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Periodontal disease severity and cancer risk in postmenopausal women: The Buffalo OsteoPerio Study

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Abstract

Purpose—Few prospective studies have reported on relationships between objective periodontal disease (PD) measures and cancer risk. This association was examined in 1,337 postmenopausal women participating in the Buffalo OsteoPerio Study.

Methods—Oral alveolar crestal bone height (ACH) was measured using oral radiographs. Incident cancers were adjudicated with medical records. Hazard ratios (HR) and 95% confidence intervals (CI) for associations between ACH and incident cancer outcomes were estimated using Cox proportional hazards models.

Results—There were 203 confirmed total incident cancer cases during follow-up (12.2±4.2 years). After adjusting for age and smoking, there were no statistically significant associations between ACH-defined PD categories and total cancer risk (mild/moderate vs. none: HR=1.33, 95%CI: 0.91–1.94; severe vs. none: HR=1.20, 95%CI: 0.77–1.86). ACH-defined PD categories were not associated with common site-specific cancers. Whole mouth mean and worst site ACH (per 1mm loss) were significantly associated with increased risk of lung (adjusted HR=1.81, 95%

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CI: 1.30–2.54; adjusted HR=1.34, 95% CI: 1.08–1.66, respectively), but not total or other site-specific cancer. Smoking status modified the associations between continuous ACH variables and total cancer risk; measures of PD were associated with total cancer among smokers but not never-smokers (interaction $p=0.02$ and $p<0.01$ for whole mouth mean and worst site ACH, respectively).

Conclusions—ACH-defined PD was associated with total cancer risk in ever but not never-smoking postmenopausal women. Whole mouth mean and worst site ACH were associated with increased lung cancer risk. However, these results need to be interpreted cautiously given the small number of lung cancer cases ($n=18$). Further research utilizing a larger sample is warranted to confirm the relationships among oral bone loss, site-specific cancers, and total cancer.

Keywords

cancer epidemiology; periodontal disease; alveolar bone loss; prospective studies; postmenopausal women; inflammation

Introduction

Periodontal disease (PD) is characterized by chronic polymicrobial infection and inflammation of the gingiva that result in loss of connective tissue and alveolar bone surrounding the teeth [1]. PD is common in the elderly. Prevalence of PD was 70.1% in U.S. adults over age 65 examined in the 2009–2010 National Health and Nutrition Examination Survey (NHANES) [2].

PD has been associated with increased risk of systemic illnesses, including cardiovascular disease, diabetes mellitus, respiratory disease, and rheumatoid arthritis [3,4]. A potential mechanism is that PD promotes systemic inflammation via translocation of oral bacteria, bacterial toxins, and inflammatory mediators through frequent transient bacteremia [5]. Notably, heightened inflammation is known to promote carcinogenesis [6]. In addition, research suggests that oral bacteria could exert direct genotoxic effects on host cells or disrupt regulation of cell proliferation and survival pathways, facilitating malignant initiation as well as progression [7,8]. Epidemiologic studies have shown that PD may be positively associated with cancers of the head and neck [9,10], pancreas [11], colorectum [12], lung [13], and breast [14]. Three prospective cohort studies have indicated that PD increases risk of total cancer as well as of certain site-specific cancers [15–17]. Additionally, greater number of tooth loss was associated with higher risk of esophageal [18,19], gastric [18,20], and lung cancer [19]. However, the majority of these studies assessed PD using self-report or used tooth loss as a proxy for PD, and were thus susceptible to misclassification bias.

Research utilizing valid and reliable measures to assess PD, with use of those measures to determine the relationship between PD and cancer risk is needed. In the current study, we examined associations between measured alveolar crestal height (ACH) – an objective clinical index of PD severity – and cancer incidence among 1,337 postmenopausal women who participated in the Buffalo Osteoporosis and Periodontal Disease (OsteoPerio) Study, a prospective ancillary study of the Women’s Health Initiative in Buffalo, New York.

Methods

Study population

Participants were postmenopausal women between 53–85 years of age enrolled in the Buffalo OsteoPerio Study, which was originally designed to investigate the role of osteoporosis in oral bone loss and periodontal disease. Details regarding enrollment of WHI as well as of OsteoPerio participants have been previously described [21,22]. Between 1997 and 2000, a total of 2,249 postmenopausal women were recruited from the WHI Observational Study at the Buffalo Clinical Center. Of these individuals, 1,359 women met all eligibility criteria and completed the OsteoPerio Study baseline visit. For these analyses, we further excluded women who failed to complete and return all study questionnaires (n=6) or had inadequate oral radiographs for ACH measurement (n=16), resulting in an analytic sample of 1,337 women (Figure 1). This study was reviewed and approved by the University at Buffalo Institutional Review Board. Written informed consent was obtained from all participants.

Measurement of alveolar crestal height

ACH is a clinical measure of cumulative history of PD that reflects alveolar bone loss resulting from long-term iterative interactions between gingival bacterial infection and the host immune response. PD severity was determined by ACH measured during standardized oral examination at baseline. ACH is the distance from the cemento-enamel junction to the most coronal portion of the alveolar crest in a plane parallel to the long axis of the tooth [22,23]. This measurement was recorded at mesial and distal sites of all teeth except for third molars and canines (maximum 24 teeth). Intraoral radiographs were taken using a high-frequency x-ray generator equipped with an adjustable anode tube head adapted specifically for the OsteoPerio study (Bennett HFQ 300 high frequency x-ray generator, Bennett X-ray Corp., Copiague, NY). During imaging, participants were positioned to maintain a constant 18° angle between the mid-sagittal plane of the head and the tube head of the radiographic unit. Exposure time ranged between 0.1 and 0.45 seconds; images were captured at 65kVP, 150mA at a focus-to-film distance of 150cm. All radiographs were developed using an automatic processor (Dent-X, Inc., Elmsford, NY) immediately after exposure and were then captured by a digital imaging system (Coreco F64PPRO DSP) for measurement. This imaging system was developed and validated by Hausmann and colleagues [23–25]. Intra-examiner and inter-examiner variability was 0.27mm (mean SD) and 0.42mm (SD), respectively, for repeated measures [23].

Ascertainment of cancer end points

Participants were followed from the beginning of the study (1997–2000) through September 30, 2014. Cancer cases excluding non-melanoma skin cancers were identified from annual health updates in the WHI-OS and were adjudicated by trained physicians using medical records [26]. Non-melanoma skin cancers were excluded because these types of cancer are relatively common, are often curable via surgical excision, and are associated with low mortality. Death certificates were used for adjudication when no medical records were available. For analyses of total cancer risk, time-to-event was defined as the interval between dates of enrollment and diagnosis of the first primary cancer at any location. For

analysis of site-specific cancer risk, time-to-event was defined as the interval between dates of enrollment and diagnosis of the first primary invasive cancer at that location.

Assessment of other variables

Participants also completed at baseline a physical examination and questionnaires regarding their medical history, health behaviors and medication use. Variables assessed as potential confounders include age at visit, race (white/other), highest level of education (high school/college/post college), smoking history, secondhand smoke exposure (never/ever), alcohol consumption (ounces/day), physical activity (total metabolic equivalent task (MET) hours/week), total energy intake (kcal/day), fruit and vegetables intake (servings/day), red meat intake (servings/day), caffeine intake (mg/day), lactose intake (g/day), hormone use (estrogen plus progesterone; never/former/current), current regular use of non-steroidal anti-inflammatory drugs (NSAIDs) (yes/no), current dietary supplement use (any vitamin, calcium, and vitamin D; yes/no), history of diagnosis of diabetes (yes/no), dental hygiene (frequency of tooth-brushing, flossing, and dental visits), family history of cancer (yes/no), age at menopause, age at menarche (9–11/12–13/ 14), parity (never pregnant or never had term pregnancy/1–2/3–4/ 5), and use of oral contraceptives (never/ever). Body mass index (BMI; kg/m²) was calculated using measured height and weight, and was further categorized as under- or normal weight (<25.0), overweight (25.0–29.9), and obese (≥ 30.0) according to WHO criteria [27]. Information on smoking history included smoking status (never/former/current), packs smoked per day, age at smoking initiation, and age at smoking cessation. Pack-years of smoking was computed by multiplying packs smoked per day by number of years smoked.

Statistical analysis

Comparisons of characteristics between women with incident cancer and the cancer-free participants were performed using Chi-square tests or Fisher's exact tests for categorical variables, and independent t-tests or Wilcoxon tests for continuous variables. Comparisons of characteristics across ACH-defined PD severity categories were performed using Chi-square tests or Fisher's exact tests for categorical variables, and analysis of variance (ANOVA) or Kruskal-Wallis tests for continuous variables. Follow-up time for each participant was calculated from the date of the OsteoPerio Study baseline visit to the date of cancer diagnosis, death from any reason, loss to follow-up, or the end of the follow-up.

Cox proportional hazards regression was used to evaluate the associations among PD severity (defined categorically and continuously using whole mouth mean and worst site ACH), risk of total cancer, and risk of common site-specific cancers with more than 10 incident cases (i.e. breast, lung, colorectal, endometrial, hematological cancers, and melanoma). For ACH-defined PD category, participants were classified as having severe PD if they had whole mouth mean ACH ≥ 3mm, or at least two sites ACH ≥ 5mm, or tooth loss due to PD; as having mild/moderate PD if they had whole mouth mean ACH ≥ 2mm to <3mm, or at least one site ACH ≥ 4mm, and no tooth loss due to PD; or as having no PD if they had whole mouth mean ACH <2mm, no sites ACH ≥ 4mm and no tooth loss due to PD [22]. This operational definition incorporated self-reported tooth loss due to PD because ACH would be unobtainable at a particular site after tooth extraction. We further

categorized PD status as any PD (mild/moderate/severe ACH loss) or no PD (no ACH loss). Moreover, we analyzed ACH as a continuous variable (mm) to maximize statistical power for both whole mouth mean loss and worst-site of loss. Hazard ratios (HR) and 95% confidence intervals (CI) of the associations were estimated in crude, age-adjusted, and multivariable-adjusted models. Potential confounding variables were selected on the basis of their associations with PD, total cancer and common site-specific cancers, as well as biologic plausibility. We assessed for the potential confounding effects of age, BMI, education, smoking, secondhand smoke exposure, family history of cancer, combined hormone use, and frequency of tooth flossing on the associations among ACH-defined periodontal disease categories, total cancer, and the most common site-specific cancers. For colorectal cancer, we additionally assessed for the effects of alcohol consumption, physical activity, NSAIDs use, history of diabetes, and dietary variables (i.e. total energy intake, red meat intake, fruits and vegetables intake, lactose intake, calcium intake, and vitamin D intake). For breast cancer and endometrial cancer, we additionally assessed for the effects of physical activity, alcohol consumption, age at menopause, age at menarche, parity, and use of oral contraceptives. Since age is a well-established risk factor for many different types of cancer, we included it in all multivariable-adjusted models. Confounders were included in all multivariable-adjusted models if the addition of them, one at a time, changed the age-adjusted HR by more than 10% for total or site-specific cancer outcomes. A parsimonious model-building approach was used to maximize statistical power and minimize potential selection bias. Participants with missing confounding variables were excluded from multivariable-adjusted models. Effect modification by smoking status (never/ever smokers) was tested by adding an interaction term (smoking status*ACH) to the multivariable-adjusted model. A two-sided p value of 0.05 was used to evaluate statistical significance. All data analysis was performed using SAS 9.3 (SAS Institute, Cary, N.C.).

Results

After an average 12.2 (± 4.2) years of follow-up, there were 203 incident cancer cases. Common site-specific cancers with more than 10 cases included breast cancer (n=89), hematologic malignancies (n=24), colorectal cancer (n=19), lung cancer (n=18), melanoma (n=13), and endometrial cancer (n=12). Participant baseline age ranged from 53 to 84 years. Most were white (97.4%), and more than half of the women were overweight or obese (56.0%). A small proportion was current smokers (3.3%), or had been diagnosed with diabetes mellitus (5.0%). Approximately 76% of participants had some forms of PD, among whom two-thirds of the women had mild/moderate ACH loss. Participant characteristics by ACH-defined periodontal disease category are presented in Table 1.

The associations among ACH-defined PD, total cancer and the common site-specific cancers are presented in Table 2. In crude models, mild/moderate PD was positively associated with total cancer risk (HR=1.49, 95%CI: 1.02–2.16), and a suggestive association was seen for severe PD and increased total cancer risk (HR=1.41, 95%CI: 0.93–2.15). These associations were attenuated and not statistically significant after adjusting for age at visit and pack-years of smoking (mild/moderate vs. none: HR=1.33, 95%CI: 0.91–1.94; Severe vs. None: HR=1.20, 95%CI: 0.77–1.86). Although not statistically significant, there was suggestive evidence of increased risk of total cancer among individuals with any PD

compared to those with no PD in the multivariable-adjusted model (HR=1.29, 95% CI: 0.89–1.87). Regarding site-specific cancers, severe ACH was significantly associated with lung cancer risk in both crude and age-adjusted models, but not when pack-years of smoking was added to the model. There were no statistically significant associations between ACH-defined PD severity categories and any site-specific cancers in multivariable-adjusted models. Further adjustment for BMI, education, secondhand smoke exposure, family history of cancer, physical activity, tooth flossing, total energy intake, and dietary factors (i.e. consumption of alcohol, red meat, fruit and vegetables, caffeine, and lactose) did not appreciably change the results (data not shown).

When analyzed as continuous variables in models adjusting for age at visit and pack-years of smoking, significantly increased lung cancer risk was seen for whole mouth mean ACH (per millimeter loss, HR=1.81, 95% CI: 1.30–2.54) and worst-site ACH (per millimeter loss, HR=1.34, 95% CI: 1.08–1.66). Neither ACH measure was statistically significantly associated with risk of total cancer or of breast, colorectal, endometrial, hematological cancer or melanoma (Table 3).

Due to the potential synergism that smoking and PD could have on cancer risk, we performed a stratified analysis of the association by smoking status (never vs. ever) (Table 4). For women who were ever smokers, PD status, ACH categories and continuous ACH variables were all statistically associated with total cancer risk in crude, age-adjusted, and multivariable-adjusted regression models. These associations were not observed among never-smokers. Statistical tests of interaction indicated smoking status significantly modified the associations of whole mouth mean ($p=0.02$) and worst-site ACH ($p<0.01$) with total cancer risk.

Discussion

To our knowledge, the present study is the first longitudinal investigation of the association between measured oral bone loss as an indicator of PD severity and total cancer risk in postmenopausal women. ACH measures as continuous variables were found to be positively associated with lung cancer risk after multivariable adjustment. The continuous measures of ACH were not associated with risk of total cancer or of other site-specific cancers. Stratified analyses revealed a significant interaction between continuous ACH measurements and smoking status on total cancer risk; PD and measures of ACH were significantly associated with total cancer among smokers but not among non-smokers. There were no statistically significant associations between ACH-defined PD severity categories and risk of total or other site-specific cancers. However, the numbers of cancers were small and limited the power of analyses.

There has been evidence of longitudinal positive associations between periodontal disease and risk of total and lung cancer [28,15–17]. In NHANES I Epidemiologic Follow-up Study, PD (assessed by probing measures and tooth mobility) was shown to be related to increased total cancer risk (OR=1.55, 95% CI: 1.01–2.97) [15]. In addition, PD was associated with lung cancer risk after adjusting for confounding variables including smoking (OR=1.73, 95% CI: 1.01–2.97). Similarly, in the Health Professionals Follow-Up Study, men with self-

reported PD were at increased risk of total cancer (HR=1.14, 95% CI: 1.07–1.22) and lung cancer (HR=1.36, 95% CI: 1.15–1.60) after multivariable adjustments [16]. In a Swedish study, PD determined by self-report of tooth mobility was found to be positively associated with risk of total cancer (HR=1.15, 95% CI: 1.01–1.32) [17]. Although smoking was adjusted in previous studies and our analyses, the observed association between PD and lung cancer could be partially explained by residual confounding of smoking, in that smoking is a strong confounding factor of this relationship.

Measurements of PD have varied across studies, including tooth mobility/loss, self-reported PD history, probing pocket depth and attachment loss. Few studies have examined cancer risk with PD severity assessed using clinically measured ACH [9,10]. This difference in measurement makes comparisons across studies difficult. Using tooth loss as a proxy for PD could be misleading as people may lose teeth for other reasons, such as dental caries and trauma. Self-reported PD is prone to misclassification bias, especially among participants with mild PD [29,30] and among those who infrequently see a dentist. Probing measures could vary with gingival inflammation and recession [31], and could improve after periodontal treatment, thus not reflect cumulative PD history which may be relevant to carcinogenesis. In contrast, ACH represents the irreversible loss of alveolar bone resulting from long-term exposure to PD by way of subgingival bacterial infection and altered host immune response. Progression of ACH loss could be mitigated by conventional periodontal treatment but the lost bone would not be significantly regained [10]. Therefore, ACH serves as an optimal measure in assessing the association between chronic PD and cancer risk, though it is not typically available in large epidemiologic studies.

Results from stratified analysis suggest that whole mouth mean and worst-site ACH were not associated with total cancer risk in never-smokers but were associated with total cancer risk in ever smokers after controlling for age at visit and pack-years of smoking. Although the interaction between PD status and smoking status did not reach statistical significance, there appears to be a qualitative difference between the effects of PD status on total cancer risk in ever smokers compared with never-smokers. Smoking has been shown to increase chronic inflammation [32] and may compromise the protective immune response to bacterial infection [33]. Moreover, several types of oral bacteria are capable of metabolizing components of tobacco smoke into carcinogens such as nitrosamines [34]. Thus the present findings may reflect a synergistic effect of PD and smoking on cancer risk. However, an alternative explanation is that the significant associations observed in ever smokers may be due to the residual confounding by smoking, despite adjustment for pack-years of smoking in our study. Previous studies have found stronger associations of PD with lung cancer [13] and head and neck cancer [10] in former smokers than in current smokers. Our study lacks statistical power to investigate these differential associations since only 36 cancer-free participants and 8 cancer patients were current smokers. Further research utilizing a larger study sample is needed to validate the modifying effect of smoking on the association between PD and cancer risk.

Our study had several limitations. Most importantly, there were relatively few cancer cases in this cohort, and therefore the results should be interpreted with caution, particularly for site-specific cancers. Power calculations indicated that we had sufficient statistical power to

detect an HR of 1.5 for total cancer for comparison of women with PD to those without. However, we may have had insufficient power to detect the possible associations between PD and risk of certain site-specific cancers. The power of our study for the stratified analyses for site-specific cancers was also restricted by small cell sizes. Additionally, this cohort of postmenopausal women consisted of volunteers, and may be more health-conscious than the general population. In general, these women had healthier behaviors and lower prevalence of risk factors common to PD and cancer including smoking, obesity and diabetes. Therefore, the generalizability of our results may be somewhat limited. However, the potential influences of these risk factors on the association of interest were minimized. Furthermore, the definition of ACH-defined PD was partially based on self-reported tooth loss due to PD. A validation study comparing the reasons for tooth loss obtained from self-reports with dental records conducted in a subset of the OsteoPerio cohort found that women tended to underreport PD as the reason for their tooth loss [35]. Therefore, women with severe ACH might be mistakenly classified into the mild/moderate category, which may explain the observed lower increase in total cancer risk in individuals with severe ACH loss compared to individuals with mild/moderate ACH loss.

Strengths of the study included the prospective design, allowing for demonstration of the temporality of the association of interest. In addition, each participant underwent a detailed oral examination with assessment of ACH conducted according to rigorous standardized protocols by trained dental examiners. Information on baseline characteristics related to both PD and cancer was extensively collected, allowing adjustment for potential confounding variables. Furthermore, cancer cases were adjudicated by trained physicians using medical records, which reduced the likelihood of outcome misclassification.

Conclusions

In this sample of postmenopausal women, there were no statistically significant associations between ACH-defined PD severity categories and risk of total cancer or of common site-specific cancers. Whole mouth mean and worst site ACH were statistically significantly associated with lung cancer risk. Smoking status modified the association of continuous ACH and total cancer risk, such that PD severity was associated with increased cancer risk among ever but not never-smokers. Interpretation of these results is limited by the low number of incident cancers. Further research utilizing a larger sample is warranted to confirm the relationships among oral bone loss, site-specific cancers, and total cancer.

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Figure 1.
Flow chart of the Buffalo OsteoPerio Study participant

Table 1
 Characteristics of participants by ACH-defined periodontal disease severity in the Buffalo OsteoPerio Study (N=1,337)

	Total N=1,337	None N=315	Mild/Mod N=665	Severe N=357	P value ^a
N (%)					
Total cancer					0.13
No	1134 (84.8)	278 (88.3)	554 (83.3)	302 (84.6)	
Yes	203 (15.2)	37 (11.7)	111 (16.7)	55 (15.4)	
Breast cancer					0.58
No	1248 (93.3)	296 (94.0)	616 (92.6)	336 (94.1)	
Yes	89 (6.7)	19 (6.0)	49 (7.4)	21 (5.9)	
Colorectal cancer					0.40
No	1318 (98.6)	313 (99.4)	654 (98.3)	351 (98.3)	
Yes	19 (1.4)	2 (0.6)	11 (1.7)	6 (1.7)	
Lung cancer					0.02
No	1319 (98.7)	314 (99.7)	658 (99.0)	347 (97.2)	
Yes	18 (1.3)	1 (0.3)	7 (1.0)	10 (2.8)	
Endometrial cancer					1.00
No	1325 (99.1)	312 (99.0)	659 (99.1)	354 (99.2)	
Yes	12 (0.9)	3 (1.0)	6 (0.9)	3 (0.8)	
Melanoma					1.00
No	1324 (99.0)	312 (99.0)	658 (98.9)	354 (99.2)	
Yes	13 (1.0)	3 (1.0)	7 (1.1)	3 (0.8)	
Hematological cancer^b					0.09
No	1313 (98.2)	310 (98.4)	657 (98.8)	346 (96.9)	
Yes	24 (1.8)	5 (1.6)	8 (1.2)	11 (3.1)	
BMI category					0.36
Under- or normal weight (<25.0)	588 (44.0)	132 (41.9)	301 (45.3)	155 (43.4)	
Overweight (25.0–29.9)	465 (34.8)	107 (34.0)	238 (35.8)	120 (33.6)	
Obese (≥ 30.0)	284 (21.2)	76 (24.1)	126 (18.9)	82 (23.0)	
Highest level of education					<0.01

	Total N=1,337	None N=315	Mild/Mod N=665	Severe N=357	P value ^a
High School	280 (21.3)	49 (15.8)	149 (22.8)	82 (23.4)	
College	585 (44.5)	145 (46.6)	271 (41.4)	169 (48.1)	
Post College	451 (34.3)	117 (37.6)	234 (35.8)	100 (28.5)	
Missing	21	4	11	6	
Race					0.35
White	1,302 (97.4)	310 (98.4)	647 (97.3)	345 (96.6)	
Other	35 (2.6)	5 (1.6)	18 (2.7)	12 (3.4)	
Cigarette smoking status					<0.01
Never	705 (52.8)	199 (63.2)	368 (55.4)	138 (38.7)	
Former	587 (43.9)	113 (35.9)	279 (42.0)	195 (54.6)	
Current	44 (3.3)	3 (1.0)	17 (2.6)	24 (6.7)	
Missing	1	0	1	0	
Secondhand smoke exposure					0.01
None	60 (4.5)	13 (4.2)	40 (6.1)	7 (2.0)	
Yes	1,259 (95.5)	300 (95.8)	617 (93.9)	342 (98.0)	
Missing	18	2	8	8	
Calcium intake					<0.01
No	382 (28.6)	72 (22.9)	186 (28.0)	124 (34.7)	
Yes	955 (71.4)	243 (77.1)	479 (72.0)	233 (65.3)	
Vitamin D intake					0.02
No	563 (42.1)	114 (36.2)	281 (42.3)	168 (47.1)	
Yes	774 (57.9)	201 (63.8)	384 (57.7)	189 (52.9)	
Any supplement intake					0.09
No	199 (14.9)	45 (14.3)	89 (13.4)	65 (18.4)	
Yes	1,134 (85.1)	270 (85.7)	576 (86.6)	288 (81.6)	
Missing	4	0	0	4	
Diagnosed/treated with diabetes					0.71
No	1,270 (95.0)	302 (95.9)	630 (94.7)	338 (94.7)	
Yes	67 (5.0)	13 (4.1)	35 (5.3)	19 (5.3)	
Hormone combined therapy					<0.01
Never	436 (32.6)	82 (26.0)	223 (33.5)	131 (36.7)	

	Total N=1,337	None N=315	Mild/Mod N=665	Severe N=357	P value ^a
Former	269 (20.1)	62 (19.7)	127 (19.1)	80 (22.4)	
Current	632 (47.3)	171 (54.3)	315 (47.4)	146 (40.9)	
Oral contraceptives use					<0.01
Never	779 (58.3)	162 (51.4)	389 (58.5)	228 (63.9)	
Ever	558 (41.7)	153 (48.6)	276 (41.5)	129 (36.1)	
Any NSAIDs use					0.44
No	722 (54.2)	178 (56.5)	349 (52.5)	195 (55.2)	
Yes	611 (45.8)	137 (43.5)	316 (47.5)	158 (44.8)	
Missing	4	0	0	4	
Frequency of tooth brushing					0.86
<twice/day	304 (22.7)	73 (23.2)	147 (22.1)	84 (23.5)	
twice/day	1,033 (77.3)	242 (76.8)	518 (77.9)	273 (76.5)	
Frequency of tooth flossing					<0.01
Not every day	749 (56.3)	205 (65.1)	362 (54.6)	182 (51.7)	
Every day	581 (43.7)	110 (34.9)	301 (45.4)	170 (48.3)	
Missing	7	0	2	5	
Frequency of dental visits					0.50
> once/year	1024 (76.6)	239 (75.9)	518 (77.9)	267 (74.8)	
once/year	313 (23.4)	76 (24.1)	147 (22.1)	90 (25.2)	
Family history of cancer					0.93
No	426 (32.8)	100 (32.9)	215 (33.2)	111 (32.0)	
Yes	873 (67.2)	204 (67.1)	433 (66.8)	236 (68.0)	
Missing	38	11	17	10	
Age at menarche					0.21
9–11	287 (21.5)	75 (23.9)	134 (20.2)	78 (21.9)	
12–13	785 (58.9)	183 (58.3)	406 (61.2)	196 (55.1)	
>=14	261 (19.6)	56 (17.8)	123 (18.6)	82 (23.0)	
Missing	4	1	2	1	
Parity					0.10
Never pregnant or never had term	168 (12.6)	40 (12.7)	75 (11.3)	53 (14.9)	
1–2	375 (28.1)	103 (32.7)	183 (27.6)	89 (25.1)	

	Total N=1,337	None N=315	Mild/Mod N=665	Severe N=357	P value ^a
3-4	570 (42.8)	128 (40.6)	298 (45.0)	144 (40.6)	
>=5	220 (16.5)	44 (14.0)	107 (16.1)	69 (19.4)	
Missing	4	1	1	1	
Mean (SD)					
Age at visit	66.7 (7.0)	63.6 (6.3)	67.1 (6.9)	68.6 (7.1)	<0.01
Age at menopause	49.3 (5.7)	48.9 (5.7)	49.5 (5.7)	49.2 (5.8)	0.27
Missing	43	7	23	13	
BMI	26.6 (5.2)	27.0 (5.1)	26.4 (5.0)	26.6 (5.5)	0.25
Pack-years of smoking	10.1 (18.1)	4.9 (11.2)	8.2 (15.9)	18.4 (23.5)	<0.01
Missing	30	5	14	11	
Physical activity (MET-hour/week)	14.3 (14.3)	16.5 (16.1)	13.6 (13.5)	13.6 (13.8)	0.05
Missing	42	9	20	13	
Alcohol (ounces/day)	0.5 (0.7)	0.4 (0.6)	0.4 (0.7)	0.5 (0.7)	0.58
Missing	18	6	6	6	
Energy intake (Kcal/day)	1548.5 (544.6)	1617.0 (561.3)	1525.0 (526.6)	1530.7 (558.6)	0.04
Missing	54	9	29	16	
Fruit & vegetables intake (medium servings/day)	4.6 (2.1)	4.5 (2.2)	4.7 (2.0)	4.4 (2.1)	0.08
Missing	54	9	29	16	
Red meat intake (medium servings/day)	0.6 (0.5)	0.6 (0.5)	0.6 (0.5)	0.6 (0.5)	0.08
Missing	54	9	29	16	
Caffeine intake (mg/day)	168.5 (128.4)	160.3 (129.5)	164.5 (122.0)	183.3 (137.9)	0.09
Missing	54	9	29	16	
Lactose intake (g/day)	19.2 (15.4)	18.4 (13.8)	19.2 (15.0)	19.9 (17.3)	0.05
Missing	54	9	29	16	

^a P-value for ANOVA or Kruskal-Wallis test for continuous variables and for Chi-square or Fisher's exact tests for categorical variables

^b Hematological cancer includes leukemia, lymphoma (Hodgkin's and Non-Hodgkin's), and multiple myeloma

Table 2

Associations between ACH-defined periodontal disease severity and cancer risk

	Total N	Case N	None N=315	Mild/moderate N=665	Severe N=357
			Ref	HR (95% CI)	HR (95% CI)
Total cancer (n=203)			37	111	55
Crude model	1,337	203	1.00	1.49 (1.02–2.16)	1.41 (0.93–2.15)
Adjusted model ^a	1,337	203	1.00	1.37 (0.94–2.00)	1.27 (0.83–1.94)
Adjusted model ^b	1,307	202	1.00	1.33 (0.91–1.94)	1.20 (0.77–1.86)
Breast cancer (n=89)			19	49	21
Crude model	1,337	89	1.00	1.25 (0.74–2.12)	1.03 (0.55–1.92)
Adjusted model ^a	1,337	89	1.00	1.20 (0.70–2.05)	0.97 (0.51–1.83)
Adjusted model ^b	1,307	88	1.00	1.15 (0.67–1.99)	0.94 (0.49–1.82)
Colorectal cancer (n=19)			2	11	6
Crude model	1,337	19	1.00	2.66 (0.59–11.98)	2.79 (0.56–13.82)
Adjusted model ^a	1,337	19	1.00	2.15 (0.47–9.91)	2.09 (0.41–10.69)
Adjusted model ^b	1,307	19	1.00	2.09 (0.45–9.67)	1.94 (0.36–10.35)
Lung cancer (n=18)			1	7	10
Crude model	1,337	18	1.00	3.35 (0.41–27.25)	9.29 (1.19–72.60)
Adjusted model ^a	1,337	18	1.00	3.28 (0.40–26.95)	9.00 (1.12–71.99)
Adjusted model ^b	1,307	18	1.00	2.54 (0.30–21.22)	4.61 (0.55–38.70)
Endometrial cancer (n=12)			3	6	3
Crude model	1,337	12	1.00	0.95 (0.24–3.80)	0.91 (0.18–4.53)
Adjusted model ^a	1,337	12	1.00	0.86 (0.21–3.56)	0.80 (0.15–4.17)
Adjusted model ^b	1,307	12	1.00	0.95 (0.23–3.93)	1.10 (0.20–5.93)
Melanoma (n=13)			3	7	3
Crude model	1,337	13	1.00	1.11 (0.29–4.31)	0.92 (0.19–4.58)

	Total N	Case N	None N=315	Mild/moderate N=665	Severe N=357
			Ref	HR (95% CI)	HR (95% CI)
Adjusted model ^a	1,337	13	1.00	0.97 (0.24–3.86)	0.76 (0.15–3.96)
Adjusted model ^b	1,307	13	1.00	0.89 (0.22–3.61)	0.61 (0.11–3.38)
Hematological cancer (n=24)					
			5	8	11
Crude model	1,337	24	1.00	0.77 (0.25–2.35)	2.09 (0.73–6.02)
Adjusted model ^a	1,337	24	1.00	0.70 (0.22–2.17)	1.83 (0.61–5.45)
Adjusted model ^b	1,307	24	1.00	0.72 (0.23–2.26)	2.09 (0.68–6.47)

^aModel adjusted for age at visit (continuous)

^bModel adjusted for age at visit (continuous) and pack-years of smoking (continuous)

Table 3The hazard ratio of cancer with each 1mm increase in whole mouth mean and worst site ACH

	Total N	Case N	Whole Mouth Mean ACH	Worst Site ACH
			HR (95% CI)	HR (95% CI)
Total cancer (n=203)				
Crude model	1,337	203	1.14 (0.97–1.33)	1.05 (0.96–1.14)
Adjusted model ^a	1,337	203	1.07 (0.91–1.27)	1.03 (0.94–1.12)
Adjusted model ^b	1,307	202	1.04 (0.87–1.25)	1.02 (0.93–1.11)
Breast cancer (n=89)				
Crude model	1,337	89	0.96 (0.72–1.26)	0.96 (0.83–1.11)
Adjusted model ^a	1,337	89	0.92 (0.68–1.23)	0.95 (0.82–1.10)
Adjusted model ^b	1,307	88	0.90 (0.66–1.22)	0.94 (0.81–1.10)
Colorectal cancer (n=19)				
Crude model	1,337	19	1.40 (0.92–2.13)	1.24 (0.99–1.56)
Adjusted model ^a	1,337	19	1.25 (0.79–1.97)	1.19 (0.94–1.52)
Adjusted model ^b	1,307	19	1.21 (0.75–1.97)	1.18 (0.92–1.51)
Lung cancer (n=18)				
Crude model	1,337	18	1.96 (1.51–2.54)	1.44 (1.18–1.75)
Adjusted model ^a	1,337	18	1.97 (1.49–2.62)	1.43 (1.16–1.75)
Adjusted model ^b	1,307	18	1.81 (1.30–2.54)	1.34 (1.08–1.66)
Endometrial cancer (n=12)				
Crude model	1,337	12	0.65 (0.26–1.65)	0.82 (0.52–1.29)
Adjusted model ^a	1,337	12	0.57 (0.21–1.56)	0.78 (0.49–1.26)
Adjusted model ^b	1,307	12	0.68 (0.24–1.88)	0.83 (0.52–1.34)
Melanoma (n=13)				
Crude model	1,337	13	0.95 (0.45–1.98)	1.03 (0.73–1.46)
Adjusted model ^a	1,337	13	0.85 (0.38–1.89)	1.00 (0.70–1.43)
Adjusted model ^b	1,307	13	0.74 (0.31–1.75)	0.97 (0.66–1.41)
Hematological cancer (n=24)				
Crude model	1,337	24	1.23 (0.79–1.90)	1.20 (0.96–1.49)
Adjusted model ^a	1,337	24	1.15 (0.73–1.84)	1.17 (0.94–1.47)
Adjusted model ^b	1,307	24	1.19 (0.75–1.90)	1.19 (0.94–1.49)

^a Model adjusted for age at visit (continuous)^b Model adjusted for age at visit (continuous) and pack-years (continuous)

Table 4

Association of Alveolar Crestal Height (ACH) with total cancer stratified by smoking status (never vs. ever)

	Crude model	Age-adjusted model	Age- and smoking-Adjusted model ^a
Smoking status	HR	HR	HR
Never-smokers			
Total N	705	705	705
Cancer N	111	111	111
Periodontal disease (yes vs. no)	1.15 (0.76–1.76)	1.04 (0.68–1.61)	N/A
ACH (Mild/moderate vs. none)	1.19 (0.77–1.86)	1.09 (0.70–1.71)	N/A
ACH (Severe vs. none)	1.05 (0.59–1.85)	0.90 (0.51–1.62)	N/A
Mean ACH (per mm)	0.92 (0.69–1.22)	0.82 (0.61–1.11)	N/A
Worst ACH (per mm)	0.92 (0.80–1.05)	0.88 (0.76–1.02)	N/A
Ever smokers			
Total N	631	631	602
Cancer N	92	92	91
Periodontal disease (yes vs. no)	2.56 (1.24–5.29)	2.36 (1.14–4.88)	2.20 (1.05–4.60)
ACH (Mild/moderate vs. none)	2.56 (1.21–5.40)	2.37 (1.12–5.02)	2.23 (1.05–4.74)
ACH (Severe vs. none)	2.57 (1.19–5.54)	2.32 (1.07–5.03)	2.12 (0.96–4.70)
Mean ACH (per mm)	1.35 (1.10–1.65)	1.30 (1.05–1.60)	1.25 (1.00–1.56)
Worst ACH (per mm)	1.17 (1.05–1.31)	1.16 (1.04–1.29)	1.15 (1.03–1.29)
P for multiplicative interaction			
Smoking status*periodontal disease status	0.06	0.06	0.08
Smoking status*ACH categories	0.16	0.14	0.19
Smoking status*mean ACH (continuous)	0.03	0.01	0.02
Smoking status*worst ACH (continuous)	<0.01	<0.01	<0.01

^a Adjusted for age at visit (continuous) and pack-years of smoking (continuous)