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Citation	Babic, Ana, Elizabeth M. Poole, Kathryn L. Terry, Daniel W. Cramer, Ricardo P. Teles, and Shelley S. Tworoger. 2015. "Periodontal Bone Loss and Risk of Epithelial Ovarian Cancer." <i>Cancer Causes & Control</i> 26 (6) (April 3): 941–947. doi:10.1007/s10552-015-0575-7.
Published Version	10.1007/s10552-015-0575-7
Citable link	http://nrs.harvard.edu/urn-3:HUL.InstRepos:33840787
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Published in final edited form as:

Cancer Causes Control. 2015 June ; 26(6): 941–947. doi:10.1007/s10552-015-0575-7.

Periodontal bone loss and risk of epithelial ovarian cancer

Ana Babic^{a,b}, Elizabeth M. Poole^b, Kathryn L. Terry^{a,c}, Daniel W. Cramer^{a,c}, Ricardo P. Teles^d, and Shelley S. Tworoger^{a,b}

^aDepartment of Epidemiology, Harvard School of Public Health, 677 Huntington Avenue, Boston, MA 02115, USA

^bChanning Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, 181 Longwood Avenue, Boston, MA 02115, USA

^cObstetrics and Gynecology Epidemiology Center, Department of Obstetrics and Gynecology, Brigham and Women's Hospital and Harvard Medical School, 221 Longwood Avenue, Boston, MA 02115, USA

^dDepartment of Periodontology, University of North Carolina School of Dentistry, Chapel Hill, NC 27599-7450, USA

Abstract

Purpose—Periodontitis, a chronic inflammatory response to pathogenic bacteria in the oral microbiome, is common among adults. It is associated with several medical conditions, including cardiovascular diseases, and potentially with esophageal, lung, oral and pancreatic cancer. One of the proposed mechanisms behind these associations is systemic inflammation, which has also been implicated in ovarian cancer etiology. The aim of this study was to evaluate association between ovarian cancer and periodontal bone loss.

Methods—The association between periodontal bone loss, a marker of periodontitis, and risk of epithelial ovarian cancer was estimated among 60,560 participants of the prospective Nurses' Health Study using Cox proportional hazards analysis. Competing risks analysis was used to estimate association by histological subtype.

Results—We did not observe an increased risk of ovarian cancer among participants with periodontal bone loss (HR=0.86, 95% CI: 0.64–1.15). Among women younger than 69 years, periodontal bone loss was associated with a 40% (HR=0.60, 95% CI: 0.36–0.98) decreased ovarian cancer risk, while there was no association in women older than 69 (HR=1.09, 95% CI: 0.75–1.58), although this difference did not reach statistical significance (p-heterogeneity=0.06). We observed a suggestive decreased risk for serous tumors (HR=0.76, 95% CI: 0.53–1.09). The number of natural teeth and root canals, other metrics of oral health, were not associated with ovarian cancer risk.

Corresponding author: Ana Babic, Channing Division of Network Medicine, 181 Longwood Avenue, Boston, MA 02115, USA, Phone: +1.617.525.2562. Fax: +1.617.525.2008. hpanb@channing.harvard.edu.

Conflict of interest statement

The authors declare that they have no conflict of interest.

Conclusion—Our results do not support an increased ovarian cancer risk in women with periodontal bone loss, however there was a significant decrease in risk in women younger than 69. Given the unexpected association between periodontal bone loss and ovarian cancer risk in younger women, further research is warranted.

Keywords

ovarian cancer; periodontitis; oral microbiome; cohort study

Introduction

Ovarian cancer is the fifth most common cause of cancer deaths in women and the deadliest of all gynecological cancers [1]. Although ovarian cancer has been extensively studied, its etiology is far from being fully elucidated. Several hypotheses have been proposed to explain ovarian cancer. While some risk factors, such as parity and use of oral contraceptives (OC), lessen the repeated damage and repair of ovarian epithelium associated with ovulation [2–4], other risk factors such as endometriosis, use of genital powder, and tubal ligation likely act through inflammatory pathways [5]. Furthermore, in a recently published study including participants from 3 prospective cohorts, women in the top quartile of CRP levels had a 53% increase in ovarian cancer risk compared to women in the bottom quartile [6].

Periodontitis is a chronic inflammatory disease of tooth supporting structures, affecting 47% of adults aged 30 years and older in the United States, leading to gradual loss of periodontal tissues including periodontal bone, and in aggressive and severe cases (5–10%) to tooth loss [7, 8]. Periodontitis is a chronic inflammatory response to pathogenic bacteria present in dental plaque [9]. It might lead to systemic inflammation, as suggested by increased blood levels of several inflammatory markers, such as C-reactive protein (CRP), IL-6 and TNF- α [10, 11] among patients with periodontitis. Periodontitis has been associated with several diseases, including cardiovascular diseases, psoriasis, diabetes mellitus, preterm birth, as well as with esophageal, lung, oral and pancreatic cancers [12–17].

We hypothesized that periodontitis and the associated inflammation may be associated with an increased risk of ovarian cancer. To our knowledge, no previous studies have evaluated this association. We investigated whether periodontal bone loss, a hallmark of periodontitis, was associated with epithelial ovarian cancer risk among 60,560 participants of the Nurses' Health Study (NHS).

Materials and Methods

Study population

The Nurses' Health Study (NHS) was established in 1976 with 121,700 US registered nurses aged 30–55 years [18]. Participants responded to baseline and biennial follow-up questionnaires providing detailed information on a variety of lifestyle factors and medical history. In this study, we excluded women who never provided information on periodontal bone loss, including those who died before 1998 (the first year in which periodontal bone

loss was queried; n=38,825). In addition, we excluded women with a prior history of cancer except non-melanoma skin cancer (n=11,763), bilateral oophorectomy (n=15,539), or menopause due to radiation (n=49), leading to a total of 60,560 eligible participants. This study was approved by the Institutional Review Board at Brigham and Women's Hospital.

Case and exposure ascertainment

The primary exposure of interest in this study was self-reported periodontal bone loss. In 1998, participants self-reported periodontal bone loss as none, mild, or moderate/severe; women who reported mild or moderate/severe were considered to have bone loss. In 2000, exposure information was updated based on self-reported periodontal bone loss in the previous 2 years (yes or no). A total of 60,560 women provided information on periodontal bone loss in 1998 and/or 2000.

Information on covariates was obtained from the biennial questionnaires, while data on nutritional factors was obtained from food frequency questionnaires that were updated every 4 years. Women were first asked their number of natural teeth in 1992; this was updated in 1996 and 2000. Number of root canals was asked in 2000, and duration and reason of antibiotic use was first assessed in 2004 and updated in 2008.

We identified 395 confirmed incident cases of ovarian cancer through biennial questionnaires from 2000 to 2012, or through death certificates. Deaths were identified through family members or the US Postal Service and the National Death Index. Medical and pathology reports were evaluated by a gynecological pathologist to confirm the diagnosis, and to obtain information on cancer grade, stage, invasiveness and histologic subtype; when medical records were unavailable, we linked to the appropriate tumor registry to obtain this information. Cases were considered rapidly fatal if the participant died within 3 years of diagnosis.

Statistical analysis

Person-years were calculated from the baseline questionnaire return date (1998 or 2000, depending on when the participant first provided information on periodontal bone loss) to the date of ovarian or other cancer (except for non-melanoma skin cancer) diagnosis, bilateral oophorectomy, menopause due to radiation, death, or end of study follow-up (June 2012), whichever occurred first. We used Cox proportional hazards models to estimate hazard ratios (HR) and 95% confidence intervals (CI) for periodontal bone loss (yes vs. no). In the multivariate model, we adjusted for known ovarian cancer risk factors including duration of OC use, number of pregnancies, duration of estrogen hormone therapy (HT), duration of estrogen and progesterone HT, tubal ligation and family history of ovarian cancer. We also considered potential confounding by smoking, menopausal status, body mass index (BMI), alternative healthy eating index (AHEI) [19], predicted vitamin D score [20], regularity of menstrual periods while menstruating, history of diabetes, physical activity, energy-adjusted alcohol, lactose and caffeine intake, current use of nonsteroidal anti-inflammatory drugs NSAIDs, antibiotic use, reason for use of antibiotics, median income of the participant's neighborhood, number of natural teeth, osteoporosis, hip/arm fractures, wrist fractures and vertebral fractures; however none of these factors altered the

association and therefore were not included in the final multivariate model. Since use of antibiotics was ascertained for the first time in 2004, when adjusting for antibiotics we restricted the analysis to 2004 onward. In secondary analyses we also considered the association for exposure of number of teeth (restricted to periods >1998) and number of root canals (restricted to periods >2000). We performed stratified analysis by median BMI (<25.7 or ≥25.7), median age (<69 or ≥69), use of estrogen HT (ever or never), use of any HT (ever or never), history of diabetes (yes or no), current use of NSAIDs (non-use, use of aspirin only, use of non-aspirin NSAIDs only) and smoking status (never, past, current). Likelihood ratio tests were used to obtain the P-value for interaction. We also evaluated whether the association between periodontal bone loss and ovarian cancer differed by histological subtype, invasiveness and fatality using competing-risk Cox models [21]. All analysis was conducted using Statistical Analysis Software version 9.3 (SAS Institute, Cary, North Carolina).

Results

We confirmed 395 incident epithelial ovarian cancer cases over a total of 705,125 years of follow-up. The majority of tumors were serous/poorly differentiated (295), followed by endometrioid (37), mucinous (16), clear cell (9) and other (38). Participants suffering from periodontal bone loss were more likely to suffer from osteoporosis, to be current or past smokers and to consume more caffeine and alcohol than those with no bone loss (Table 1). Participants with periodontal bone loss had fewer natural teeth, and were more likely to have root canal procedures. While the total duration of antibiotic use was similar between two groups, there was more antibiotic use for dental reasons among participants with bone loss. Other characteristics did not differ substantially by periodontal bone loss status.

In age-adjusted models, participants with periodontal bone loss had a non-significant 14% lower risk of ovarian cancer (HR=0.86, 95% CI: 0.64–1.16) (Table 2). The results were similar after adjusting for known ovarian cancer risk factors (HR=0.86, 95% CI: 0.64–1.15). In the multivariate competing risk model, we observed a suggestively different association for serous/poorly differentiated versus non-serous tumors (p-heterogeneity=0.06). Periodontal bone loss was associated with a 24% lower risk of serous/poorly differentiated ovarian cancer compared to those with no bone loss (HR=0.76, 95% CI: 0.53–1.09), while there was no association for non-serous cancers (OR=1.56, 95% CI: 0.84–2.87). This difference reached statistical significance (p-heterogeneity=0.05) after adjusting for smoking, which is differentially associated with histologic subtypes [22]. There was no difference in association between invasive and borderline cancers (p-heterogeneity=0.28), or between rapidly fatal and less aggressive cases (p-heterogeneity=0.86).

Periodontal bone loss was suggestively more strongly inversely associated with ovarian cancer risk in women younger than 69 years (HR=0.60, 95% CI: 0.36–0.98), but not in those older than 69 (HR=1.09, 95% CI: 0.75–1.58), although the difference did not reach statistical significance (p-heterogeneity=0.06). A similar result was observed when considering only serous cancers (HR: 0.52, 95% CI: 0.28–0.97 in women <69, HR: 0.96, 95% CI: 0.61–1.49 in women ≥69 years). Associations were similar by current use of NSAIDs, smoking, diabetes, BMI or HT use (p-heterogeneity>0.11; data not shown).

There was no association between the number of root canals and risk of ovarian cancer (HR: 1.00, 95% CI: 0.79–1.27 for women with 1–4 root canals, and HR: 1.24, 95% CI: 0.83–1.85 for women with 5 root canals, compared to no root canals). Further, compared to women with 25–32 natural teeth, risk of ovarian cancer was similar in women with 0 (HR: 0.75, 95% CI: 0.45–1.25), 1–10 (HR: 1.11, 95% CI: 0.74–1.67), 11–16 teeth (HR: 0.91, 95% CI: 0.57–1.46) and 17–24 teeth (HR: 0.86, 95% CI: 0.65–1.13).

Discussion

In this first report of association between periodontal bone loss and risk of ovarian cancer, contrary to our hypothesis, we did not observe increased risk of ovarian cancer among women with periodontal bone loss. Our results support a possible inverse association for women <69 years old and for serous/poorly differentiated tumors. We did not observe an association with ovarian cancer for other markers of dental health, including number of root canals and number of natural teeth, possibly because these factors are acute, or can be caused by dental issues besides periodontitis.

While these observed inverse associations could be due to chance, there are several other possible explanations for this observation. Periodontitis and ovarian cancer share several well established etiological factors, such as OC or HT use [23, 24], and less established ovarian cancer risk factors such as smoking, coffee and alcohol use, unhealthy eating patterns and diabetes [25, 26]. Given that the risk estimates were essentially unchanged when adjusting for these factors, this is not a likely explanation for observed results. Alternatively, periodontal bone loss might reflect a more general bone loss due to osteoporosis. Low estrogen levels are characteristic of osteoporosis [27] while higher levels of endogenous estrogen might be associated with an increased risk of ovarian cancer [4]. However, studies on the association between endogenous estrogen and ovarian cancer risk are equivocal. Furthermore, adjusting for osteoporosis, or fractures that might be consequences of osteoporosis, did not change our estimate.

Another possibility is that medications used to treat periodontitis could be associated with a reduced risk of ovarian cancer. Non-surgical treatments for periodontal bone loss include antibacterial mouthwashes and antibiotics. While there are no data on association between antibiotic use and ovarian cancer risk, one might speculate that prolonged antibiotic use could potentially have a protective role, since some bacterial infections such as pelvic inflammatory disease have been associated with increased risk of ovarian cancer [28]. Adjusting for antibiotic use in our study did not change the estimate, although our ability to adjust for antibiotic use was restricted to periods after 2004, and therefore only to women older than 69, an age group for which the association was no longer significant.

It has been shown that adults with periodontitis have increased salivary levels of MUC1 [29], a membrane-bound, high molecular weight protein expressed by many types of normal epithelial cells at low levels, and at high levels in several epithelial cancers, including breast and ovarian cancer [30]. MUC1 is also expressed in salivary glands and in oral epithelium [31], and it has been proposed to be up-regulated as a host response to chronic infection with specific oral pathogens [32]. Direct stimulation of oral cell line KB with *Porphyromonas*

gingivalis, one of the major pathogens involved in periodontitis, led to increased expression of MUC1 [32]. Indirectly, *P. gingivalis* and other periodontal pathogens *Actinobacillus actinomycetemcomitans* and *Candida albicans*, can increase production of IL-6 and IFN-gamma [33, 34], leading to MUC1 up-regulation in oral KB cells [32]. It has been shown that conditions that involve increased expression of MUC1, such as pregnancy and breastfeeding, are associated with increased levels of circulating anti-MUC1 antibodies [35, 36]. Anti-MUC1 antibodies have been suggestively associated with a decreased risk of ovarian cancer [37], possibly because they could be eliminating ovarian cancer cells that express MUC1 [35]. Although there are no direct studies of this, it is possible that the salivary increase in MUC1 due to periodontitis could lead to increased levels of anti-MUC1 antibodies, which in turn may influence ovarian cancer risk.

We only observed a significant inverse association in women <69 years old. Interestingly, in the study of circulating anti-MUC1 antibodies referenced above, the association was only observed among women <64 years [37]. This could be possibly due to the phenomenon of immunosenescence, or aging of immune system, where antibodies decrease with age and time since antigen presentation [38]. In our secondary analysis we equally observed a suggestion of different associations between periodontal bone loss and ovarian cancer in women younger than 64 (HR: 0.52, 95% CI: 0.25–1.09) than in those older than 64 (HR: 0.96, 95% CI 0.70–1.33), even though the difference did not reach statistical significance (p -heterogeneity=0.15) due to small number of cases among women younger than 64.

Our study has several limitations. There is currently no standardized measure for periodontitis in epidemiological research. Several studies have used tooth loss as a marker for periodontitis. However, tooth loss may not be an appropriate marker for periodontitis since in people above 45 years of age periodontitis accounts for approximately half of tooth loss cases, while dental caries accounts for the rest [8]. Self-reported periodontitis was compared with radiographic bone loss measurement among non-dentist participants of the Health Professionals Study (HPFS). The positive predictive value for self-reported periodontitis with bone loss ranged from 71.8 to 83.1%, and the negative predictive value ranged from 68.7 to 73.9% [39]. Even though a similar validation study has not been conducted in the NHS, our participants are of similar demographic characteristics, consisting of non-dentist, medically trained professionals, and the validity of self-reported bone loss is likely to be comparable. While self-reported periodontal bone loss likely has some misclassification, it is likely to be non-differential, and thus would bias the estimate toward the null. Due to relatively small number of non-serous cancers, we were not able to separately evaluate association between periodontal bone loss and endometrioid, mucinous or clear cell carcinoma, which could perhaps give further insight into underlying mechanisms of this association. Since the majority of participants were menopausal in 1998, we were unable to evaluate this association among premenopausal women.

In summary, this is the first report of association between periodontal bone loss, as a marker for periodontitis, and ovarian cancer. Our results do not support that periodontal bone loss increases risk of ovarian cancer. However, given the unexpected possible inverse association in some subgroups, this exposure should be further investigated in independent populations.

Acknowledgments

This work was supported by the National Cancer Institute at the National Institutes of Health (UM1 CA186107, P01 CA87969, 5T32CA009001-38), and the Department of Defense (W81XWH-10-1-0280). We would like to thank the participants and staff of the Nurses' Health Study for their valuable contributions as well as the following state cancer registries for their help: AL, AZ, AR, CA, CO, CT, DE, FL, GA, ID, IL, IN, IA, KY, LA, ME, MD, MA, MI, NE, NH, NJ, NY, NC, ND, OH, OK, OR, PA, RI, SC, TN, TX, VA, WA, WY.

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Table 1

Characteristics of participants by periodontal bone loss status in 2004

	Periodontal bone loss	
	No bone loss (n=43,957)	Bone loss (n=7,505)
Means (SD)		
Age (years) ^a	69.3 (7.1)	69.6 (6.8)
Body mass index, kg/m ²	26.6 (5.4)	26.2 (5.2)
Lactose, g/day	15.7 (11.5)	15.8 (11.7)
Caffeine, g/day	134.4 (127.1)	150.7 (136.8)
Alcohol, g/day	5.2 (10.0)	6.4 (11.4)
Alternative healthy eating index	56.1 (11.3)	56.7 (11.2)
Vitamin D prediction score	3.4 (3.7)	3.8 (3.7)
Physical activity, MET-hrs/week	20.1 (24.2)	20.3 (23.9)
OC use (months)	24.8 (40.9)	26.6 (42.8)
Estrogen HT (months)	24.7 (59.5)	24.7 (59.0)
Estrogen and progesterone HT (months)	30.3 (50.5)	32.8 (52.0)
Duration of antibiotic use (weeks)	17.9 (68.1)	18.8 (70.8)
Percentages		
Postmenopausal	100	100
Tubal ligation	21	22
Parous	95	94
Menstrual period regularity		
Very regular	53	54
Usually regular	19	19
Usually irregular	9	9
Very irregular	3	3
Family history of ovarian cancer	5	5
Smoking status		
Never smoker	47	30
Past smoker	45	56
Current smoker	7	13

	Periodontal bone loss	
	No bone loss (n=43,957)	Bone loss (n=7,505)
Number of natural teeth		
0 natural teeth	5	6
1–10 natural teeth	6	8
11–16 natural teeth	5	7
17–24 natural teeth	19	23
25–32 natural teeth	66	57
Number of root canals		
0	39	30
1–4	54	58
>5	7	12
Diabetes	11	11
Osteoporosis	30	39
Hip/arm fractures	7	8
Wrist fractures	9	10
Vertebral fractures	4	6
Current NSAID use,		
Non-users	27	26
Aspirin only	34	35
Non-aspirin NSAID only	14	14
Use of antibiotics for dental reason	17	27

^aValue is not age adjusted

Table 2

Association between periodontal bone loss and ovarian cancer risk in the Nurses' Health Study (1998–2012)

	Number of cases	No periodontal bone loss HR (95% CI)	Periodontal bone loss HR (95% CI)	p-heterogeneity
Age-adjusted, all cancers ^a	395	1.00 (ref)	0.86 (0.64–1.16)	
Multivariate-adjusted, all cancers ^{a,b}	395	1.00 (ref)	0.86 (0.64–1.15)	n/a
Serous cancers ^c	295	1.00 (ref)	0.76 (0.53–1.09)	
Non-serous cancers ^{c,d}	62	1.00 (ref)	1.56 (0.84–2.87)	0.06
Age <69 years ^{a,b}	181	1.00 (ref)	0.60 (0.36–0.98)	
Age ≥69 years ^{a,b}	214	1.00 (ref)	1.09 (0.75–1.58)	0.06

^a Cox proportional hazard model^b Adjusted for age, OC use (continuous in months), tubal ligation, family history of ovarian cancer, parity (continuous), duration of estrogen HT (continuous in months), duration of estrogen and progesterone HT (continuous in months)^c Competing risk model adjusted for age, parity (both unconstrained), tubal ligation, family history of ovarian cancer, OC use in months (all 3 constrained)^d Mucinous, endometrioid and clear cell