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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Acknowledgments

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Financial support: J. Wactawski-Wende; number of grants: 2.

Grant Support

This work was supported by the WHI program which is funded by the National Heart, Lung, and Blood Institute, National Institutes of Health, U.S. Department of Health and Human Services through contracts N01WH22110, 24152, 32100-2, 32105-6, 32108-9, 32111-13, 32115, 32118–32119, 32122, 42107-26, 42129-32, 44221, HHSN268201100046C, HHSN268201100001C, HHSN268201100002C, HHSN268201100003C, HHSN268201100004C, and HHSN271201100004C, R01DE013505 from the National Institute of Dental and Craniofacial Research, National Institutes of Health, Bethesda, MD (to J. Wactawski-Wende), and U.S. Army, Medical Research and Materiel Command, Fort Detrick, grant OS950077 (to J. Wactawski-Wende).

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Received March 13, 2017; revised May 2, 2017; accepted May 15, 2017; published OnlineFirst August 1, 2017.

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