A Prospective Study of Periodontal Disease and Risk of Rheumatoid Arthritis

ELIZABETH V. ARKEMA, ELIZABETH W. KARLSON, and KAREN H. COSTENBADER

ABSTRACT. ***Objective.*** To test for an association between periodontal disease (PD) and incident rheumatoid arthritis (RA) in a large prospective cohort.

Methods. We conducted a prospective analysis of history of periodontal surgery, tooth loss, and risk of RA among 81,132 women in the Nurses' Health Study prospective cohort. Periodontal surgery and tooth loss were used as proxies for history of PD. There were 292 incident RA cases diagnosed from 1992 to 2004. Information on periodontal surgery and tooth loss in the past 2 years was collected by questionnaire in 1992. Cox proportional hazards models were used to assess relationships between periodontal surgery, tooth loss, and risk of RA adjusting for age, smoking, number of natural teeth, body mass index, parity, breastfeeding, postmenopausal status, postmenopausal hormone use, father's occupation, and alcohol intake.

Results. Compared with those who reported no history of periodontal surgery or tooth loss, women with periodontal surgery or tooth loss did not have a significantly elevated risk of RA in multivariable-adjusted models (RR 1.24, 95% CI 0.83, 1.83; and RR 1.18, 95% CI 0.47, 2.95, respectively). In analyses stratified by ever and never-smokers, ever-smokers with periodontal surgery had an increased risk that was also nonsignificant. Those with severe PD (both history of periodontal surgery and tooth loss) did not have a significant increased risk.

Conclusion. In this large cohort of American women, there was no evidence of an increased risk of later-onset RA among those with a history of periodontal surgery and/or tooth loss. (First Release July 1 2010; J Rheumatol 2010;37:1800–4; doi:10.3899/jrheum.091398)

Key Indexing Terms:

RHEUMATOID ARTHRITIS | PERIODONTAL DISEASE | TOOTH LOSS
PERIODONTITIS | ORAL HEALTH | INFLAMMATION

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease marked by high levels of circulating cytokines and acute-phase proteins that cause destruction of the joints. In most Western countries, the prevalence of RA is approximately 0.5%–1%[1], affecting more females than males, with an average age of onset of 58 years. Estimates of the incidence range from 24 to 48 cases per 100,000 depending on country, time period, and age of the population[2]. RA has been shown to be associated with both genetic and environmental factors, although the cause is unknown.

In periodontal disease (PD), chronic inflammation results from the body's response to a bacterial infection of the gingiva. Inflammatory cells accumulate, destroying the periodontal ligament and bone, causing vascular damage and bone resorption. It is estimated that 30%–35% of dentate US adults have periodontal disease. Important risk factors include older age, male sex, and smoking[3,4].

RA and PD have similar underlying pathological processes and share a general dysregulation of the host inflammatory response[5]. It has been hypothesized that PD is associated with subsequent development of RA, but studies on this association have reported conflicting results, and no prospective study has been conducted. Two cross-sectional studies and a retrospective case-control study showed no association[6,7,8]. Other studies found a higher prevalence of PD and tooth loss among patients with existing RA[9,10,11,12,13,14,15]. Severity of PD has been shown to be correlated with RA disease duration, inflammatory markers, and disease activity[14,16,17]. From these cross-sectional studies, one cannot determine whether onset of RA preceded PD, PD preceded RA, or another underlying factor is responsible for their association.

We examined the relationship between severe PD, measured by a history of periodontal surgery and/or tooth loss, and the subsequent risk of RA in a large prospective cohort of nurses in the US. This cohort is a relatively homogenous

From the Department of Epidemiology, Harvard School of Public Health; and Division of Rheumatology, Immunology, and Allergy, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts, USA.

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E.V. Arkema, SM, Department of Epidemiology, Harvard School of Public Health; E.W. Karlson, MD; K.H. Costenbader, MD, MPH, Division of Rheumatology, Immunology, and Allergy, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School.

Address correspondence to E.V. Arkema, 44 Hilltop Road, Weston, MA 02493, USA. E-mail: earkema@post.harvard.edu

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population with respect to socioeconomic status and detailed data on many factors allow for adjustment for confounding.

MATERIALS AND METHODS

Study population. The Nurses' Health Study (NHS) is a prospective cohort of 121,700 female nurses aged 30–55 years in 1976 living in 11 states in the United States. Information on medical history and lifestyle factors was collected from the participants every 2 years by questionnaire. Followup rate of the original cohort through 2004 as a percentage of total possible person-years was 95.5%. The Brigham and Women's Hospital institutional review board approved all aspects of this study.

Identification of RA. From 1976 to 1982, participants self-reported a diagnosis of RA or other connective tissue diseases in a write-in section of the questionnaire. Starting in 1982, participants were asked specifically whether they had been diagnosed with RA by a physician. All nurses who self-reported any connective tissue disease underwent a screening questionnaire for symptoms as described[18,19]. If positive for symptoms, a detailed medical record review for American College of Rheumatology diagnostic criteria for RA[20] was performed. Participants were excluded if they denied diagnosis of RA after self-reporting it, had RA at the start of the cohort, or denied permission for medical record review, or the connective tissue diseases screening questionnaire result was negative.

Population for analysis. For this study, we included all women who answered the 1992 questionnaire and answered the question, "In the last two years have you had periodontal surgery (not including root canals)?". Those participants who did not respond or answered "not sure" were excluded from analysis. Women were censored after their last response to the questionnaires because incident RA cases could not be identified in those lost to followup. The final group studied included 81,132 women followed from 1992 to 2004 (898,069 total person-years), among which 292 developed RA.

Information on periodontal disease, tooth loss, and potential confounding variables. All exposure information was obtained by self-report from mailed questionnaires administered every 2 years. On the 1992 questionnaire, participants reported whether they had periodontal surgery in the past 2 years and how many teeth they had lost. History of periodontal surgery was a proxy for history of PD. Because PD is a primary cause of tooth loss in older adults, the number of teeth lost was also a marker for PD.

Number of natural teeth was reported in 1992. Age was updated in each cycle and smoking was assessed every 2 years. Participants reported if they currently smoked and the number of cigarettes smoked per day. Pack-years of smoking, the product of years of smoking and packs of cigarettes per day, was calculated and used as a categorical variable. Body mass index (BMI) was computed for each 2-year interval using the most recent weight reported in kilograms divided by height in 1976 in meters squared. Father's occupation, assessed in 1992, was dichotomized as professional or nonprofessional and served as a proxy for socioeconomic level in childhood. Alcohol intake was reported every 2 years and measured in grams per day. Important reproductive covariates were chosen on the basis of past findings of associations between reproductive factors and the risk of developing RA in this cohort[19]. Age at menarche, regularity of menses between the ages 20 and 35 years, parity, duration of breastfeeding, and postmenopausal hormone use were included as potential confounders of the PD and risk of RA relationship.

Statistical analysis. Age-standardized characteristics of the study population were calculated within categories of history of periodontal surgery. The characteristics of RA cases at diagnosis according to their history of periodontal surgery were compared using t-tests for continuous variables and Fisher's exact tests for categorical variables. Person-years of followup accrued from the date of return of the 1992 baseline questionnaire until the date of diagnosis of RA, as defined in the medical record, death, or loss to followup, defined as no further return of questionnaires. Age- and multivariable-adjusted Cox proportional hazards models were used to study the association between RA (developing from ages 46 to 81 yrs) and history of periodontal surgery. The association between RA and history of tooth loss was also modeled. Information from each biennial questionnaire was used to analyze the risk of RA in the next 2-year cycle. Age was categorized as less than 50, 50–54, 55–59, 60–64, 65–69, and 70 or more years in age-adjusted models and in months in multivariable models. Final multivariable-adjusted models included age, pack-years of cigarette smoking, BMI, parity, total duration of breastfeeding, postmenopausal hormone use, age at menarche, menstrual regularity, father's occupation, and number of natural teeth.

Stratified analyses were used to examine the association among periodontal surgery history, tooth loss, and risk of RA among never and ever-smokers and among heavy and never/light smokers. To test for additive interaction between smoking and PD, the relative excess risk of interaction (RERI) and its 95% CI was calculated according to the methodology of Hosmer and Lemeshow[21]. SAS statistical software, version 9, was used for all analyses.

RESULTS

The characteristics of the NHS participants in 1992 are shown in Table 1 according to history of periodontal surgery. Alcohol intake was higher among those with a history of periodontal surgery than among those with no history. A greater proportion of women with a history of periodontal surgery had ever smoked and among those who smoked, more women with periodontal surgery were heavy smokers

Table 1. Age standardized characteristics of the Nurses' Health Study women in 1992 within categories of periodontal surgery history (n = 81,132).

Characteristic	Periodontal Surgery in Past 2 Years	
	No	Yes
Age, yrs, mean	58.5	58.5
Body mass index, kg/m^2, mean	26.1	26.1
Alcohol intake, g/day, mean	3.4	3.7
Father's occupation nonprofessional, %	64.8	64.3
Age at menarche, yrs, mean	12.5	12.5
Usually/very irregular menses at age 20–35 yrs, %	13.1	13.2
Nulliparous, %	5.5	6.2
Breastfeeding ≥ 12 mo, %*	13.1	13.2
Postmenopausal hormone use, % **		
Current	39.7	40.1
Past	20.6	20.7
Never smoked, %	44.9	34.4
Packs of cigarette smoking, %***		
> 10 pack-years	37.1	47.6
No. teeth lost past 2 years, %		
None	85.8	64.9
1–4	12.9	30.4
5 or more	1.4	4.6
No. teeth, %		
None	5.3	3.0
1–10	6.4	6.0
11–16	5.1	7.6
17–24	19.8	26.4
25–36	62.2	55.4

* Among parous women only. ** Among postmenopausal women only. *** Among ever-smokers only.

(> 10 pack-years). Those with a history of periodontal surgery lost more teeth in the previous 2 years.

The 292 RA cases had a mean age at diagnosis of 64.6 years; 56.8% were rheumatoid factor-seropositive and 22% had radiographic changes characteristic of RA at diagnosis (Table 2). There were no significant differences in these characteristics between those with a history of periodontal surgery and those without.

The age-adjusted relative risk (RR) of developing RA was 1.27 (95% CI 0.86, 1.88) among those with a history of periodontal surgery (Table 3). The risk was also elevated for those who had lost any number of teeth in the past 2 years, although this association was also nonsignificant. Adjusting for multiple potentially important confounders did not substantially change the risk estimates. The RR in those with a history of periodontal surgery adjusted for number of natural teeth, alcohol intake, pack-years of smoking, BMI, father's occupation, age at menarche, postmenopausal hormone use, duration of breastfeeding, and regularity of menses was 1.24 (95% CI 0.83, 1.83). The RR for those who had lost 1–4 teeth was 1.02 (95% CI 0.74, 1.43) and for those who lost 5 or more was 1.18 (95% CI 0.47, 2.95). The p value for trend for the teeth-lost variable was nonsignificant (p = 0.76).

In an analysis stratifying the cases of RA by ever and never-smokers, risk of RA associated with PD was higher among ever-smokers than never-smokers (Table 4). Stratifying by heavy smokers and not heavy smokers, the RR in heavy smokers was elevated but the p value remained nonsignificant (Table 4). The relative excess risk due to interaction (RERI) between smoking and PD was greater than zero, but also nonsignificant (0.74; 95% CI –0.79, 2.27).

A joint analysis of history of periodontal surgery with history of tooth loss showed no dose response (Table 5), although there was little power to detect an association with few cases in some strata. More severe PD (having both surgery and tooth loss), was not significantly associated with the risk of RA (RR 1.27, 95% CI 0.65, 2.49).

DISCUSSION

In this large cohort of US women followed prospectively for the development of RA over 12 years, there was no evidence of an increased risk of RA among those with a history of periodontal surgery and/or tooth loss. Strengths of this study were its large size and the prospective nature of its research design. No previous study has examined the association between PD and RA in such a large prospective cohort over

Table 2. Characteristics of the 292 RA cases at diagnosis (1992–2004), according to history of periodontal surgery reported in 1992.

Characteristic	Periodontal Surgery in Past 2 Years: No	Yes	Overall	p*
Age at RA diagnosis, mean (SD) yrs	64.5 (7.4)	66.1 (7.0)	64.6 (7.4)	0.26
Rheumatoid factor-positive, %	56.8	60.7	57.2	0.84
Radiographic changes, %	22.0	25.0	22.3	0.81

* t test with equal variances was used for age at RA diagnosis and Fisher's exact tests were used for categorical variables.

Table 3. Relative risk of RA by history of periodontal surgery and teeth lost among women in the Nurses' Health Study, 1992–2004 (n = 81,132).

Factor	Cases, n	Person-yrs	Age-adjusted RR (95% CI)	Multivariate RR (95% CI)*
Periodontal surgery				
No	264	829,194	1.0 (ref)	1.0 (ref)
Yes	28	68,876	1.27 (0.86, 1.88)	1.24 (0.83, 1.83)
p			0.23	0.29
Teeth lost				
None	243	758,614	1.0 (ref)	1.0 (ref)
1–4	44	125,686	1.09 (0.79–1.50)	1.02 (0.74, 1.43)
5 or more	5	13,769	1.13 (0.46, 2.74)	1.18 (0.47, 2.95)
p for trend			0.58	0.76

* Adjusted for number of natural teeth, alcohol intake, pack-years of smoking, body mass index, father's occupation, age at menarche, postmenopausal status and hormone use, parity and duration of breastfeeding, and regularity of menses.

Table 4. Relative risk of RA by history of periodontal surgery among women in the Nurses' Health Study, 1992–2004, stratified by ever (n = 45,376) and never (n = 35,745) smokers and by heavy (n = 29,514) and not heavy (n = 50,410) smokers.

Factor	Smoking	Cases, n	Person-years	Multivariate RR (95% CI)*	p
Periodontal surgery					
No	Ever	157	451,123	1.0 (ref)	
Yes		22	44,890	1.44 (0.92, 2.27)	0.11
No	Never	106	375,690	1.0 (ref)	
Yes		6	23,747	0.91 (0.40, 2.08)	0.82
No	≤ 10 pack-years	136	527,434	1.0 (ref)	
Yes		9	36,368	0.99 (0.50, 1.94)	0.97
No	> 10 pack-years	117	288,171	1.0 (ref)	
Yes		18	31,244	1.48 (0.89, 2.45)	0.13

* Adjusted for number of natural teeth, alcohol intake, cigarettes smoked per day (among smokers), body mass index, father's occupation, age at menarche, postmenopausal status and hormone use, duration of breastfeeding, and regularity of menses.

Table 5. Multivariable relative risk* of RA by joint exposure (history of periodontal surgery and/or teeth lost) among women in the Nurses' Health Study, 1992–2004 (n = 81,132).

	Periodontal Disease	
	No	Yes
Tooth Loss		
No	1.0 (ref)	1.34 (0.83, 2.14)
Yes	1.09 (0.77, 1.53)	1.27 (0.65, 2.49)

* Multivariable RR and 95% CI adjusted for number of natural teeth, alcohol intake, pack-years of smoking, body mass index, father's occupation, age at menarche, postmenopausal status and hormone use, parity and duration of breastfeeding, and regularity of menses.

so many years. The availability of many potential confounding factors allowed for controlling them in multivariable models. Further, the stratified analyses to assess the possibility of any residual confounding by smoking suggest that any increased risk seen in previous studies might be due to the strong confounding factor of smoking. Studies have shown that smoking is an important risk factor for both PD and RA. The risk of PD is increased 4-fold in current smokers and almost doubled in former smokers[22]. Smoking is associated with an elevated risk of RA as well, with a risk ratio of 1.4 among current and former smokers[18].

The incidence rate in our study, 33 cases per 100,000 person-years, is comparable with most studies of US and northern European RA (estimates range from 24 to 48 cases per 100,000 person-years)[2]. However, the relatively small number of women with incident RA in this analysis limited the power to detect modest associations. We calculated post-hoc that we had 24% power to detect a risk ratio of 1.7 or greater and thus these results are able to exclude only a very strong association.

Misclassification of exposure due to inaccurate reporting is likely to have occurred in this analysis because we did not ask about PD but about periodontal surgery. It is more likely that those who answered "yes" had more severe PD. This measurement error would attenuate the association toward the null given the binary exposure, thus weakening the underlying association. The classification of history of periodontal surgery with tooth loss (Table 5) may better measure the presence of PD and thus decrease measurement error. Using this classification, there remained no significant association.

History of periodontal surgery was not validated in our study. Genco, *et al* determined that past gum surgery had a 25% sensitivity and 91% specificity for severe periodontal disease in a population-based study[23]. Asking health professionals about history of periodontal surgery may identify PD better. Joshipura, *et al* conducted a validation study among male health professionals and found that 78% of people that say they have had periodontal surgery actually have bone loss and 71% of people who report no periodontal surgery have no bone loss[24]. The investigators determined that self-reported periodontal surgery was a reasonable surrogate for bone loss and thus periodontal disease. In Joshipura's study, the population included dentists who may have been more accurate at reporting dental histories, but a comparison of non-dentists with dentists found that the groups did not differ significantly. Utilization of dental care could be an important factor affecting the validity of self-reported measures, and information on this variable was not available in this study.

The generalizability of our results may be limited due to the late onset of RA in this restricted cohort. Because the cohort under analysis started in 1992 when exposure was measured, cases of RA that had been diagnosed at younger ages were excluded. The average age of diagnosis in the RA cases was 64.6 years, 7 years older than the average age of onset in the US. Therefore, our study may not capture an association between PD and subsequent RA if the association is seen in earlier onset RA.

In summary, no significant association between history

of severe PD and risk of middle to older age onset RA was observed. It has been suggested that RA and PD share a genetic link, and some theorize that the antibodies developed during a periodontal infection or the periodontal pathogen itself leads to the development of RA[5,25,26,27]. Given that the pathogenesis of RA is unknown, further investigation into this relationship is necessary to illuminate the workings of the inflammatory cells that destroy the bone in both diseases. Nevertheless, if there is an association that could not be detected by this study, it is minimal. In this prospective study, severe PD, estimated by history of periodontal surgery and/or tooth loss, did not significantly increase the risk of middle to older age onset RA, but the question remains whether RA increases the subsequent risk of PD.

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