.89%		
60–69	1524	15 679	14 487	2043	33 733	
	41.91%	43.39%	45.55%	43.20%		
70–79+	1053	9135	7098	705	17 991	
	28.96%	25.28%	22.32%	14.91%		
BMI category						
<25	1691	15 409	12 899	2226	32 225	<0.0001
	46.51%	42.64%	40.56%	47.07%		
25–<30	1204	12 048	10 905	1525	25 682	
	33.11%	33.34%	34.29%	32.25%		
≥30	741	8678	8000	978	18 397	
	20.38%	24.02%	25.15%	20.68%		
Ethnicity/race						
American Indian or Alaskan Native	15	140	112	36	303	<0.0001
	0.41%	0.39%	0.35%	0.76%		
Asian or Pacific Islander	204	1529	508	82	2323	
	5.61%	4.23%	1.60%	1.73%		
Black or African-American	212	2528	2087	593	5420	
	5.83%	7.00%	6.56%	12.54%		
Hispanic/Latino	246	1403	741	186	2576	
	6.77%	3.88%	2.33%	3.93%		
White (not of Hispanic origin)	2905	30 126	28 057	3785	64 873	
	79.90%	83.37%	88.22%	80.04%		
Other	54	409	299	47	809	
	1.49%	1.13%	0.94%	0.99%		
Prior history of lung cancer						
No	3630	36 104	31 678	4716	76 128	<0.0001
	99.83%	99.91%	99.60%	99.73%		
Yes	6	31	126	13	176	
	0.17%	0.09%	0.40%	0.27%		
Cancer, male relative						
No	2504	23 136	20 225	3123	48 988	<0.0001
	68.87%	64.03%	63.59%	66.04%		
Yes	1132	12 999	11 579	1606	27 316	
	31.13%	35.97%	36.41%	33.96%		
Cancer, female relative						
No	1982	18 371	15 926	2491	38 770	<0.0001
	54.51%	50.84%	50.08%	52.67%		
Yes	1654	17 764	15 878	2238	37 534	
	45.49%	49.16%	49.92%	47.33%		
Education						
Primary	100	538	252	79	969	<0.0001
	2.75%	1.49%	0.79%	1.67%		
Some high school	104	1083	899	249	2335	
	2.86%	3.00%	2.83%	5.27%		
High school	455	6416	4534	840	12 245	
	12.51%	17.76%	14.26%	17.76%		
Some college	913	12 928	11 976	2012	27 829	
	25.11%	35.78%	37.66%	42.55%		
College					9019	

Continued

Table 1. *Continued*

Covariate	Smoking exposure category (number, %)				Total	*P*-value (χ^2 test)
	Never, no passive	Never, passive	Former	Current		
	537	4129	3880	473		
	14.77%	11.43%	12.20%	10.00%		
Graduate school	1527	11 041	10 263	1076	23 907	
	42.00%	30.55%	32.27%	22.75%		
Supplemental and dietary vitamin D						
<400 IU	1822	19 047	16 374	2886	40 129	<0.0001
	50.11%	52.71%	51.48%	61.03%		
≥400 IU	1814	17 088	15 430	1843	36 175	
	49.89%	47.29%	48.52%	38.97%		
Main occupation						
Managerial/professional	1746	15 289	14 652	1829	33 516	<0.0001
	48.02%	42.31%	46.07%	38.68%		
Technical/sales/admin	638	10 629	9165	1483	21 915	
	17.55%	29.41%	28.82%	31.36%		
Service/labor	604	6298	4964	998	12 864	
	16.61%	17.43%	15.61%	21.10%		
Full-time homemaker	648	3919	3023	419	8009	
	17.82%	10.85%	9.51%	8.86%		
Physical activity (MET hours per week)						
0–≤1.67	592	6917	5442	1408	14 359	<0.0001
	16.28%	19.14%	17.11%	29.77%		
>1.67–≤8.33	943	9812	7644	1458	19 857	
	25.94%	27.15%	24.03%	30.83%		
>8.33–≤20	1130	10 811	9867	1121	22 929	
	31.08%	29.92%	31.02%	23.70%		
>20	971	8595	8851	742	19 159	
	26.71%	23.79%	27.83%	15.69%		
Alcohol intake						
Non-drinker	1026	6344	904	179	8453	<0.0001
	28.22%	17.56%	2.84%	3.79%		
Past drinker	480	6338	6208	953	13 979	
	13.20%	17.54%	19.52%	20.15%		
<1 drink/month	437	4724	3141	630	8932	
	12.02%	13.07%	9.88%	13.32%		
1 drink/month–<1 drink/week	686	7658	6177	876	15 397	
	18.87%	21.19%	19.42%	18.52%		
1–<7 drinks/week	768	8263	9670	1170	19 871	
	21.12%	22.87%	30.40%	24.74%		
≥7 drinks/week	239	2808	5704	921	9672	
	6.57%	7.77%	17.93%	19.48%		
Hormone therapy use (estrogen or progesterone, not as part of WHI study)						
Never used	1590	14 806	11 818	2137	30 351	<0.0001
	43.73%	40.97%	37.16%	45.19%		
Past user	516	5192	4898	689	11 295	
	14.19%	14.37%	15.40%	14.57%		
Current user	1530	16 137	15 088	1903	34 658	
	42.08%	44.66%	47.44%	40.24%		
Oral contraceptives						
No	2400	22 180	17 956	2581	45 117	<0.0001
	66.01%	61.38%	56.46%	54.58%		
Yes	1236	13 955	13 848	2148	31 187	
	33.99%	38.62%	43.54%	45.42%		
Diet: red meat servings per day (avg, SD)	0.55, 0.50	0.60, 0.56	0.58, 0.54	0.77, 0.70	0.60, 0.56	<0.0001
Diet: fruit medium servings per day (avg, SD)	2.27, 1.34	2.11, 1.30	2.01, 1.26	1.47, 1.20	2.04, 1.29	<0.0001
Diet: vegetables medium servings per day (avg, SD)	2.39, 1.40	2.27, 1.33	2.35, 1.36	1.85, 1.22	2.28, 1.35	<0.0001

Continued

Table 1. *Continued*

Covariate	Smoking exposure category (number, %)				Total	*P*-value (χ^2 test)
	Never, no passive	Never, passive	Former	Current		
Total MET hours per week (avg, SD)	14.63, 14.81	13.39, 14.10	14.78, 14.60	9.74, 12.22	13.80, 14.29	<0.0001
General health construct (SF 36) (avg, SD)	75.61, 17.71	74.23, 17.95	74.57, 18.10	71.28, 19.18	74.26, 18.10	<0.0001
Lung cancer during follow-up						
No	3620	35 999	31 273	4511	75 403	<0.0001
	99.56%	99.62%	98.33%	95.39%		
Yes	16	136	531	218	901	
	0.44%	0.38%	1.67%	4.61%		
Died during follow-up						
No	3334	33 201	28 368	3901	68 804	<0.0001
	91.69%	91.88%	89.20%	82.49%		
Yes	302	2934	3436	828	7500	
	8.31%	8.12%	10.80%	17.51%		

χ^2 test between different smoking categories. Significant for all categories.
METs, metabolic equivalent tasks; SD, standard deviation.

postmenopausal women, whereas most studies have focused on this relationship in men [7] or in case–control studies [3, 13, 14, 19–21, 27]. FS had lower lung cancer risk than CS, which also corroborates prior findings [3, 5, 6]. This analysis also confirms a dose-dependent relationship for active smoking and lung cancer development [4, 5]. For both CS and FS, lung cancer risk increased with 5-year pack-year categories up to ≥35 pack-years, suggesting that the dose-dependent relationship of smoking and lung cancer development continues at high cumulative smoking levels, without plateauing.

Our findings on active smoking and lung cancer subtypes are also consistent with literature [3, 6, 23, 27]. Smoking had the strongest relationship with SCLC and SqCC incidence, and the smallest with adenocarcinoma. Quitting smoking decreases risk of developing all lung cancer subtypes. We found large HRs and CIs for SCLC and SqCC among CS, which may have been due to small number of reference cases. We were unable to examine passive smoking and lung cancer subtypes due to sample size.

Among NS, we found that passive smokers (ever-exposed, as well as predefined categories including childhood, adult home, and work) were not at significantly increased lung cancer risk; however, several passive exposure categories, particularly adult home ≥30 years, had elevated point estimates and approached significance. Literature on passive smoking has been inconsistent with considerable heterogeneity of findings and many case–control studies, which are more susceptible to recall bias than cohort studies. While some publications have reported positive associations [11–14, 17, 27], including dose-dependent relationships [13, 20, 27], other studies have not found significant associations between lung cancer incidence and childhood passive smoking exposure [6, 19, 23, 28], adult spouse/residential passive smoking [11, 28], and workplace exposure [11, 18]. Additionally, some studies have found these associations only at extensive levels (40 or 80 pack-years in some cases) or exposure combinations [18–22, 28].

There are several possible explanations as to why we did not find a clear association between overall passive smoking and lung cancer risk. There may be inaccuracies in self-report of passive exposures, which is likely most pronounced for childhood exposures. However, as exposure information was collected at baseline before lung cancer diagnosis, true recall bias is unlikely. The WHI-OS measured passive smoking exposure in 'years' rather than the more precise 'pack-years'; consequently, varying exposure levels may be combined into a single category. However, prospective studies containing passive smoking data are extremely rare, and self-report of passive smoking pack-years may be impractical and inaccurate. The relatively small overall reference group (NS, no passive exposure) also resulted in wide CIs for some passive smoking categories, and sample size prevented further passive smoking segmentation.

We must also consider that passive smoking may have a weaker than expected association with lung cancer development for postmenopausal women, which some previous prospective cohort studies have suggested (see supplementary Table S5, available at *Annals of Oncology* online, for comparison to prior prospective studies). Two large Japanese prospective studies with ∼38 000 total participants found excess but insignificant lung cancer risk from overall spousal passive smoking, which is similar to our result [18, 29]; another large Japanese cohort study found significantly increased risk for wives of heavy smokers only [22]. The Nurses' Health Study also found insignificant associations for passive adult smoking exposure with lung cancer in US women, though few cases among NS were reported in the cohort [30]. Additionally, the American Cancer Society CPS-I/II cohort studies did not find a significant relationship between passive smoking and lung cancer mortality (both sexes) [31]. These results from prospective cohort studies are more conservative than many reviews and case–control studies [10, 13–17, 23, 27]. Though our results were not statistically significant, our findings suggest that high levels of passive smoking exposure may increase lung cancer risk, with adult home exposure possibly the greatest contributor. Further passive smoking research is warranted, particularly in a prospective cohort setting with pack-years measurement.

Table 2. Cox proportional hazards models for time to lung cancer incidence in the WHI-OS cohort: current/former and never smokers

Models for time to development of lung cancer	Cases/ non-cases	Annualized incidence rates (cases per 100 000 person-years)	Age-adjusted model hazard ratio (95% CI)	Multivariable- adjusted model hazard ratio (95% CI)
Current/former smokers				
Smoking status for the entire cohort ($N = 76\,304$)	901/75 403	112.3	$P < 0.001$	$P < 0.001$
Never smoker	152/39 619	36.2	Ref	Ref
Former smoker	531/31 273	158.1	4.48 (3.75, 5.38)	4.20 (3.48, 5.08)
Current smoker	218/4511	472.9	15.26 (12.39, 18.79)	13.44 (10.80, 16.74)
Pack-years smoked among current and former smokers ($N = 36\,484$)				
Pack-years			$P < 0.0001$	$P < 0.0001$
0–<5 (reference)	52/11 286	42.9	Ref	Ref
5–<10	37/4132	83.0	1.81 (1.19, 2.75)	1.80 (1.18, 2.75)
10–<15	53/4887	100.6	2.26 (1.54, 3.32)	2.26 (1.54, 3.31)
15–<25	143/6231	216.0	3.86 (2.79, 5.32)	3.86 (2.80, 5.35)
25–<35	82/2792	273.3	5.59 (3.94, 7.94)	5.68 (3.98, 8.06)
≥35	382/6456	567.6	9.62 (7.14, 12.99)	9.80 (7.25, 13.33)
Interaction of pack-years with smoking status (former or current)			$P = 0.4282$	$P = 0.4910$
Pack-years trend			$P < 0.0001$	$P < 0.0001$
Increase in pack-year category			1.57 (1.49, 1.64)	1.58 (1.50, 1.65)
Never smokers				
Any passive smoking exposure among never smokers only ($N = 39\,771$)			$P = 0.6044$[a]	$P = 0.8449$[a]
No passive exposure	16/3620	42.0	Ref[b]	Ref[b]
Passive exposure	136/35 999	35.6	0.87 (0.52, 1.45)	0.88 (0.52, 1.49)
Passive exposure categories among never smokers only ($N = 39\,771$)				
Live with smoker as a child			$P = 0.8830$	$P = 0.8240$
No	65/16 766	36.9	Ref[c]	Ref[c]
Yes	87/22 853	35.7	1.03 (0.73, 1.43)	1.04 (0.74, 1.46)
Live with smoker as adult (adult home)			$P = 0.3785$	$P = 0.3012$
No	51/15 170	31.4	Ref[d]	Ref[d]
Yes	101/24 449	39.2	1.17 (0.83, 1.66)	1.21 (0.85, 1.72)
Work with a smoker (work)[e]			$P = 0.9544$	$P = 0.8437$
No	48/12 749	35.6	Ref[f]	Ref[f]
Yes	104/26 870	36.5	1.01 (0.72, 1.43)	1.04 (0.73, 1.47)
Interaction of childhood and adult home exposure			$P = 0.6445$	$P = 0.5868$
Interaction of childhood and work exposure			$P = 0.9870$	$P = 0.9906$
Interaction of adult home and work exposure			$P = 0.0792$	$P = 0.0643$
Interaction of childhood, adult home, and work exposure			$P = 0.7872$	$P = 0.7843$
Passive exposure durations/categories among never smokers only ($N = 39\,771$)				
Childhood exposure category			$P = 0.9928$	$P = 0.9783$
No childhood exposure	65/16 766	36.9	Ref[c]	Ref[c]
<10 years	13/3552	34.6	1.02 (0.56, 1.85)	1.03 (0.57, 1.88)
10–18 years	74/19 301	35.9	1.02 (0.72, 1.45)	1.04 (0.73, 1.47)
Adult home exposure category			$P = 0.3406$	$P = 0.2448$
No adult home exposure	51/15 170	31.4	Ref[d]	Ref[d]
<20 years	52/14 211	34.1	1.09 (0.74, 1.63)	1.11 (0.74, 1.65)
20–<30 years	17/4560	35.8	1.07 (0.61, 1.88)	1.11 (0.63, 1.96)
≥30 years	32/5678	55.0	1.52 (0.95, 2.42)	1.61 (1.00, 2.58)
Work exposure category			$P = 0.4017$	$P = 0.4349$
No work exposure	48/12 749	35.6	Ref[f]	Ref[f]
<10 years	59/14 281	38.5	1.14 (0.78, 1.67)	1.16 (0.79, 1.70)
10–<20 years	18/6385	26.5	0.72 (0.42, 1.24)	0.74 (0.43, 1.29)
≥20 years	27/6204	42.0	1.02 (0.63, 1.64)	1.05 (0.64, 1.72)
Passive exposure combinations among never smokers only ($N = 39\,771$)				
Category of exposure			$P = 0.4438$	$P = 0.2938$
No passive exposure (childhood, adult home, work)	16/3620	42.0	Ref[b]	Ref[b]

Continued

Table 2. *Continued*

Models for time to development of lung cancer	Cases/ non-cases	Annualized incidence rates (cases per 100 000 person-years)	Age-adjusted model hazard ratio (95% CI)	Multivariable- adjusted model hazard ratio (95% CI)
Adult home + work + no childhood	49/13 146	35.5	0.81 (0.46, 1.43)	0.83 (0.47, 1.46)
Any childhood + no adult home or work	9/2338	35.4	0.97 (0.43, 2.20)	0.96 (0.42, 2.17)
Childhood <10 + any adult (work or home)	13/3043	40.5	1.01 (0.49, 2.11)	1.04 (0.50, 2.18)
Childhood ≥ 10 + adult <20 + work <10 years	21/7467	25.8	0.70 (0.36, 1.34)	0.70 (0.36, 1.36)
Childhood ≥ 10 + adult <20 + work ≥ 10 years	5/2186	21.1	0.56 (0.20, 1.53)	0.57 (0.21, 1.58)
Childhood ≥ 10 + adult ≥ 20 + work <10 years	5/1425	33.6	0.83 (0.30, 2.25)	0.81 (0.30, 2.24)
Childhood ≥ 10 + adult ≥ 20 + work ≥ 10 years	2/535	35.7	0.87 (0.20, 3.79)	0.96 (0.22, 4.22)
Childhood ≥ 10 + adult < 30 + work ≥ 20 years	8/2381	32.0	0.76 (0.33, 1.78)	0.80 (0.34, 1.89)
Childhood ≥ 10 + adult ≥ 30 + work < 20 years	15/2390	60.7	1.35 (0.67, 2.73)	1.48 (0.72, 3.04)
Childhood ≥ 10 + adult ≥ 30 + work ≥ 20 years	9/1088	81.1	1.76 (0.78, 3.98)	1.96 (0.85, 4.55)

Multivariable-adjusted model is adjusted for age group, BMI category, ethnicity, prior history of lung cancer, family history of cancer in female and male relatives, education, vitamin D category, main occupation, hormone therapy use, oral contraceptive use, fruit servings per day, vegetable servings per day, red meat servings per day, alcohol use and physical activity.

Models of pack-years among current and former smokers further adjust for age started smoking.

All passive exposure categories defined a priori.

[a]All *P*-values in this table represent Global Wald *t*-tests.

[b]No passive smoking exposure during childhood, adult home, or work. Note: Reference groups in this table differ depending on category of passive smoking tested.

[c]No passive smoking exposure during childhood only.

[d]No passive smoking exposure during adult home only.

[e]Work passive smoking exposure is likely to be during adulthood, but not explicitly defined as such.

[f]No passive smoking exposure during work only.

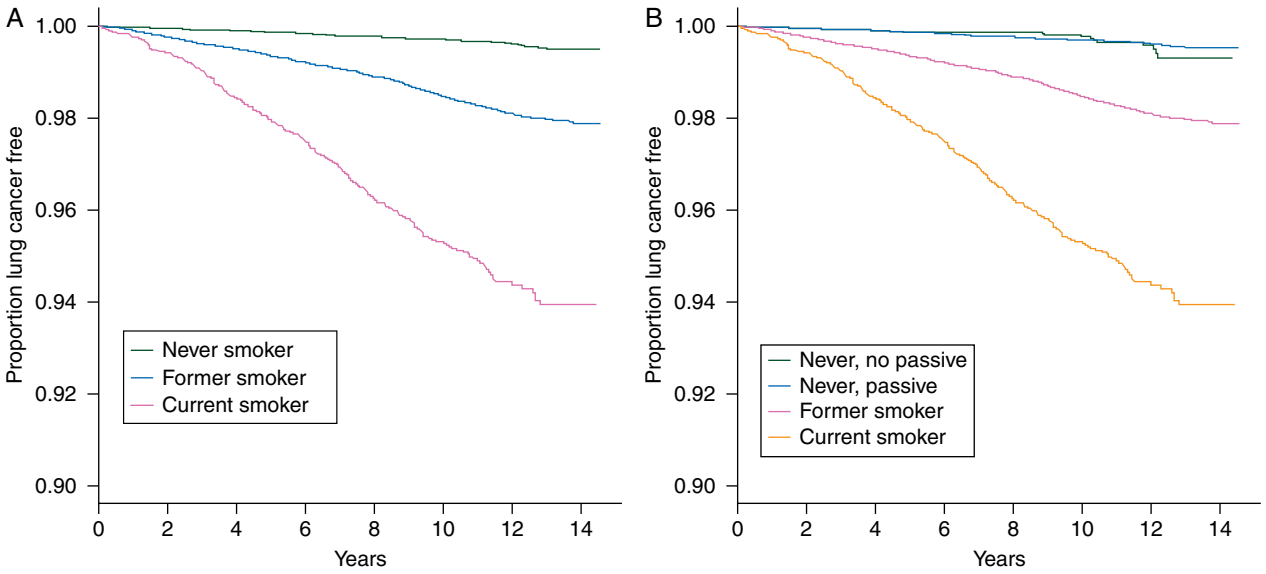

Figure 1. Event-free survival estimates with (A) number of subjects at risk, stratified by smoking status; and (B) number of subjects at risk, with further stratification of never smokers (passive/no passive exposure). Kaplan–Meier event-free survival plots are presented stratified by smoking status (current, former, never–no passive, and never-passive). Log-rank test of equality over smoking categories has $P < 0.0001$. When never smokers are further segmented, the hazards for never, no passive exposure and never, passive exposure cross over each other at several points and do not seem to be different from each other.

strengths and limitations of the study

Strengths of our study include the prospective cohort design, large size and geographical distribution, high number and pathological confirmation of lung cancer cases/subtypes, and detailed information on active/ passive smoking exposure variables in multiple settings and confounders. Limitations include

Table 3. Multinomial logistic regression models NSCLC and SCLC incidence by smoking status in the WHI-OS cohort

Lung cancer histology	Cases/non-cases	Annualized incidence rates (cases per 100 000 person-years)	Odds ratios by smoking status (95% CI)			*P*-value
			Never smoker	Former smoker (95% CI)	Current smoker (95% CI)	
NSCLC/SCLC (*N* = 76 267)[a]						
Age-adjusted model						
NSCLC	785/75 403	97.9	Ref	4.66 (3.84, 5.66)	13.81 (10.99, 17.35)	<0.0001
SCLC	79/75 403	9.9	Ref	17.95 (5.57, 57.91)	113.29 (34.73, 369.53)	
Multivariable-adjusted model						
NSCLC	785/75 403	97.9	Ref	4.22 (3.45, 5.16)	12.05 (9.48, 15.32)	<0.0001
SCLC	79/75 403	9.9	Ref	16.76 (5.12, 54.86)	100.84 (30.13, 337.45)	
Further lung cancer histology breakdown (*N* = 76 267)[a]						
Age-adjusted model						
NSCLC: adenocarcinoma	441/75 403	55.0	Ref	3.62 (2.87, 4.57)	7.28 (5.35, 9.91)	<0.0001
NSCLC: squamous cell	119/75 403	14.8	Ref	21.09 (7.69, 57.83)	120.10 (43.29, 333.23)	
NSCLC: large cell/ neuroendocrine/other	56/75 403	7.0	Ref	5.23 (2.52, 10.86)	12.52 (5.16, 30.36)	
NSCLC: unspecified	169/75 403	21.1	Ref	6.10 (3.80, 9.77)	24.43 (14.62, 40.82)	
SCLC	79/75 403	9.9	Ref	17.95 (5.57, 57.91)	113.29 (34.73, 369.53)	
Multivariable-adjusted model						
NSCLC: adenocarcinoma	441/75 403	55.0	Ref	3.27 (2.56, 4.16)	6.75 (4.88, 9.32)	<0.0001
NSCLC: squamous cell	119/75 403	14.8	Ref	18.55 (6.69, 51.47)	86.80 (30.66, 245.72)	
NSCLC: large cell/ neuroendocrine/other	56/75 403	7.0	Ref	5.21 (2.46, 11.06)	12.87 (5.10, 32.43)	
NSCLC: unspecified	169/75 403	21.1	Ref	5.37 (3.31, 8.72)	19.42 (11.36, 33.21)	
SCLC	79/75 403	9.9	Ref	16.76 (5.12, 54.86)	100.84 (30.13, 337.45)	

[a]Sample size is reduced as participants for whom NSCLC/SCLC histology was not assigned were excluded from the subtype analysis (32 'other' cases and 5 missing cases—this results in a total of *N* = 864 cases with known histology rather than *N* = 901 total cases, and *N* = 76 267 total sample size rather than *N* = 76 304 total sample size).

collection of passive smoking exposure as 'years' rather than 'pack-years', and potential inaccuracies in self-reported data. Our analytic cohort also had a relatively small overall reference group (NS without passive exposure). We used baseline values for smoking status, as data were collected at study entry. However, as there were relatively few CS, exposure misclassification was likely minimal. Yearly WHI reassessments indicated that 99% of NS abstained from smoking, and ~60% of CS continued smoking for 6 follow-up years. Lastly, the cohort was primarily Caucasian.

conclusions and policy recommendations

In conclusion, for a prospective cohort of US postmenopausal women, our study confirms literature findings that smoking increases the risk of all lung cancer subtypes. This relationship is dose-dependent with no plateau up to 35 pack-years. Smoking cessation decreases lung cancer risk. Our study did not find a significant relationship between overall passive smoking exposure and lung cancer among NS; however, adult home exposure ≥30 years was associated with borderline significant elevations in risk, suggesting that high levels of passive smoking may contribute to lung cancer risk. These passive smoking findings are intriguing and add to the controversy on this subject; more precise pack-years quantification of passive smoking in a prospective cohort setting is warranted. This study focused only on smoking and lung cancer; public policy must also consider that active and passive smoking have been established as strong contributors to morbidity and mortality associated with many health conditions, including cardiopulmonary disease, other cancers, and pregnancy complications and asthma in children [32].

As lung cancer is the leading cause of US cancer deaths, our prospective study underscores the need for development and implementation of smoking prevention and cessation interventions for all ages, and for women as well as men. Additionally, given the high incidence and mortality of lung cancer with at least 10%–15% cases occurring NS in the United States [8, 9], our results suggest that more research is needed on non-smoking-related lung cancer risk factors, including but not limited to genetic, behavioral, hormonal, dietary, and environmental factors.

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ethical approval

This study was approved by the ethics committees at the Women's Health Initiative Coordinating Center, Fred Hutchinson Cancer Research Center, and all 40 clinical centers.

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disclosure

The authors have declared no conflicts of interest.

references

1. Jemal A, Murray T, Samuels A et al. Cancer statistics, 2003. CA Cancer J Clin 2003; 53: 5–26.
2. Centers for Disease Control (U.S.), Centers for Disease Control and Prevention (U. S.). Morbidity and mortality weekly report: MMWR.: HEW Publication, Atlanta, GA. U.S. Dept. of Health, Education, and Welfare, Public Health Service v, 19 March 1976–2 May 1980.
3. Agudo A, Ahrens W, Benhamou E et al. Lung cancer and cigarette smoking in women: a multicenter case-control study in Europe. Int J Cancer 2000; 88: 820–827.
4. Alberg AJ, Samet JM. Epidemiology of lung cancer. Chest 2003; 123: 21S–49S.
5. Peto R, Darby S, Deo H et al. Smoking, smoking cessation, and lung cancer in the UK since 1950: combination of national statistics with two case-control studies. BMJ 2000; 321: 323–329.
6. Svensson C, Pershagen G, Klominek J. Smoking and passive smoking in relation to lung cancer in women. Acta Oncol 1989; 28: 623–629.
7. Doll R, Peto R, Boreham J, Sutherland I. Mortality in relation to smoking: 50 years' observations on male British doctors. BMJ 2004; 328: 1519.
8. Samet JM, Avila-Tang E, Boffetta P et al. Lung cancer in never smokers: clinical epidemiology and environmental risk factors. Clin Cancer Res 2009; 15: 5626–5645.
9. Wakelee HA, Chang ET, Gomez SL et al. Lung cancer incidence in never smokers. J Clin Oncol 2007; 25: 472–478.
10. World Health Organization & International Agency for Research on Cancer. Tobacco Smoke and Involuntary Smoking: IARC Working Group in Lyon, 11–18 June 2002. Lyon: France 2004.
11. Janerich DT, Thompson WD, Varela LR et al. Lung cancer and exposure to tobacco smoke in the household. N Engl J Med 1990; 323: 632–636.
12. Rachtan J. Smoking, passive smoking and lung cancer cell types among women in Poland. Lung Cancer 2002; 35: 129–136.
13. Lam TH, Kung IT, Wong CM et al. Smoking, passive smoking and histological types in lung cancer in Hong Kong Chinese women. Br J Cancer 1987; 56: 673–678.
14. Trichopoulos D, Kalandidi A, Sparros L, MacMahon B. Lung cancer and passive smoking. Int J Cancer 1981; 27: 1–4.
15. Hackshaw AK, Law MR, Wald NJ. The accumulated evidence on lung cancer and environmental tobacco smoke. BMJ 1997; 315: 980–988.
16. Stayner L, Bena J, Sasco AJ et al. Lung cancer risk and workplace exposure to environmental tobacco smoke. Am J Public Health 2007; 97: 545–551.
17. Wells AJ. Lung cancer from passive smoking at work. Am J Public Health 1998; 88: 1025–1029.
18. Kurahashi N, Inoue M, Liu Y et al. Passive smoking and lung cancer in Japanese non-smoking women: a prospective study. Int J Cancer 2008; 122: 653–657.
19. Brownson RC, Alavanja MC, Hock ET, Loy TS. Passive smoking and lung cancer in nonsmoking women. Am J Public Health 1992; 82: 1525–1530.
20. Kirkland LR. Environmental tobacco smoke and lung cancer in nonsmoking women. JAMA 1995; 273: 519–520.
21. Correa P, Pickle LW, Fontham E et al. Passive smoking and lung cancer. Lancet 1983; 2: 595–597.
22. Hirayama T. Non-smoking wives of heavy smokers have a higher risk of lung cancer: a study from Japan. Br Med J (Clin Res Ed) 1981; 282: 183–185.
23. Boffetta P, Tredaniel J, Greco A. Risk of childhood cancer and adult lung cancer after childhood exposure to passive smoke: a meta-analysis. Environ Health Perspect 2000; 108: 73–82.
24. Langer RD, White E, Lewis CE et al. The Women's Health Initiative Observational Study: baseline characteristics of participants and reliability of baseline measures. Ann Epidemiol 2003; 13: S107–S121.
25. Edge SB, American Joint Committee on Cancer. AJCC Cancer Staging Manual. New York: Springer 2010; 253–271.
26. Luo J, Margolis KL, Wactawski-Wende J et al. Association of active and passive smoking with risk of breast cancer among postmenopausal women: a prospective cohort study. BMJ 2011; 342: d1016.
27. Brennan P, Buffler PA, Reynolds P et al. Secondhand smoke exposure in adulthood and risk of lung cancer among never smokers: a pooled analysis of two large studies. Int J Cancer 2004; 109: 125–131.
28. Kreuzer M, Krauss M, Kreienbrock L et al. Environmental tobacco smoke and lung cancer: a case-control study in Germany. Am J Epidemiol 2000; 151: 241–250.
29. Nishino Y, Tsubono Y, Tsuji I et al. Passive smoking at home and cancer risk: a population-based prospective study in Japanese nonsmoking women. Cancer Causes Control 2001; 12: 797–802.
30. Speizer FE, Colditz GA, Hunter DJ et al. Prospective study of smoking, antioxidant intake, and lung cancer in middle-aged women (USA). Cancer Causes Control 1999; 10: 475–482.
31. Cardenas VM, Thun MJ, Austin H et al. Environmental tobacco smoke and lung cancer mortality in the American Cancer Society's Cancer Prevention Study. II. Cancer Causes Control 1997; 8: 57–64.
32. Taylor AE, Johnson DC, Kazemi H. Environmental Tobacco-Smoke and ardiovascular-Disease—a Position Paper from the Council on Cardiopulmonary and Critical Care, American-Heart-Association. Circulation 1992; 86: 699–702.