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History of periodontal disease diagnosis and lung cancer incidence in the Women's Health Initiative Observational Study

Xiaodan Mai,

Department of Epidemiology and Environmental Health, School of Public Health and Health Professions, University at Buffalo, The State University of New York, xiaodanm@buffalo.edu

Michael J. LaMonte,

Department of Epidemiology and Environmental Health, School of Public Health and Health Professions, University at Buffalo, The State University of New York, mlamonte@buffalo.edu

Kathleen M. Hovey,

Department of Epidemiology and Environmental Health, School of Public Health and Health Professions, University at Buffalo, The State University of New York, koreilly@buffalo.edu

Ngozi Nwizu,

Department of Cancer Pathology and Prevention, Roswell Park Cancer Institute, Ngozi.Nwizu@roswellpark.org

Jo L. Freudenheim,

Department of Epidemiology and Environmental Health, School of Public Health and Health Professions, University at Buffalo, The State University of New York, jfreuden@buffalo.edu

Mine Tezal,

Department of Oral Biology, School of Dental Medicine, University at Buffalo, The State University of New York, mtezal@buffalo.edu

Frank Scannapieco,

Department of Oral Biology, School of Dental Medicine, University at Buffalo, The State University of New York, fas1@buffalo.edu

Andrew Hyland,

Department of Health Behavior, Roswell Park Cancer Institute, andrew.hyland@roswellpark.org

Christopher A. Andrews,

Department of Ophthalmology and Visual Sciences, University of Michigan, candrews@buffalo.edu

Robert J. Genco, and

Department of Oral Biology, School of Dental Medicine, University at Buffalo, The State University of New York, rjgenco@buffalo.edu

Jean Wactawski-Wende

Correspondence to: Jean Wactawski-Wende.

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The authors declare that they have no conflict of interest.

Department of Epidemiology and Environmental Health, School of Public Health and Health Professions, University at Buffalo, The State University of New York, 270 Farber Hall, Buffalo, N.Y. 14214, jww@buffalo.edu, telephone number (716)829-5374, fax number (716)829-2979

Abstract

Purpose—While some evidence suggests that periodontal disease (PD) might be positively associated with lung cancer, prospective studies in women are limited. Previous findings may reflect residual confounding by smoking. The study aims to determine whether history of PD diagnosis is associated with incident lung cancer in a large cohort of postmenopausal women.

Methods—Prospective analyses were conducted in a cohort of 77,485 postmenopausal women enrolled in the Women's Health Initiative Observational Study. History of PD (prevalence of 26.1%) was self-reported and 754 incident lung cancer cases occurred during an average 6.8 (SD ± 2.6) years of follow-up. Cox regression analysis was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs).

Results—Overall, PD was positively associated with lung cancer risk after adjusting for detailed smoking history including smoking status and pack-years of smoking (HR=1.24, 95% CI: 1.07–1.45). There was a positive additive interaction between PD with pack-years of smoking ($P=0.02$), suggesting a potential synergistic effect between PD and smoking intensity on lung cancer. The association between PD and lung cancer was stronger in former smokers. When restricted to never-smokers, PD was not associated with lung cancer (HR=1.02, 95% CI: 0.68–1.53).

Conclusions—PD was not independently associated with lung cancer in non-smoking postmenopausal women. However, smoking and PD jointly increased lung cancer risk beyond that expected from the sum of the each effect separately. The potential synergism between PD and smoking on lung cancer warrants further examination.

Keywords

lung cancer; periodontal disease; postmenopause; smoking; chronic inflammation; interaction

Introduction

Lung cancer is the second most common cancer and the leading cause of cancer death in U.S. women, accounting for 14% of incident cancers and 26% of total cancer mortality in 2013 [1]. Although tobacco is the primary cause, 53% of lung cancer cases in women worldwide are not attributable to smoking [2], suggesting other factors may independently increase risk or modify the effects of smoking on risk. In particular, chronic inflammation may initiate and promote carcinogenesis by supplying bioactive molecules to the tumor microenvironment, enabling neoplastic cells to acquire core hallmark capabilities [3]. Indeed, studies have shown that history of inflammatory lung disease, such as chronic bronchitis, may increase lung cancer risk among non-smoking women [4].

Periodontal disease (PD) is an oral bacterial infection leading to periodontal inflammation, resulting in loss of supporting connective tissue surrounding the teeth and resorption of alveolar bone [5]. According to the National Health and Nutrition Examination Survey

(NHANES) 2009–2010, the prevalence of periodontitis is 47.2% in U.S. adults over age 30 and 70.1% in adults over age 65 [6]. PD serves as a source of systemic inflammation via spread of cytokines and other biologically active components, as well as oral bacteria resulting in frequent transient bacteremia. The “mobile” microbiome could colonize extra-oral sites leading to distant infections and a pro-inflammatory state [7]. A recent study detected elevated *Fusobacterium nucleatum*, an invasive periodontal anaerobe, in colorectal tumors compared to normal tissues taken from the same patients [8,9].

Few epidemiological studies have reported on the association between PD and lung cancer, and no study has reported on this association among postmenopausal women. Comparisons across studies are complicated by differences in study design and participant characteristics. In a Japanese hospital-based case-control study, number of remaining teeth was inversely associated with lung cancer (OR=1.54, 95% CI: 1.05–2.27) [10]. In contrast, the Glasgow Alumni Cohort study found no association between tooth loss and lung cancer [11]. Notably, the use of missing teeth as a proxy for PD limits interpretation, since tooth loss could occur for reasons other than PD [12]. Analyses in the NHANES I Epidemiologic Follow-up Study showed an association between clinically measured periodontitis and combined lung and bronchus cancer (OR=1.73, 95% CI: 1.01–2.97). However, the authors concluded that the association might be spurious due to residual confounding by smoking [13]. In the U.S. Health Professionals Follow-Up Study, after 18 years of follow-up among white middle-aged males, self-reported PD was associated with a significant increased risk for lung cancer, even after adjusting for confounding factors including smoking (HR=1.36, 95% CI: 1.15–1.60) [14]. It remains unclear whether these results are generalizable to older women and populations with lower smoking prevalence.

To clarify further the prospective relationship between PD and lung cancer risk in postmenopausal women, we analyzed data from the Women’s Health Initiative (WHI).

Methods

Study participants

The WHI is a long-term national health study focusing on risk factors and prevention strategies for chronic diseases in postmenopausal women. From 1993 through 1998, 161,808 women, aged 50–79 years, were recruited from 40 clinical centers across the U.S. Of those, 93,676 women joined the Observational Study (OS) [15]. Details about recruitment and eligibility are described elsewhere [16]. The study protocols and procedures were approved by the institutional review boards at all participating institutions. All participants signed informed consent forms. History of PD was ascertained on the WHI OS year-5 follow-up questionnaire (Form 145, “F145”). We excluded women who did not complete F145 (n=11,262), had omitted dental health questions on F145 (n=1,208), were lost to follow-up after year-5 (n=848), had a history of lung cancer at baseline (n=148), were diagnosed with lung cancer before year-5 (n=176), or had missing data on smoking (n=2,549), resulting in an analytic sample of 77,485 women.

Exposure and confounders assessments

Participants completed self-administered questionnaires on demographics, health behaviors, and medical conditions at baseline and yearly thereafter. PD was assessed on F145 by asking “Has a dentist or dental hygienist ever told you that you had periodontal or gum disease?”. Two other dental health related questions asked, “During the past 3 years, how often have you gone to the dentist or dental hygienist for routine check-ups or cleaning?” and “Have you lost all of your permanent teeth, both upper and lower?”.

Extensive information on smoking history was collected at baseline including questions regarding smoking status (never, former, current), packs smoked per day, age at smoking initiation, age at smoking cessation, secondhand smoke exposure. Smoking status and cigarettes smoked per day were updated annually. Years since smoking cessation was determined by subtracting age at cessation from age at year-5. To account for the potential effect of smoking cessation, a new variable was created, classifying individuals on both smoking status and years since quitting: never-smokers, former smokers quit ≥20 years, former smokers quit <20 years, current smokers. Pack-years was computed by multiplying packs smoked per day by number of years smoked, and was also categorized in tertiles among ever smokers (light ≤5, moderate>5 to ≤24.5, heavy>24.5). Secondhand smoke exposure was categorized as: none, childhood (<18 years old) only, adult at home only, adult at work only, childhood + adult at home, childhood + adult at work, adult at home + adult at work, childhood + adult at home + adult at work.

Other potential confounders included educational level, race/ethnicity, body mass index (BMI, kg/m²; categorized as underweight (<18.5), normal-weight (18.5–24.9), overweight (25.0–29.9), or obese (≥30) based on WHO criteria [17]), menopausal hormone therapy (ever; type), recreational physical activity (total metabolic equivalent task [MET] hours per week), regional residence (Northeast, South, Midwest, West), aspirin use (yes/no) and alcohol consumption (average drinks per day).

Ascertainment of End Points

Lung cancers were self-reported on annual health updates occurring through September 30, 2010 and were confirmed by physician adjudicators after review of medical records [18]. Lung cancer characteristics were coded according to the International Classification of Diseases for Oncology (ICD-O-2) from the Surveillance Epidemiology and End Result (SEER) [19]. Lung cancer deaths were confirmed after review of death certificates. National Death Index searches were done to enhance mortality ascertainment [18].

Statistical Analysis

Baseline characteristics of lung cancer cases and noncases were compared using chi-square, independent t-tests, or Wilcoxon tests. Follow-up time (person-years) was computed for each participant from the date of completion of F145 to the date of: lung cancer diagnosis, lung cancer death, loss to follow-up, or end of follow-up. Cox proportional hazards regression was employed to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for crude, age-adjusted and multivariable-adjusted models. A parsimonious model-

building approach was utilized to maximize statistical power and reduce the probability of bias.

Interaction between PD and smoking intensity was examined on both the additive and multiplicative scales. To increase statistical power, we categorized participants by pack-years of smoking as moderate/heavy smokers (>5) vs. never/light smokers (≤ 5). Additive interaction was evaluated by computing the relative excess risk for interaction (RERI), its 95% CI and associated *P*-value using methods described by Li and Chambless [20]. Multiplicative interaction was evaluated using the cross-product term of PD and pack-years in the multivariable-adjusted models. Evaluation of differences according to lung cancer subtypes were done by stratifying on tumor subtype, grade and stage. All data analyses were performed using SAS version 9.2 statistical software package (SAS Institute, Cary, N.C.).

Results

Baseline characteristics are summarized in Table 1. Most women were white and had completed some college education. About half were never-smokers, and 4% were current smokers. Participants who developed lung cancer were older ($P < 0.001$), ever smokers ($P < 0.001$), and reported a history of PD ($P < 0.001$). Lung cancer cases also were less overweight/obese ($P = 0.04$), and reported higher alcohol intake ($P < 0.001$), fewer dental checkups ($P < 0.01$) and lower physical activity ($P = 0.01$). Hormone therapy use did not differ ($P = 0.197$) according to lung cancer status.

During an average of 6.8 years of follow-up, 754 incident lung cancer cases were ascertained in 77,485 participants (524,357 person-years) and 486 lung cancer deaths occurred. Cox proportional hazards analyses are provided in Table 2. In unadjusted models, there was a positive, significant association between PD and lung cancer (HR=1.70, 95% CI: 1.47–1.97), that was attenuated but remained significant after adjusting for age, smoking status, and pack-years of smoking (HR=1.24, 95% CI: 1.07–1.45). Addition of education, race/ethnicity, alcohol consumption, hormone use, dental visit frequency, physical activity, residence region, aspirin use, and secondhand smoke exposure did not change the models (HR=1.25, 95% CI: 1.06–1.48) and were not considered further. When stratified on smoking status, there was no association between PD and lung cancer in never-smokers (HR=1.02, 95% CI: 0.68–1.53) or current smokers (HR=1.15, 95% CI: 0.81–1.63), though lung cancer risk associated with PD remained significantly higher in women who quit smoking <20 years (HR=1.34, 95% CI: 1.05–1.70) and marginally for those who quit ≥ 20 years ($P = 0.07$). Associations between PD and lung cancer mortality was 75% higher in age-adjusted models ($P < 0.01$), but was attenuated and was no longer statistically significant after multivariable adjustment.

Analyses of interaction are shown in Table 3. Stratification across levels of pack-years of smoking demonstrates PD adds little to lung cancer risk beyond that of smoking among women with ≤ 5 pack-years smoking history (risk difference <1 case per 1,000; HR = 1.02 (95% CI: 0.73–1.43)), but adds appreciably to lung cancer risk among women with >5 pack-years smoking history (risk difference = 8.8 cases per 1,000; HR = 1.29 (95% CI: 1.09–1.53)). The pattern of findings was similar when PD and pack-years of smoking were

considered as joint exposures. A significant additive interaction was seen for PD and smoking (RERI = 0.60, $P = 0.02$), whereas interaction was not seen on the multiplicative scale (product term P -value = 0.22).

Associations between PD and lung cancer subtypes are shown in Table 4. PD was significantly associated with moderately differentiated tumors (HR=1.41, 95% CI: 1.01–1.98) and poorly differentiated tumors (HR=1.43, 95% CI: 1.02–2.01). PD was positively associated with non-small cell lung cancer (NSCLC) (HR=1.29, 95% CI: 1.10–1.51), but not with small cell lung cancer (SCLC) (HR=0.88, 95% CI: 0.52–1.49). In particular, PD was significantly associated with adenocarcinoma (HR=1.46, 95% CI: 1.18–1.79) and squamous cell carcinoma (HR=1.54, 95% CI: 1.01–2.34). No association was seen by stage.

Discussion

In one of the largest epidemiological studies on PD and lung cancer risk to date, we found that self-reported PD history was significantly associated with a 25% higher risk of incident lung cancer after extensive adjustment for smoking and other confounding factors in a well-characterized cohort of postmenopausal women. PD was not independently associated with lung cancer in never-smokers or current smokers, however there was about a 30% increased risk in former smokers. When examined jointly, there was synergism between PD and smoking on lung cancer risk such that women with a moderate to heavy smoking history (>5 pack-years) and history of PD had increased risk beyond that expected from the separate effect of each exposure. PD was associated with NSCLC as well as with more poorly differentiated tumors. Women with PD had higher risk of lung cancer death in the unadjusted model. However, this positive association was not statistically significant after multivariate adjustment. The present findings extend the small amount of evidence regarding PD and lung cancer to a large U.S. cohort of older women.

The extant published literature on PD and lung cancer is limited which somewhat constrains bringing our findings into context. Two large and comprehensive observational epidemiologic studies have reported a positive association between PD and lung cancer [13,14]. However, the associations were attributed, at least in part, to potential residual confounding by smoking. We utilized extensive available information on smoking to further understand its influence on the association between PD and lung cancer in a large prospective epidemiologic study of comparable scope as the two previous investigations. In the present seven year follow-up study of postmenopausal women, the observed significant multivariable-adjusted HR of 1.25 is comparable to the significant multivariable adjusted HR of 1.36 for self-reported PD and lung cancer reported by Michaud et al. [14] in a 18 year follow-up of U.S men, and somewhat lower than the significant multivariable adjusted HR of 1.73 for clinically measured PD and combined lung and bronchus cancer reported by Hujoel et al [13] in a 20 year follow-up of US adults (60% women) in the NHANES Follow-up Study. In our study we additionally accounted for detailed secondhand smoke exposure but it did not change the significant positive association seen here. When restricted to never-smokers, we no longer observed an association between PD and lung cancer incidence, as was also reported previously [13,14]. Our overall findings are similar to, and confirm results from the two previously published large epidemiologic investigations on PD and lung

cancer, and we extend findings to a well-characterized U.S. cohort of older postmenopausal women.

We hypothesized that PD would interact with smoking in relation to lung cancer incidence. We demonstrated a positive significant additive interaction between PD and smoking among women with at least moderate pack-years smoking history. The absolute excess risk of lung cancer per 1,000 women followed an average of seven years was 9 additional cases associated with PD beyond that attributed to smoking. This finding suggests that the presence of PD may increase susceptibility to lung cancer in women with more intensive smoking history. Given the high prevalence of PD in smokers at all ages, extrapolation of these findings to a broader population of older adults, suggests the population risk of lung cancer associated with PD among smokers could be substantial which, if confirmed, could in turn identify opportunity for targeted public health intervention to enhance lung cancer control at advanced ages.

The association between PD and lung cancer was observed to be weaker in current smokers than in former smokers. Previous research has similarly observed stronger associations for periodontitis and head and neck cancer among former smokers, but not current smokers [21]. This seemingly paradoxical observation may be accounted for by the lower prevalence of current smoking in our cohort or possibly by the biological effects of smoking itself. Current smoking causes acute gingival vasoconstriction and less inflammatory response in the gum [22], potentially concealing the overt manifestation of traditional clinical signs of PD. However, these potent immunosuppressive responses are reversible within a short time of quitting smoking [23]. In smokers with PD, the gingival damage and chronic bacterial infections do not resolve with quitting. In the absence of the acute anti-inflammatory effects of current smoking, local oral inflammatory responses are more pronounced and presence of PD can be more readily detected, which may be particularly relevant to studies in which PD is assessed by self-report. However, in the study conducted by Hiraki et al. [10], the association between tooth loss and lung cancer was strengthened when analysis was restricted to current smokers. Thus, the lack of association currently observed may be due to the small sample size of current smokers. Further investigation is needed to better understand how the acute and chronic effects smoking influence associations between PD and lung cancer.

It is plausible that chronic inflammation secondary to persistent oral infection interacts with smoking at different points of the multistage carcinogenic process to increase lung cancer risk. Both local and systemic chronic inflammation associated with PD may elevate lung cancer risk. Aspiration of oral bacteria could potentially result in bacterial colonization of the lungs [24]. Translocation of oral bacteria due to frequent transient bacteremia could also lead to bacterial seeding of the lungs [7]. Presence of oral bacteria in the lungs may stimulate a chronic inflammatory condition that fosters increased generation of chemokines, cytokines, and prostaglandins which then promote proliferation and survival of malignant cells, promotes angiogenesis and metastasis, and subverts the adaptive immune response [25]. Alternatively, recurrent bacteremia could incite a systemic inflammatory response that is involved in carcinogenesis. Individuals with periodontitis have been shown to have higher circulating levels of proinflammatory mediators, including C-reactive protein [26], which

have been associated with increased risk of lung cancer development [27,28]. PD also could be a global marker of weakened immune function and increased susceptibility to tumor initiation and progression. Additional research is necessary to clarify these putative pathways and other potential mechanisms linking PD with lung cancer.

The PD and lung cancer association may vary according to tumor characteristics. PD was significantly associated with more poorly differentiated lung tumors, which may be due to larger effect of chronic inflammation on carcinogenesis. High expression of inflammatory marker interleukin-10 in tumor-associated macrophage has been shown to be associated with poorly differentiated lung tumors [29]. Furthermore, women with PD were at elevated risk of developing NSCLC, especially adenocarcinoma and squamous cell carcinoma, indicating chronic inflammation may play a more profound role in NSCLC than SCLC. Cyclooxygenase (COX)-2 is known to be induced by numerous physiologic stimuli including inflammation [30]. There is evidence of a significant increase in COX-2 expression in adenocarcinomas in lung, but not in small cell lung cancer [31]. However, we cannot rule out the possibility that the heterogeneity across tumor characteristics was due to random variation.

There are limitations that should be considered when interpreting results of the present study. Our study included only postmenopausal women, therefore results may not be generalizable to men or premenopausal women, however our findings are consistent with those of two previous epidemiologic studies including men only [14] and men and women combined [13]. PD was self-reported and may be misclassified. However, the accuracy of self-reported PD was examined in 972 WHI-OS women enrolled in an ancillary study in Buffalo NY where oral examinations were available [32]. Self-reported PD was significantly ($P<0.001$) correlated with the presence and severity of periodontitis determined by clinical examination. Sensitivity, specificity, positive and negative predictive values for self-reported PD status were 56.2%, 78.8%, 32.8%, and 90.7%, respectively, when the criterion was severe PD defined by CDC/AAP criteria [33] (prevalence = 15%); and were 76.0%, 77.4%, 22.0%, and 97.4% when tooth loss due to periodontitis (prevalence = 7%) was the criterion. These findings support that self-reported PD provides a reasonable and accurate characterization of PD status in WHI OS women, particularly in those with more severe disease. Over 50% of the cohort reported being never-smokers and the prevalence of current smoking was small, potentially minimizing the influence smoking has on the association between PD and lung cancer. Although we employed extensive attempts to statistically account for the effect of smoking, including multivariable adjustment, stratification, and joint classification analysis, smoking exerts a powerful influence on lung cancer that is difficult to fully control in observational studies. Thus, residual confounding by smoking remains plausible.

Strengths of our study include the prospective design, allowing us to establish temporality of the association between PD and lung cancer. The large national cohort of community-dwelling postmenopausal women with average 7 years of follow-up provided sufficient statistical power to test the primary study hypothesis, although power for examining interaction is less certain. Incident lung cancer cases were adjudicated by trained physicians, reducing the probability of outcome misclassification. Our analyses included extensive

information on potential confounding factors, especially smoking-related variables, to address alternate explanations for an association between PD and lung cancer. Moreover, our study was able to evaluate this association according to various histological subtypes of lung cancer.

Conclusion

In summary, we found that PD was significantly associated with a 25% higher risk of incident lung cancer after adjustment of relevant cofactors including smoking within the overall cohort of smokers and nonsmokers combined. PD was associated with elevated risk among former smokers. PD was not independently associated with lung cancer among never-smokers or current smokers. Moderate to heavy smoking and PD jointly increased risk of developing lung cancer compared to the sum of the increased risk due to PD and pack-years of smoking alone. This suggests that presence of PD may increase susceptibility to lung cancer in heavier smokers and may identify a subgroup in whom more vigilant efforts to control both PD and smoking are warranted. Given the projected doubling of the older adult population in coming decades, and the increasing burden of periodontitis in older US adults, our epidemiologic findings are relevant to public health. Additional assessment in other cohorts is needed to further confirm the findings of the present study.

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Short List of WHI Investigators:

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Investigators and Academic Centers: (Brigham and Women's Hospital, Harvard Medical School, Boston, MA) JoAnn E. Manson; (MedStar Health Research Institute/Howard University, Washington, DC) Barbara V. Howard; (Stanford Prevention Research Center, Stanford, CA) Marcia L. Stefanick; (The Ohio State University, Columbus, OH) Rebecca Jackson; (University of Arizona, Tucson/Phoenix, AZ) Cynthia A. Thomson; (University at Buffalo, Buffalo, NY) Jean Wactawski-Wende; (University of Florida, Gainesville/Jacksonville, FL) Marian Limacher; (University of Iowa, Iowa City/Davenport, IA) Robert Wallace; (University of Pittsburgh, Pittsburgh, PA) Lewis Kuller; (Wake Forest University School of Medicine, Winston-Salem, NC) Sally Shumaker

Women's Health Initiative Memory Study: (Wake Forest University School of Medicine, Winston-Salem, NC) Sally Shumaker

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Table 1

Characteristics of participants by lung cancer incidence in Women's Health Initiative Observational Study, 1993–2010 (N=77,485)

Characteristics	Lung cancer Incidence		P-value
	No (N=76,731)	Yes (N=754)	
	N (%)		
Periodontal disease			<0.001
	No	56,789 (74.0)	467 (61.9)
	Yes	19,942 (26.0)	287 (38.1)
Education			<0.01
	<= high school diploma	15,319 (20.1)	126 (16.8)
	College or some college	36,661 (48.1)	409 (54.6)
	Post-graduate	24,166 (31.7)	214 (28.6)
Race/ethnicity			<0.001
	American Indian or Alaskan Native	305 (0.4)	4 (0.5)
	Asian or Pacific Islander	2,160 (2.8)	12 (1.6)
	Black or African-American	5,104 (6.7)	37 (4.9)
	Hispanic/Latino	2,421 (3.2)	6 (0.8)
	White (not of Hispanic origin)	65,721 (85.9)	685 (91.2)
	Other	823 (1.1)	7 (0.9)
Body Mass Index			0.04
	Underweight (<18.5)	899 (1.2)	10 (1.3)
	Normal (18.5–24.9)	29,583 (38.6)	329 (43.6)
	Overweight (25.0–29.9)	26,516 (34.6)	244 (32.4)
	Obese (≥ 30)	19,612 (25.6)	171 (22.7)
Alcohol consumption (drinks/day)			<0.001
	Never	22,808 (31.1)	189 (26.4)
	0–0.02	11,124 (15.2)	82 (11.5)
	0.03–0.09	10,339 (14.1)	90 (12.6)
	0.10–0.40	8,557 (11.7)	74 (10.3)
	0.40–1.00	8,506 (11.6)	95 (13.3)
	1	11,959 (16.3)	186 (26.0)
Hormone use			0.20
	Never used hormones	22,121 (29.7)	227 (30.8)
	Former E-alone user	8,287 (11.1)	95 (12.9)
	Current E-alone user	15,087 (20.3)	154 (20.9)
	Former E+P user	13,823 (18.6)	133 (18.1)
	Current E+P user	15,137 (20.3)	127 (17.3)
Routine dental check-ups			<0.01

Characteristics	Lung cancer Incidence		P-value
	No (N=76,731)	Yes (N=754)	
	N (%)		
Have not gone in past three years	4,720 (6.2)	67 (8.9)	
2 or more times per year	52,377 (68.3)	501 (66.4)	
Once per year	11,511 (15.0)	94 (12.5)	
Less than once per year	2,187 (2.9)	18 (2.4)	
Whenever needed	5,936 (7.7)	74 (9.8)	
Physical activity (MET-hr/wk)			<0.01
<5	26,027 (33.9)	304 (40.3)	
5–<10	12,662 (16.5)	100 (13.3)	
10–<20	19,585 (25.5)	173 (22.9)	
20–<30	9,978 (13.0)	95 (12.6)	
30	8,479 (11.1)	82 (10.9)	
US region of residence			<0.01
Northeast	17,646 (23.0)	209 (27.7)	
South	19,202 (25.0)	190 (25.2)	
Midwest	17,464 (22.8)	141 (18.7)	
West	22,419 (29.2)	214 (28.4)	
Aspirin use			0.05
No	50,824 (72.8)	476 (69.5)	
Yes	18,999 (27.2)	209 (30.5)	
Second hand smoke			<0.001
None	4,376 (5.8)	21 (2.9)	
Childhood Only	2,918 (3.9)	15 (2.0)	
Adult Home Only	4,185 (5.6)	29 (3.9)	
Adult Work Only	6,825 (9.1)	40 (5.4)	
Childhood + Adult Home	7,686 (10.3)	51 (6.9)	
Childhood + Adult Work	5,959 (8.0)	36 (4.9)	
Adult Home + Work	11,679 (15.6)	130 (17.7)	
Childhood + Adult Home + Work	31,267 (41.7)	413 (56.2)	
Smoking status			<0.001
Never	40,421 (52.7)	139 (18.4)	
Quit 20yrs	22,519 (29.3)	209 (27.7)	
Quit<20yrs	10,695 (13.9)	276 (36.6)	
Current	3,096 (4.0)	130 (17.2)	
Cigarettes smoked per day			<0.001
Never	40,421 (52.7)	139 (18.4)	
<1	2,321 (3.0)	21 (2.8)	
1–4	7,821 (10.2)	75 (10.0)	

Characteristics	Lung cancer Incidence		P-value
	No (N=76,731)	Yes (N=754)	
N (%)			
5–14	11,531 (15.0)	162 (21.5)	
15–24	8,991 (11.7)	195 (25.9)	
25–34	2,903 (3.8)	81 (10.7)	
35–44	1,895 (2.5)	49 (6.5)	
45	848 (1.1)	32 (4.2)	
Mean (SD)			
Age	68.80 (7.24)	70.76 (6.46)	<0.001
Years of follow-up	6.79 (2.62)	4.23 (2.48)	<0.001
Pack-years of smoking	9.42 (17.23)	31.10 (26.63)	<0.001
Years of smoking	11.07 (15.21)	28.68 (18.40)	<0.001

Abbreviations: MET, metabolic equivalent task.

Table 2
Associations between periodontal disease and lung cancer incidence, stratified by smoking status and edentulous status, and lung cancer mortality in Women’s Health Initiative Observational Study, 1993–2010

Lung cancer incidence	N	Lung cancer cases	HR	95% CI	P-value
Unadjusted	77,485	754	1.70	1.47–1.97	<0.01
Age adjusted	77,485	754	1.77	1.53–2.05	<0.01
Multivariable adjusted ^a	77,485	754	1.24	1.07–1.45	<0.01
Multivariable adjusted ^b	66,171	645	1.25	1.06–1.48	<0.01

Stratified by smoking status ^c					
Never smokers	40,560	139	1.02	0.68–1.53	0.93
Quit 20 years	22,728	209	1.31	0.98–1.74	0.07
Quit < 20 years	10,971	276	1.34	1.05–1.70	0.02
Current smokers	3,226	130	1.15	0.81–1.63	0.44

Stratified by edentulous status ^a					
Yes	5,258	94	1.64	1.07–2.52	0.02
No	72,227	660	1.21	1.03–1.43	0.02

Lung cancer mortality	N	Lung cancer deaths	HR	95% CI	P-value
Unadjusted	77,485	486	1.65	1.37–1.98	<0.01
Age adjusted	77,485	486	1.75	1.46–2.11	<0.01
Multivariable adjusted ^a	77,485	486	1.16	0.96–1.40	0.12
Multivariable adjusted ^b	66,171	417	1.16	0.94–1.42	0.16

Abbreviations: CI, confidence interval; HR, hazard ratio.

^a Adjusted for age, smoking status (never, quit 20yrs, quit<20yrs, current), pack-years (continuous)

^b Adjusted for age, smoking status (never, quit 20yrs, quit<20yrs, current), pack-years continuous), education, race/ethnicity, BMI, alcohol consumption, hormone use, dental visits, physical activity (MET-hr/wk), region of residence, aspirin use, secondhand smoke

^c Adjusted for age, pack-years (continuous)

Table 3

Interaction between periodontal disease and pack-years smoking on the lung cancer incidence in Women’s Health Initiative Observational Study, 1993–2010 (N=77,485)

Pack-years	PD	N	Lung cancer cases	Cumulative Incidence (per 1,000 population)	Stratified effect HR ^a (95% CI)	Joint effect HR ^a (95% CI)	Additive Interaction RERI	Multiplicative Interaction Product term P-value
Never/light (5)	No	41,275	148	3.59	1.00 (ref)	1.00 (ref)	0.60 (0.05–1.15)	P = 0.22
	Yes	11,755	43	3.66	1.02 (0.73–1.43)	1.02 (0.73–1.43)		
Moderate/heavy (>5)	No	15,981	319	19.96	1.00 (ref)	2.12 (1.52–2.96)		P = 0.02
	Yes	8,474	244	28.79	1.29 (1.09–1.53)	2.75 (1.95–3.87)		

Abbreviations: CI, confidence interval; HR, hazard ratio; PD, periodontal disease; RERI, the relative risk for interaction

^aModels adjusted for age, smoking status (never, quit 20yrs, quit < 20yrs, current), pack-years (continuous)

Table 4

Associations between periodontal disease and incident lung cancer subtypes in Women's Health Initiative Observational Study, 1993–2010

	Lung cancer	HR ^a	95% CI	P-value
Tumor Grading ^b				
Well differentiated	92	1.03	0.66–1.61	0.89
Moderately differentiated	146	1.41	1.01–1.98	0.04
Poorly differentiated	140	1.43	1.02–2.01	0.04
Anaplastic	26	1.37	0.62–3.02	0.44
Unknown	349	1.18	0.95–1.48	0.14
Tumor Histology ^b				
Small cell lung cancer	62	0.88	0.52–1.49	0.63
Non-small cell lung cancer	691	1.29	1.10–1.51	<0.01
Adenocarcinoma	379	1.46	1.18–1.79	<0.01
Squamous cell	91	1.54	1.01–2.34	0.04
Large cell/neuroendocrine	28	1.31	0.61–2.84	0.49
Other	193	0.94	0.69–1.28	0.68
Tumor Stage ^b				
Localized	216	1.30	0.98–1.72	0.07
Regional	180	1.24	0.92–1.69	0.16
Distant	270	1.15	0.89–1.47	0.29
Unknown	87	1.59	1.03–2.44	0.04

Abbreviations: CI, confidence interval; HR, hazard ratio.

^aHR (95% CI) for lung cancer comparing those with PD to those without PD (referent), models adjusted for age, smoking status (never, quit 20yrs, quit < 20yrs, current), pack-years (continuous)

^bTumor characteristics were classified according to SEER 1988, ICD-O-2 codes