Research Article

Cancer Epidemiology, Biomarkers & Prevention

Periodontal Disease and Incident Cancer Risk among Postmenopausal Women: Results from the Women's Health Initiative Observational Cohort

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Abstract

Background: Periodontal pathogens have been isolated from precancerous and cancerous lesions and also shown to promote a procarcinogenic microenvironment. Few studies have examined periodontal disease as a risk factor for total cancer, and none have focused on older women. We examined whether periodontal disease is associated with incident cancer among postmenopausal women in the Women's Health Initiative Observational Study.

Methods: Our prospective cohort study comprised 65,869 women, ages 54 to 86 years. Periodontal disease information was obtained via self-report questionnaires administered between 1999 and 2003, whereas ascertainment of cancer outcomes occurred through September 2013, with a maximum follow-up period of 15 years. Physician-adjudicated incident total cancers were the main outcomes and site-specific cancers were secondary outcomes. HRs and 95% confidence intervals (CI) were calculated using Cox proportional hazards regression. All analyses were conducted two-sided.

Results: During a mean follow-up of 8.32 years, 7,149 cancers were identified. Periodontal disease history was associated with increased total cancer risk (multivariable-adjusted HR, 1.14; 95% CI, 1.08–1.20); findings were similar in analyses limited to 34,097 never-smokers (HR, 1.12; 95% CI, 1.04–1.22). Associations were observed for breast (HR, 1.13; 95% CI, 1.03–1.23), lung (HR, 1.31; 95% CI, 1.14–1.51), esophagus (HR, 3.28; 95% CI, 1.64–6.53), gallbladder (HR, 1.73; 95% CI, 1.01–2.95), and melanoma skin (HR, 1.23; 95% CI, 1.02–1.48) cancers. Stomach cancer was borderline (HR, 1.58; 95% CI, 0.94–2.67).

Conclusions: Periodontal disease increases risk of total cancer among older women, irrespective of smoking, and certain anatomic sites appear to be vulnerable.

Impact: Our findings support the need for further understanding of the effect of periodontal disease on cancer outcomes.
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Introduction

Periodontal disease has been linked to an increased risk of total cancer (1–2) and certain site-specific cancers (3–6). The mechanism for the association is not clear. Periodontal pathogens could potentially translocate extra-orally in saliva via ingestion to infect esophageal (7) or colonic tissues (8), or by aspiration into the lungs (9, 10). These pathogens could also permeate through diseased periodontal tissues into the systemic circulation to reach distant sites (11). There are numerous scientific reports of periodontal pathogen isolates in various organ systems including lymph nodes (12), arteries (13, 14), lung aspirates (9, 10), precancerous gastric (15) and colon lesions (16), and esophageal (17) and colorectal cancers (18, 19). At the target site, periodontopathogens may promote a permissive microenvironment conducive to cancer progression (8, 16, 20).

Few epidemiologic studies have examined periodontal disease in relation to incident total cancer risk (1, 2), and no large-scale studies have specifically targeted postmenopausal women. Because periodontal disease is more prevalent with increasing age (21) and most cancers tend to have a long latency period, examination of periodontal disease and cancer risk among older women is particularly important. The public health implications could be significant given the projected increase in numbers of older women in the United States in the coming decades.

Materials and Methods

Study participants

We conducted a prospective cohort study among Women's Health Initiative Observational Study (WHI-OS) participants. The WHI-OS is a national ongoing prospective study designed to investigate factors affecting risk of morbidity and mortality in

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older women (22). Recruitment occurred between 1994 and 1998 and involved relatively healthy, community-dwelling postmenopausal women, ages 50 to 79 years, at 40 participating U.S. clinical centers (23). Structured self-, and interviewer-administered questionnaires; physical measurements; and blood draws were the main modes of data collection at baseline enrollment. Subsequently, annual appraisals were conducted via study questionnaires in order to capture health outcomes and additional information on risk factors. One in-person follow-up visit occurred at year 3. Detailed information on the WHI-OS has been published previously (23). This study was approved by the Institutional Review Boards at the participating institutions, and all women provided written consent.

A total of 93,976 women enrolled in the WHI-OS. Our analytical cohort comprised women who completed the annual Year-5 WHI-OS follow-up questions relating to periodontal disease and oral health. In total 65,869 women were included in this present analysis. Our exclusions included 12,173 participants who failed to return the Year 5 Questionnaire or were missing information on the questionnaire pertaining to periodontal disease. Other study exclusion criteria included history of any invasive cancer prior to Year-5, which served as the baseline for this analysis, ($n = 14,271$); missing follow-up information after Year 5 ($n = 879$); and missing information on smoking status ($n = 784$; Fig. 1).

Periodontal disease history ascertainment

Year-5 (Form 145) was used to assess periodontal disease history. Participants were asked: "*Has a dentist or dental hygienist ever told you that you had periodontal or gum disease? (No/Yes)*." This question has been previously compared against a standardized clinical periodontal examination within a subset of this study population (24). The sensitivity, specificity, positive predictive value, and negative predictive value obtained for periodontal disease via the self-report questionnaires were 56.2%, 78.8%, 32.8%, and 90.7%, respectively, when compared with the findings from participants diagnosed with severe periodontal disease, based on the Centers for Disease Control and Prevention/American Academy of Periodontology case definition for periodontal disease.

Confounder assessment

Confounding variables were considered from detailed information collected on risk factors for cancer using questionnaires administered at WHI-OS enrollment. Specific questions focused on age, race/ethnicity, educational level, region of residence, family history of cancer, history of diabetes, recreational physical activity, smoking status, pack-years of smoking, secondhand smoke exposure, alcohol consumption, total dietary energy intake, fruit and vegetable intake, total (dietary and supplement) intake of calcium and vitamin D, and menopausal hormone therapy (HT) use. Frequency of dental visits was captured in the Year-5 WHI-OS questionnaire. Body mass index (BMI) was calculated from measured weight and height of participants by trained examiners at the clinical centers.

Outcomes measures

The primary outcome was incident total cancer which comprised the first invasive cancer diagnosed after completion of the Year 5 Questionnaire, excluding nonmelanoma skin cancers. Secondary outcomes of interest include region- and site-specific cancers. Time-to-event analysis for each site-specific cancer was assessed independent of other cancer sites (for those reporting more than one cancer). For region-specific and total cancer analyses, the time-to-event analyses were based on whichever cancer occurred first for that group. Cancers were identified via annual participant health updates from Year-5 through September 2013, the last date of complete outcome collection for these analyses. Self-reported cancers were confirmed by both local and central physician adjudicators using participants' medical records (25). Central adjudicators were responsible for the final cancer outcome coding, based on the Surveillance Epidemiology and End Result (SEER), International Classification of Diseases for Oncology (ICD-O-2; ref. 26).

Statistical analyses

Participants with and without a cancer diagnosis were compared using independent t tests and χ^2 tests. Person-time was calculated from the date of Year-5 WHI-OS questionnaire completion until date of the first incident cancer diagnosis (or site-specific cancer diagnosis in secondary analyses), or until censoring from death, loss to follow-up, or end of follow-up period (September 2013). For the site-specific cancer cases in our secondary analyses, all primary cancer cases were by default included in our study, regardless if it was the first or second primary cancer. This ensured we captured all cancer occurrences. Annualized incidence was estimated using the following formula: [no. of events/(no. at risk $\times$ mean follow-up years)] $\times$ 100. Cox regression analyses were utilized in estimating HRs and 95% confidence intervals (CI; ref. 27). Unadjusted and age-adjusted models were initially conducted and then evaluated for the contribution of each additional covariate to determine their inclusion in the final multivariate models, using the change-in-estimate method, defining an appreciable change in HR as 10%. A fixed set of covariates was used in the final multivariable-adjusted analyses for total-, region-, and site-specific cancer risks. HRs were calculated for total cancer and individual sites or regions with at least 20 reported cancer cases.

Multiplicative interactions of periodontal disease with each of the following factors determined *a priori* were tested: age, smoking status, BMI, history of diabetes, and HT use. Interaction was assessed using cross-product terms in multivariate regression models, and an interaction term P value level of significance was set *a priori* at 0.2. Because smoking is such an important risk factor for cancer, stratified analyses by smoking status (never, former, current) were conducted. To address possible residual confounding by smoking, analyses restricted to never-smokers were reported and pack years of smoking was included in the multivariate-adjusted models of former and current smokers. Finally, a sensitivity analysis was conducted to examine the association between periodontal disease and total cancer in those who obtained dental checkups at least 1/year (combining 1/year and $\geq$2/year). The Statistical Analysis System (SAS) for Windows 9.3 (SAS Institute, Inc.) was utilized for all analyses. All analyses were conducted two-sided with alpha set at 0.05. Proportional hazards assumption was tested and met.

Results

In total, 7,149 cancers occurred in 65,869 women during a mean follow-up of 8.32 (SD $\pm$3.95) years yielding an annualized percent of 1.4. Breast cancers constituted the majority of cases ($n = 2,416$), followed by lung and bronchus ($n = 855$), and colon and rectum ($n = 639$). Digestive organ cancers made up 1,262 of the

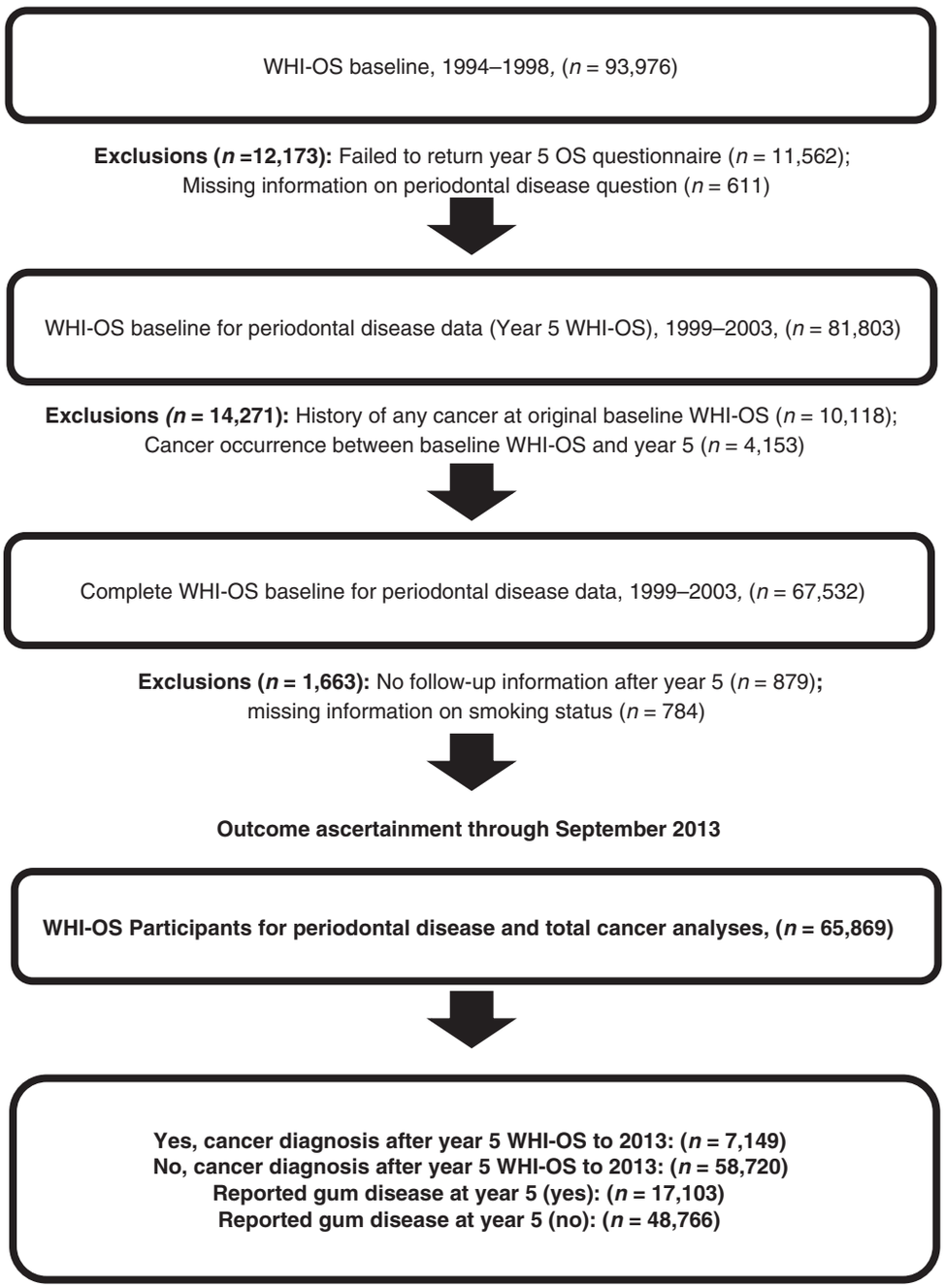

Figure 1.
Enrollment flowchart for the Women's Health Initiative Observational Study (WHI-OS).

cases, with 478 upper digestive- and 712 lower digestive tract/organ cases. There were also 1,186 genitourinary cancers, 820 lymphoid and hematopoietic malignancies, and 68 lip, oral cavity, and oral pharynx cancers combined.

Mean age of participants was 68.3 years, most were non-Hispanic whites, had at least some college education, and reported visiting the dentist at least 2 times/year. Periodontal disease cases were more likely to report a history of smoking, secondhand smoke exposure, alcohol consumption, HT (estrogen + progestin) use, and a cancer diagnosis. No appreciable difference was noted between the periodontal disease cases and non-cases in terms of BMI, levels of physical activity, and history of diabetes. There were statistically significant but small differences relative to total energy intake, fruit and vegetable consumption, and total intake of calcium and vitamin D (participant characteristics are summarized in Table 1).

Table 1. Characteristics of the participants by periodontal disease status, WHI-OS

	Periodontal disease Yes *N* (%)[a]	Periodontal disease No *N* (%)[a]	*P*[b]
Age	(*n* = 17,103)	(*n* = 48,766)	<0.01
Mean (SD)[c]	67.90 (6.96)	68.78 (7.29)	
(Missing *n* = 0)	0	0	
Race/ethnicity	(*n* = 17,059)	(*n* = 48,646)	<0.01
Non-Hispanic white	14,509 (85.05)	41,532 (85.38)	
Black or African American	1,378 (8.08)	3,115 (6.40)	
Hispanic/Latino	479 (2.81)	1,719 (3.53)	
Asian/Pacific Islanders	430 (2.52)	1,540 (3.17)	
American Indians	71 (0.42)	202 (0.42)	
Other	192 (1.13)	538 (1.11)	
(Missing *n* = 164)	44	120	
Region	(*n* = 17,103)	(*n* = 48,766)	<0.01
Northeast	4,346 (25.41)	11,063 (22.69)	
South	4,297 (25.12)	12,054 (24.72)	
Midwest	3,393 (19.84)	11,413 (23.40)	
West	5,067 (29.63)	14,236 (29.19)	
(Missing *n* = 0)	0	0	
Education	(*n* = 16,975)	(*n* = 48,388)	<0.01
Up to high school diploma or GED	2,653 (15.63)	10,545 (21.79)	
Some college (vocational or associate degree)	5,950 (35.05)	17,727 (36.64)	
College graduate	8,372 (49.32)	20,116 (41.57)	
(Missing *n* = 506)	128	378	
BMI (Kg/m^2)[d]	(*n* = 17,079)	(*n* = 48,682)	0.07
Underweight and normal weight (≤24.9)	6,737 (39.45)	19,568 (40.20)	
Overweight (≥25.0–29.9)	6,044 (35.39)	16,769 (34.45)	
Obesity (≥30.0)	4,298 (25.17)	12,345 (25.36)	
(Missing *n* = 108)	24	84	
Physical activity (MET hrs/wk)	(*n* = 17,103)	(*n* = 48,766)	0.42
(Mean, SD)[c]	13.51 (13.60)	13.42 (14.01)	
(Missing *n* = 0)	0	0	
Smoking status	(*n* = 17,103)	(*n* = 48,766)	<0.01
Never smoked	7,245 (42.36)	26,852 (55.06)	
Past smoker	8,811 (51.52)	20,200 (41.42)	
Current smoker	1,047 (6.12)	1,714 (3.51)	
(Missing *n* = 0)	0	0	
Pack years of smoking	(*n* = 16,664)	(*n* = 47,665)	<0.01
Mean, (SD)[c]	13.50 (20.25)	7.97 (15.78)	
(Missing *n* = 1,540)	439	1,101	
Passive smoking exposure (secondhand smoking exposure quantified)	(*n* = 16,560)	(*n* = 47,233)	<0.01
None	724 (4.37)	3,040 (6.44)	
No childhood + any adult	4,823 (29.12)	14,469 (30.63)	
Childhood < 10 yrs + any adult	1,620 (9.78)	4,350 (9.21)	
Childhood ≥ 10 yrs + adult home < 20 yrs + adult work < 10 yrs	3,272 (19.76)	10,248 (21.70)	
Childhood ≥ 10 yrs + adult home < 20 yrs + adult work ≥ 10 yrs	2,055 (12.41)	4,884 (10.34)	
Childhood ≥ 10 yrs + adult home ≥ 20 yrs + adult work < 10 yrs	1,671 (10.09)	4,882 (10.34)	
Childhood ≥ 10 yrs + adult home ≥ 20 yrs + adult work ≥ 10 yrs	2,395 (14.46)	5,360 (11.35)	
(Missing *n* = 2,076)	543	1,533	
Alcohol intake	(*n* = 17,040)	(*n* = 48,560)	<0.01
Nondrinker	1,292 (7.58)	5,724 (11.79)	
Past drinker	2,909 (17.07)	8,674 (17.86)	
<1 drink/month	1,838 (10.79)	5,808 (11.96)	
<1 drink/week	3,443 (20.21)	9,942 (20.47)	
1 to <7 drinks/week	4,899 (28.75)	12,603 (25.95)	
7+ drinks/week	2,659 (15.60)	5,809 (11.96)	
(Missing *n* = 269)	63	206	
Dietary intake	(*n* = 17,102)	(*n* = 48,762)	
Dietary energy, mean (kcal)	1,499.5 (617.3)	1,472.7 (630.9)	<0.01
(Missing *n* = 5)	1	4	
Fruit (total no.), Med servings/day	2.01 (1.30)	2.04 (1.30)	0.01
(Missing *n* = 5)	1	4	
Vegetables (total no.), Med servings/day	2.30 (1.36)	2.27 (1.37)	0.03
(Missing *n* = 5)	1	4	
Supplement use (multivitamin)	(*n* = 17,103)	(*n* = 48,766)	0.75
No	9,163 (53.58)	26,058 (53.43)	
Yes	7,940 (46.42)	22,708 (46.57)	
(Missing *n* = 0)	0	0	

(Continued on the following page)

Table 1. Characteristics of the participants by periodontal disease status, WHI-OS (Cont'd)

	Periodontal disease Yes N (%)[a]	Periodontal disease No N (%)[a]	P[b]
Dietary and supplement (calcium)	(*n* = 17,102)	(*n* = 48,762)	0.02
Mean (SD)[c]	795.1 (457.1)	785.7 (464.3)	
(Missing *n* = 5)	1	4	
Dietary and supplement (Vitamin D)	(*n* = 17,102)	(*n* = 48,762)	0.04
Mean (SD)[c]	4.46 (3.19)	4.40 (3.25)	
(Missing *n* = 5)	1	4	
E-Alone status	(*n* = 16,337)	(*n* = 46,582)	<0.01
Never used	9,233 (56.52)	25,171 (54.04)	
Past use	2,776 (16.99)	8,487 (18.22)	
Current use	4,328 (26.49)	12,924 (27.74)	
(Missing *n* = 2,950)	766	2,184	
E + P status	(*n* = 16,169)	(*n* = 45,892)	<0.01
Never used	8,975 (55.51)	27,105 (59.06)	
Past use	3,113 (19.25)	8,394 (18.29)	
Current use	4,081 (25.24)	10,393 (22.65)	
(Missing *n* = 3,808)	934	2,874	
E-Alone and E + P status combined	(*n* = 16,633)	(*n* = 47,311)	0.02
Never used either	4,616 (27.75)	13,479 (28.49)	
Past use of either E-alone or E + P	3,608 (21.69)	10,515 (22.23)	
Current use of either E-alone or E+P	8,409 (50.56)	23,317 (49.28)	
(Missing *n* = 1,925)	470	1,455	
Diabetes, diagnosed/treated	(*n* = 17,087)	(*n* = 48,710)	0.20
No	16,515 (96.65)	47,178 (96.85)	
Yes	572 (3.35)	1,532 (3.15)	
(Missing *n* = 72)	16	56	
Routine dental checkups	(*n* = 17,082)	(*n* = 48,709)	<0.01
Not gone in past 3 years	763 (4.47)	3,255 (6.68)	
≥2 times/year	13,265 (77.65)	31,566 (64.81)	
Once/year	1,602 (9.38)	8,323 (17.09)	
<1/year	416 (2.44)	1,466 (3.01)	
Whenever needed	1,036 (6.06)	4,099 (8.42)	
(Missing *n* = 78)	21	57	
Family (male or female) history of any cancer	(*n* = 16,900)	(*n* = 48,294)	0.08
No	5,937 (35.13)	17,329 (35.88)	
Yes	10,963 (64.87)	30,965 (64.12)	
(Missing *n* = 675)	203	472	
Total (any) cancer[e] diagnosis	(*n* = 17,103)	(*n* = 48,766)	<0.01
No	14,831 (86.72)	43,360 (88.91)	
Yes	2,272 (13.28)	5,406 (11.09)	
(Missing *n* = 0)	0	0	

[a]Number of valid responses with percentages (in parentheses).
[b]*P* value for *t* test (continuous variable) and χ^2 (categorical); statistical significance level set at $P < 0.05$.
[c]Mean (SD).
[d]BMI categories based on WHO classification system collapsed further into three categories as shown: (underweight + normal weight; overweight; and obese).
[e]Cancers included in the analyses of total cancer are those of the adrenal gland, anus, appendix, biliary tract, bladder, bone, limb, brain, breast, cervix, central nervous system, colon, connective tissues, endometrium, endocrine system, esophagus, eye and adnexa, gall bladder, genital organs, gums, heart, kidney, larynx, liver, lung, meninges, mouth, nasal cavity, nasopharynx, oropharynx, other digestive organs, ovary, pancreas, parotid, peritoneum, pyriform sinus, recto-sigmoid junction, rectum, renal pelvis, respiratory system, salivary gland, accessory sinus, small intestine, stomach, thymus, thyroid, tonsil, ureter, urinary organs, uterus, vagina, vulva, certain undetermined/unknown sites; malignant neoplasms of the hematopoietic system including Hodgkin lymphoma, non-Hodgkin lymphoma, leukemia and multiple myeloma, and melanoma skin cancers.

For the main analyses, none of the covariates examined, including smoking status, pack-years, secondhand smoke exposure, alcohol intake, BMI, recreational physical activity, total dietary energy intake, fruit or vegetable consumption, dietary and supplement calcium or vitamin D intake, history of diabetes, family history of any cancer, or hormone use, changed point estimates appreciably. Also point estimates obtained with the addition of smoking status and pack-years in the model, as compared with pack-years alone, were very similar. The final multivariate models included adjustment for age (continuous variable), pack-years of smoking (continuous variable), and BMI (Kg/m^2) (underweight and normal weight ≤24.9; overweight ≥25.0–29.9; obesity ≥30.0), based on biological plausibility and scientific evidence published in peer-reviewed journals, even though the point estimates did not change appreciably.

Periodontal disease history was associated with a statistically significant 14% increased risk of total cancer (multivariable-adjusted HR, 1.14; 95% CI, 1.08–1.20), similar to those obtained for the unadjusted (HR, 1.17; 95% CI, 1.12–1.23) and age-adjusted (HR, 1.20; 95% CI, 1.14–1.26) models, respectively. Statistically significant multivariable-adjusted positive associations were also observed with breast cancer (HR, 1.13; 95% CI, 1.03–1.23), lung cancer (HR, 1.31; 95% CI, 1.14–1.51), and skin melanomas (HR, 1.23; 95% CI, 1.02–1.48). There was a

suggestion of an increased risk of upper digestive organ cancers combined (esophagus, stomach, pancreas, liver, and intrahepatic bile ducts, and gall bladder and parts of biliary tract; HR, 1.19; 95% CI, 0.98–1.46), with a strong significant increased risk seen in the upper gastrointestinal tract region (esophagus and stomach only; HR, 2.04; 95% CI, 1.35–3.09). Overall, the risk associated with periodontal disease was highest for esophageal cancer (HR, 3.28; 95% CI, 1.64–6.53). Gall bladder cancer risk was also high (HR, 1.73; 95% CI, 1.01–2.95), while that for stomach cancer was elevated but did not reach formal statistical significance (HR, 1.58; 95% CI, 0.94–2.67). Periodontal disease was not associated with cancers of the pancreas, liver, lower digestive tract organs, or lip, oral cavity, and pharynx combined. Similarly, there was no association with genitourinary, and lymphoid and hematopoietic malignancies. (Findings from multivariate-adjusted models for total cancer and cancer regions/sites are displayed in Fig. 2.)

For the stratified analyses, the addition of pack-years of smoking to the multivariate-adjusted models of former and current smokers, in order to address residual confounding among these groups, did not appreciably change the point estimates, so we presented the most parsimonious model, adjusting for age and BMI only. On stratification according to cigarette smoking status, periodontal disease history was positively associated with total cancer risk among former (HR, 1.21; 95% CI, 1.13–1.30) and current smokers (HR, 1.20; 95% CI, 0.98–1.46), and persisted among never-smokers (HR, 1.12; 95% CI, 1.04–1.22). Among never smokers, the association between periodontal disease history and risk of breast or lung cancers was attenuated and nonsignificant; but significant for skin melanomas (HR, 1.42; 95% CI, 1.08–1.85), upper gastrointestinal tract cancers combined (esophagus and stomach; HR, 2.26; 95% CI, 1.19–4.29), and lymphoid and hematopoietic malignancies combined (HR, 1.34; 95% CI, 1.08–1.67). Detailed information on estimates according to smoking strata is shown in Table 2. There was a suggestion of possible interaction by HT status ($P = 0.17$), but none for the other variables examined. Risk of periodontal disease and total cancer appears to be slightly higher among current HT users (Table 3). The results of a sensitivity analyses on the association between periodontal disease and total cancer, restricted to participants who obtained dental checkups at least 1/year, showed a similar positive association (HR, 1.15; 95%CI, 1.09–1.22), as in the main analyses.

Discussion

Our findings demonstrate that periodontal disease history is associated with an increased risk of total cancer in this cohort of postmenopausal women and persists regardless of smoking status. Results here are consistent with previous smaller studies and studies in men. One study cohort of 48,735 U.S. male health professionals reported a 14% increased risk of incident cancer overall, among males with a self-reported history of periodontal disease, compared with those without such a history (2). In contrast, Wen and colleagues reported a 5% nonsignificant increase in overall cancer risk among their Taiwanese participants recently diagnosed with periodontitis (1). Their largely null findings may be due to poor measurement as their referent group had gingivitis, so these individuals may have had a higher risk than those with healthy gums. However, it may also be because they were young (ages 20–49 years), so the carcinogenicity latency period may have been too short.

With respect to individual cancer sites, we found that women with a history of periodontal disease were at a significantly higher risk for breast, lung, esophageal, gallbladder, and melanoma skin cancers. Ours is the first study to report on the association between periodontal disease and gallbladder cancer risk in women or men. The association was borderline significant with stomach cancer. No association was found for cancers of the pancreas, colorectum, genitourinary or lymphoid, and hematopoietic systems. Michaud and colleagues (2008) observed higher risks for lung and esophageal cancers, and no associations with colorectal and stomach cancers in their study of men. However, unlike ours, they also found elevated risk for cancers of the pancreas, kidney, and hematopoietic system (2). Discrepancies between studies could be due to differences in study design, population, or periodontal disease measures used. Our lack of association with lip, oral, and pharynx cancers as a group may be due to the considerable heterogeneity between these anatomic sub-sites, and our relatively small numbers of cases, in comparison with previous reports with larger numbers of head and neck cancer cases (3, 28, 29).

The strong association of smoking with periodontal disease and with some cancers may account for some of the variations in cancer risk between regions/sites and across studies. Assessment of intensity and duration in a cohort study is subject to considerable measurement imprecision, and classification by smoking status can create fuzzy boundaries. This may result in incomplete control for the impact of smoking and bias estimates of an intervening variable like periodontal disease (30, 31). Examination of never-smokers in our large group of participants allowed us to attempt to tease that out; we found the risk of total cancer among never-smokers with a history of periodontal disease remained statistically significant and largely unchanged (HR, 1.12; 95% CI, 1.04–1.22). Positive associations previously observed between periodontal disease history and risk of breast, lung, and gallbladder cancers, respectively, among our study participants, were attenuated and statistically insignificant in never-smokers. For melanoma skin cancers, the associated risk was stronger in never-smokers (HR, 1.42; 95% CI, 1.08–1.85) than the overall population combined, although the reason for this is unclear. Also, the association between periodontal disease history and malignant neoplasms of the hematopoietic system, which was near significance in the overall population (HR, 1.11; 95% CI, 0.95–1.30), was statistically significant when limited to never-smokers (HR, 1.34; 95% CI, 1.08–1.67).

The finding of a strong association between periodontal disease history and esophageal cancer risk may be because periodontopathogens may track more readily to contiguous regions of the esophagus through ingestion. Because smoking is an established risk factor for esophageal cancer, residual confounding by smoking may contribute to the strong association we observed, even after adjustment for smoking. We had too few numbers of smokers to successfully interrogate this association in stratified analyses; however, when considered along with stomach cancers, the risk appears to be elevated with upper gastrointestinal cancers, even in never-smokers (HR, 2.26; 95% CI, 1.19–4.29). Results from previous case control studies have provided additional evidence of an association between tooth loss (another proxy measure for periodontal disease) and risk of esophageal (5, 32) and stomach cancers (4, 33), respectively.

Cancer outcomes[a]	PD, Yes *n* (%) (*n* = 17,103)	PD, No *n* (%) (*n* = 48,766)	MV HR[b] (95% CI)	*P* Value
Total incident cancer	2136 (1.47)	5013 (1.24)	1.14 (1.08–1.20)	<.001
Lip, oral cavity & pharnyx	20 (0.01)	48 (0.01)	1.10 (0.64–1.87)	0.740
Digestive organs	351 (0.23)	911 (0.22)	1.09 (0.96–1.23)	0.200
Upper digestive organs	142 (0.09)	336 (0.08)	1.19 (0.98–1.46)	0.080
Upper GI tract	40 (0.03)	54 (0.01)	2.04 (1.35–3.09)	<.001
Esophagus	19 (0.01)	15 (<.01)	3.28 (1.64–6.53)	<.001
Stomach	22 (0.01)	41 (0.01)	1.58 (0.94–2.67)	0.090
Pancreas	66 (0.04)	206 (0.05)	0.89 (0.67–1.18)	0.400
Liver	19 (0.01)	43 (0.01)	1.33 (0.77–2.29)	0.320
Gall bladder & bile duct	22 (0.01)	38 (<.01)	1.73 (1.01–2.95)	0.050
Lower digestive tract	188 (0.12)	524 (0.12)	1.00 (0.85–1.19)	0.980
Small intestine	12 (<.01)	33 (<.01)	1.07 (0.54–2.08)	0.850
Colorectum	166 (0.11)	473 (0.11)	0.98 (0.82–1.17)	0.810
Colon	146 (0.10)	389 (0.09)	1.05 (0.87–1.28)	0.610
Rectosigmoid junction	2 (0.01)	30 (0.01)	0.17 (0.04–0.71)	0.020
Rectum	18 (0.01)	62 (0.01)	0.79 (0.46–1.36)	0.400
Anus and anal canal	11 (<.01)	20 (0.01)	1.50 (0.71–3.16)	0.290
Peritoneum	20 (0.01)	43 (0.01)	1.38 (0.80–2.36)	0.250
Connective/soft tissues	11 (<.01)	21 (<.01)	1.33 (0.62–2.85)	0.470
Melanoma of the skin	167 (0.11)	380 (0.09)	1.23 (1.02–1.48)	0.030
Breast cancer invasive	714 (0.48)	1702 (0.41)	1.13 (1.03–1.23)	0.009
Resp & intrathoracic organs	346 (0.23)	546 (0.13)	1.31 (1.14–1.50)	<.001
Lung and bronchus	334 (0.23)	521 (0.13)	1.31 (1.14–1.51)	<.001
Lymphoid and hematopoietic tissues	229 (0.15)	591 (0.14)	1.11 (0.95–1.30)	0.180
Leukemia	66 (0.04)	168 (0.04)	1.10 (0.83–1.47)	0.510
Lymphoma, non-Hodgkin	121 (0.08)	321 (0.08)	1.08 (0.87–1.34)	0.470
Multiple myeloma	36 (0.02)	105 (0.02)	1.05 (0.72–1.54)	0.800
Other, unspecified cancers	128 (0.08)	349 (0.08)	1.00 (0.81–1.23)	0.980
Brain	14 (<.01)	53 (0.01)	0.75 (0.41–1.36)	0.350
Thyroid	39 (0.03)	90 (0.02)	1.21 (0.82–1.78)	0.330
Other, unknown or Ill-defined	72 (0.05)	200 (0.05)	0.98 (0.74–1.29)	0.880
Female genital organs	232 (0.15)	587 (0.14)	1.10 (0.95–1.29)	0.220
Cervix	5 (<.01)	16 (<.01)	0.79 (0.29–2.18)	0.650
Corpus uteri (endometrium)	120 (0.08)	316 (0.07)	1.08 (0.87–1.34)	0.480
Ovary	84 (0.05)	208 (0.05)	1.14 (0.88–1.47)	0.340
Genital cancer	10 (<.01)	28 (<.01)	1.05 (0.51–2.19)	0.890
Vulva	13 (<.01)	25 (0.01)	1.22 (0.60–2.45)	0.580
Urinary tract system	111 (0.07)	256 (0.06)	1.16 (0.92–1.45)	0.210
Bladder	65 (0.06)	138 (0.04)	1.10 (0.81–1.49)	0.550
Kidney	41 (0.03)	112 (0.03)	1.09 (0.76–1.56)	0.660

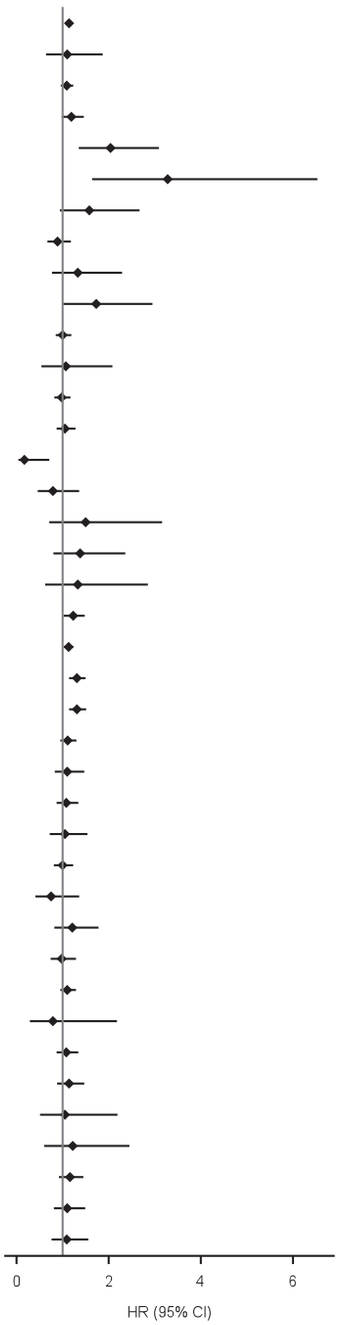

Figure 2.

Periodontal disease and incident cancer risk, WHI-OS.

[a]Cancer classifications based on ICD-CM - 10th revision of the US National Clinical Modifications of International Statistical Classification of Diseases and Related Health Problems coding system. Other, Unspecified Cancers: include eye and adnexa, brain, CNS, meninges, peripheral nerves, adrenal glands. Other, Unknown or Ill-defined: include those unknown/undocumented sites. Analyses of individual cancer sites were based on time to diagnosis of primary cancer for that particular site, independent of findings from other cancer sites; however, for the evaluation of regional and total cancers, we considered the time to first diagnosis of any cancer located within that group, whichever came first. Therefore, the sum of the individual cancers may not exactly approximate the values obtained when those cancers are considered as a group.

[b]HR (95% CI): Hazard ratio and 95% Confidence Interval based on multivariate adjusted model (Age + pack-years +BMI). Hazard ratios (HR) and annualized risk percentage NOT computed for cancer sites with <20 cases.

Table 2. Number of incident cases (annualized risk, %) and risk of incident cancer[a,b] and periodontal disease overall and according to smoking status of the WHI-OS

Outcome	Cancer cases *N*	Periodontal disease Yes *N* (%)[c] (*n* = 17,103)	Periodontal disease No *N* (%)[c] (*n* = 48,766)	Unadjusted HR (95% CI)[d]	MV-adjusted[e] HR (95% CI)[d]
Total cancer	7,149	2,136 (1.47)	5,013 (1.24)	1.17 (1.12–1.23)	1.14 (1.08–1.20)
Never-smokers	3,310	777	2,533		1.12 (1.04–1.22)
Former smokers	3,427	1,182	2,245		1.21 (1.13–1.30)
Current smokers	412	177	235		1.20 (0.98–1.46)
Melanoma of the skin	547	167 (0.11)	380 (0.09)	1.22 (1.01–1.46)	1.23 (1.02–1.48)
Never-smokers	260	74	186		1.42 (1.08–1.85)
Former smokers	272	85	187		1.03 (0.79–1.32)
Current smokers	15	8	7		N/A
Breast	2,416	714 (0.48)	1,702 (0.41)	1.17 (1.07–1.27)	1.13 (1.03–1.23)
Never-smokers	1,163	263	900		1.05 (0.92–1.21)
Former smokers	1,155	406	749		1.22 (1.08–1.37)
Current smokers	98	45	53		1.32 (0.89–1.97)
Lung and bronchus	855	334 (0.23)	521 (0.13)	1.78 (1.55–2.04)	1.31 (1.14–1.51)
Never-smokers	150	29	121		0.89 (0.59–1.33)
Former smokers	540	229	311		1.72 (1.45–2.04)
Current smokers	165	76	89		1.33 (0.98–1.81)
Upper gastrointestinal tract (i.e., esophagus and stomach)	94	40 (0.03)	54 (0.01)	2.05 (1.36–3.09)	2.04 (1.35–3.09)
Never-smokers	40	15	25		2.26 (1.19–4.29)
Former smokers	48	23	25		2.16 (1.22–3.81)
Current smokers	6	2	4		N/A
Pancreas	272	66 (0.04)	206 (0.05)	0.88 (0.67–1.17)	0.89 (0.67–1.18)
Never-smokers	141	27	114		0.89 (0.58–1.35)
Former smokers	121	35	86		0.95 (0.64–1.40)
Current smokers	10	4	6		N/A
Gall bladder, and biliary tract, parts of	60	22 (0.01)	38 (<0.01)	1.60 (0.95–2.71)	1.73 (1.01–2.95)
Never-smokers	36	9	27		1.26 (0.59–2.68)
Former smokers	22	11	11		2.24 (0.97–5.18)
Current smokers	2	2	0		N/A
Lower digestive tract/organs (i.e., small intestine, colon, recto-sigmoid junction, rectum, anus and anal canal)	712	188 (0.12)	524 (0.12)	0.99 (0.84–1.17)	1.00 (0.85–1.19)
Never-smokers	365	76	289		0.99 (0.77–1.27)
Former smokers	317	102	215		1.10 (0.87–1.40)
Current smokers	30	10	20		0.85 (0.40–1.82)
Colon	535	146 (0.10)	389 (0.09)	1.04 (0.86–1.26)	1.05 (0.87–1.28)
Never-smokers	261	60	201		1.13 (0.85–1.51)
Former smokers	252	77	175		1.05 (0.80–1.37)
Current smokers	22	9	13		1.19 (0.51–2.81)
Rectum	80	18 (0.01)	62 (0.01)	0.81 (0.48–1.36)	0.79 (0.46–1.36)
Never-smokers	49	7	42		0.63 (0.28–1.40)
Former smokers	29	11	18		1.25 (0.58–2.71)
Current smokers	2	0	2		N/A
Female genital organs (overall)	819	232 (0.15)	587 (0.14)	1.09 (0.94–1.27)	1.10 (0.95–1.29)
Never-smokers	414	99	315		1.13 (0.90–1.42)
Former smokers	368	118	250		1.06 (0.85–1.32)
Current smokers	37	15	22		1.02 (0.53–1.96)
Urinary tract system (overall)	367	111 (0.07)	256 (0.06)	1.20 (0.96–1.50)	1.16 (0.92–1.45)
Never-smokers	173	42	131		1.19 (0.84–1.68)
Former smokers	172	60	112		1.23 (0.90–1.69)
Current smokers	22	9	13		1.17 (0.49–2.78)
Lymphoid, and hematopoietic and related tissue	820	229 (0.15)	591 (0.14)	1.07 (0.92–1.25)	1.11 (0.95–1.30)
Never-smokers	419	112	307		1.34 (1.08–1.67)
Former smokers	379	111	268		0.96 (0.77–1.19)
Current smokers	22	6	16		0.60 (0.24–1.55)
Leukemia, all types	234	66 (0.04)	168 (0.04)	1.09 (0.82–1.44)	1.10 (0.83–1.47)
Never-smokers	113	32	81		1.44 (0.96–2.17)
Former smokers	115	32	83		0.89 (0.59–1.34)
Current smokers	6	2	4		N/A

(Continued on the following page)

Table 2. Number of incident cases (annualized risk, %) and risk of incident cancer[a,b] and periodontal disease overall and according to smoking status of the WHI-OS (Cont'd)

Outcome	Cancer cases *N*	Periodontal disease Yes *N* (%)[c] (*n* = 17,103)	Periodontal disease No *N* (%)[c] (*n* = 48,766)	Unadjusted HR (95% CI)[d]	MV-adjusted[e] HR (95% CI)[d]
Lymphoma, Non-Hodgkin, all types	442	121 (0.08)	321 (0.08)	1.04 (0.85–1.29)	1.08 (0.87–1.34)
Never-smokers	230	56	174		1.18 (0.87–1.59)
Former smokers	201	63	138		1.05 (0.78–1.42)
Current smokers	11	2	9		N/A
Multiple myeloma and malignant plasma neoplasms	141	36 (0.02)	105 (0.02)	0.95 (0.65–1.38)	1.05 (0.72–1.54)
Never-smokers	78	21	57		1.39 (0.85–2.30)
Former smokers	59	13	46		0.65 (0.35–1.20)
Current smokers	4	2	2		N/A

[a]Analyses of individual cancer sites were based on time to diagnosis of primary cancer for that particular site, independent of findings from other cancer sites; however, for the evaluation of regional and total cancers, we considered the time to first diagnosis of any cancer located within that group, whichever came first. Therefore, the sum of the individual cancers may not exactly approximate the values obtained when those cancers are considered as a group.
[b]Cancer classifications based on ICD-CM - 10th revision of the U.S. National Clinical Modifications of International Statistical Classification of Diseases and Related Health Problems coding system.
[c]Number of valid responses with annualized risk, percentages (in parentheses).
[d]HR (95% CI): HR and 95% CI. HRs and annualized risk percentage not computed for cancer sites with <20 cases.
[e]Multivariate-adjusted model based on model adjustment for Age + pack-years + BMI only; however, for the stratified analyses on smoking status, multivariate-adjusted model based on Age + BMI only.

In light of previous findings of a positive association between periodontal disease or its pathogens, and pancreatic cancer (6, 34, 35), we expected but did not find a positive association among our pancreatic cancer cases. Stolzenberg-Solomon and colleagues (2003) had reported tooth loss was much more associated with pancreatic cancers among male smokers (6), but Michaud and colleagues (2007) found the association remained among their subset of male never-smokers (34). Gender differences pertaining only to men, or our small numbers of current smokers may account for these disparities.

The precise mechanisms through which periodontal disease may promote cancer remain to be determined; one plausible theory relates to oral pathogens contributing to carcinogenesis at local or distant body sites. This may follow their ingestion in saliva into the gut (7), aspiration within dental plaque (9–10), or release into circulation via diseased periodontal tissues (11). Although escape of oral pathogens into the systemic circulation tends to be transient (36), certain pathogens such as *Porphyromonas gingivalis* are inherently equipped with mechanisms that prevent their subsequent uptake and elimination by neutrophils (37). *Porphyromonas gingivalis* also preferentially activates Th_2-mediated immune responses (38), inducing polarization to M_2 macrophages which are less efficient at eliminating engulfed bacterial pathogens and their lipopolysaccharide products (39). Studies have shown *Porphyromonas gingivalis* to be phagocytosed by dendritic cells but not killed, and these intracellular bacterial cells home to distal sites (40). As such, they may become cocooned within these M_2 macrophages and persist long enough within the circulatory system to reach distant organs and produce adverse effects. Scientific reports also show *Porphyromonas gingivalis* and *Fusobacterium nucleatum* can promote tumor progression by activating toll-like receptors (TLR) on oral epithelial cells to upregulate the IL6/STAT3 pathway (41). TLR activation has been linked to inflammation, cellular proliferation, invasion, and evasion of antitumoral immune responses (42, 43), and increased expression of TLR-5 has been observed in oral cancers (44, 45). Inflammatory processes can generate free radicals and active intermediates causing oxidative/nitrosative stress that may induce DNA mutations or interfere with DNA repair mechanisms (46).

In consideration of these findings, the strengths and limitations of our study need to be taken into account. One limitation is the use of a self-reported questionnaire for evaluating periodontal disease status. Results comparing responses to our case finding question with objective clinical periodontal measures (24) were similar to those reported in the Health Professions Follow-up Study (47) in which the periodontal disease question is quite similar to that used in the WHI-OS. Although both the present study and the Health Professions study demonstrate that self-reported periodontal disease is reasonably accurate in large

Table 3. Risk of incident cancer[a] and periodontal disease according to HT use (E-Alone or E+P)[b] in the WHI-OS

	Total (*N*)[c]	Total cancer cases	HR (95% CI)[d]	*P*[e]
Never	17,665	2,092	1.06 (0.96–1.17)	0.23
Former	13,762	1,495	1.08 (0.96–1.21)	0.19
Current	30,928	3,746	1.18 (1.10–1.27)	<0.01

[a]Analysis of incident (total) cancer based on time to first diagnosis of any cancer.
[b]*P* value level of significance for interaction term set *a priori* at 0.2; *P* value obtained for interaction of periodontal disease with HT use was 0.17.
[c]Number of valid responses.
[d]HR (95% CI): Hazard ratio and 95% CI. Hazard ratio and 95% CI, based on multivariate-adjusted model for age + pack-years + BMI only.
[e]*P* value for Cox proportional hazards according to various strata; statistical significance level set at $P < 0.05$.

epidemiologic study groups, clearly this exposure is measured with error and some amount of misclassification is likely to have occurred. Periodontal disease status among our study participants was probably under-reported and may have attenuated the observed associations with disease risk, as is likely the case in other similar studies.

Alternatively, it may be that these women, who are more educated and less likely current smokers, are different from the U.S. population. Overall, our assessment of periodontal disease history showed comparable validity to other self-reported assessments used in epidemiologic studies (2). Another limitation is the possibility of residual confounding. Misclassification of smoking status could affect the findings, particularly for smoking-related cancers such as esophageal cancer. However, stratified analyses suggested associations persisted even in never-smokers. Lastly, our results may not be generalizable to men or premenopausal women.

This study is significant in providing insight regarding older women. It is the first national study involving U.S. women and the first in older women. Although we had sufficient power to assess total cancer, we had more limited power to assess less common cancer sites. Nevertheless, ours may be one of the only studies large enough to assess those associations. Therefore, these analyses provide useful information on specific sites/regions, particularly regarding the esophagus and gallbladder for which no or limited prior data are available. Additional study strengths include the fact we are able to establish temporality and utilize a very large sample with comprehensive information on baseline characteristics to account for potential confounders and interactions. Furthermore, the adjudication of cases was done by trained physicians, thus minimizing the chances of misclassification of outcomes.

Our study findings support an expanding body of evidence that periodontal disease is linked to cancer risk. Studies employing more detailed and precise clinical assessments of periodontal disease would help to minimize potential misclassification. Intervention studies that include treatment of periodontal disease may be warranted to determine if cancer risk can be reduced overall or in specific high-risk sites.

Disclosure of Potential Conflicts of Interest

R.J. Genco reports receiving a commercial research grant from Sunstar has honoraria from the speakers' bureau of Cigna, Colgate Palmolive, and Sunstar, and is a consultant/advisory board member for Cigna, Colgate Palmolilve, and Sunstar. No potential conflicts of interest were disclosed by the other authors.

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Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): J.R. Marshall, J. Wactawski-Wende

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): N.N. Nwizu, J.R. Marshall, K. Moysich, R.J. Genco, K.M. Hovey, X. Mai, M.J. LaMonte, J.L. Freudenheim, J. Wactawski-Wende

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