Chronic Periodontal Disease:
A Proxy of Increased Cancer Risk

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ABSTRACT

We investigated statistical association between long-term periodontal disease and cancer in a group of patients followed-up for 24 years with the hypothesis that chronic infection affects carcinogenesis. We made a prospective study of 1676 30-40-year old subjects in Stockholm, clinically examined in 1985. The data were combined with Swedish Cancer Registry in 2009. All cancer types were registered according to WHO International Classification of Diseases. Associations between cancer and dental parameters were studied using multiple logistic regression analysis with background variables and known risk factors for cancer. Age, gender, dental visits, education, income, socioeconomic status, working history, smoking, dental plaque, calculus, gingival bleeding, periodontal disease indicated by extracted or extruded molars were the independent variables. 286 subjects had periodontal disease in 1985. Of these, 18 subjects (6.3%) got cancer by 2009. In women breast cancer dominated (50%) while in men the types of malignancies were scattered. Logistic regression analysis showed that if a subject had periodontitis with extruded/extracted first molar tooth (d. 46) of the mandible in 1985, the risk of cancer increased with odds ratio (OR) 8.43, if the second molar (d. 47) was missing, OR for cancer was 6.11. To conclude chronic periodontal disease indicated by extracted or extruded molars associated statistically with elevated incidence of cancer.

Keywords-Cancer, periodontal disease, oral infection, chronic infection, extracted molars, missing teeth.

1. INTRODUCTION

Periodontal disease is characterized by chronic infection and inflammation in periodontal tissue leading to destruction of the bone surrounding the teeth. The disease may take decades to develop and leads to tooth loss if not treated [1], [2]. An estimated 15-35% of the adult population in industrialized countries suffers from this multifactor disease [3]-[5]. Periodontal disease is initiated by a biofilm of bacteria on the teeth which trigger an immune-inflammatory response in the adjacent host tissues [1], [2]. Numerous bacteria have been identified in the etiology but no single pathogen can be addressed in this regard [6]. Bacteria are necessary for the initiation and development of periodontal disease but a susceptive host is also needed. The host response in general should be protective, but the presence of a lower or higher response to the pathogens can also lead to irreversible tissue destruction [7]. Impaired host response or defective immune function is indeed associated with the development and progression of periodontal disease [2].

Inflammation is a key feature in many chronic diseases such as in periodontal disease [8], atherosclerosis [9], but also in cancer [10]. Acute inflammation is beneficial for the host by causing elimination of pathogens and promoting wound healing. But if the problem is not resolved and the infection becomes chronic in nature then the process may even facilitate malignant transformation of cells leading to subsequent progression of cancer [11]. Inflammation caused by infections seems to be involved in 15-20% of human tumours; however, even tumours that are not involved with pathogens have an inflammatory component in their microenvironment [12]. Inflammation has been considered responsible for fostering multiple mechanisms in the development of human tumours together with genome instabilities, and also expediting their acquisition [13]. Inflammation caused by infections seems indeed to be one of the most important preventable causes of cancer [14].

Cancer is a multifactorial disease, being one of the leading causes of death worldwide, 13% of all deaths in 2008, and the burden of cancer will continue to increase in the next decades [15]. The most frequent types of cancer differ among genders, breast cancer leads in women and lung cancer in men [16]. In Europe in 2008, the most common forms of cancer were colorectal (13.6%), breast (13.1%), lung (12.2%), and prostate cancer (11.9%), respectively, and lung cancer is the most lethal of these cancers (19.9%).

Recently, we were the first to observe a statistical association between periodontal disease and breast cancer further supporting the concept of chronic infection/inflammation in cancer [17].

The results from another study from our group has shown that fairly young individuals with periodontitis indicated by extruded or extracted molars are at increased risk for premature death caused by life threatening diseases such as malignant neoplasms in general, cardiovascular diseases, and diseases of the digestive system [18]. Consequently, our hypothesis of the present study was that low degree chronic inflammation such as seen in long-term periodontal disease leading to tooth loss is involved in carcinogenesis. The specific aim was to study the association between the occurrence of cancer in subjects with periodontal disease and characteristic tooth loss in our 24-year prospective investigation. The unique national population, hospital and death registers of Sweden made conducting this study possible.

2. MATERIAL AND METHODS

2.1 Study Population

In 1985, we undertook a study comprising a random sample of 3273 individuals aged 30–40 years. The subjects were selected from a registry file of all inhabitants (n = 105,798) of Stockholm County born on the 20th of any month from 1945 to 1954. The registry file including all individuals born on the 20th of any month, from 1985 and ongoing, is a unique population register in Sweden. The subjects in present study were informed about the purpose of the study and offered to participate. In total, 1676 individuals (51.2%); 838 men and 838 women, underwent a detailed clinical oral examination. Periodontal disease was registered in 286 persons [19]. **Figure 1** shows the study profile. In all subjects following parameters were recorded: the number of remaining teeth, excluding third molars; gingival inflammation around every tooth assessed using the gingival index [20]; and oral hygiene status, determined using the plaque index [21] and the calculus index to assess all six surfaces of six representative teeth. Pocket depth was determined with a periodontal probe and recorded to the nearest higher millimetre for six sites of each tooth. The prevalence of periodontitis was determined (17.1%) based on the classification of 1 or more teeth with pocket depth ≥ 5mm and bleeding on probing excluding the 3rd molars [20]. All persons that had a clinical examination answered a structured questionnaire containing questions about factors such as education, regular dental visits and the use of tobacco.

2.2 Ethical consideration

The Ethics Committee of the Karolinska Institutet and Huddinge University Hospital, Sweden, approved the study protocol (Dnr 101/85 and Dnr 2007/1669-31). The study is in accordance with the 1975 Declaration of Helsinki, as revised in 1983.
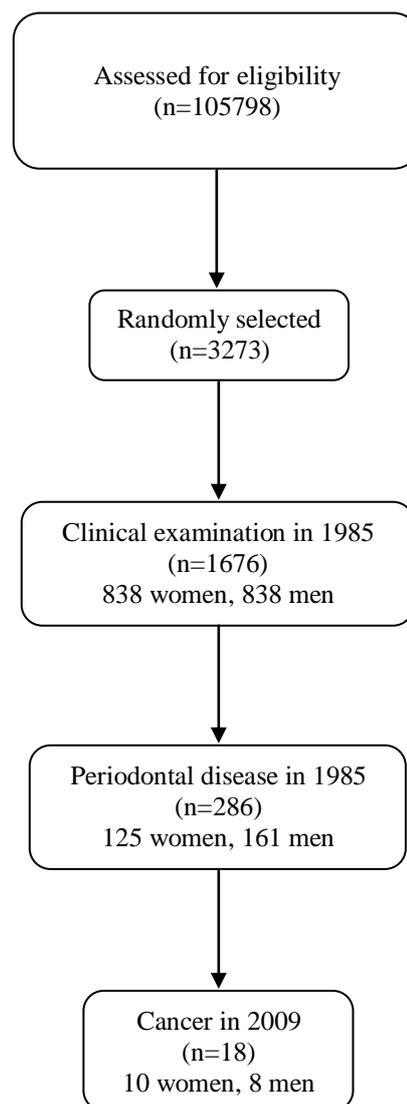

Figure 1. Study profile

2.3 Cancer data

The data for cancer (malignant neoplasms) were obtained from the Centre of Epidemiology, Swedish National Board of Health and Welfare, Sweden. The data have been classified according to the WHO International Statistical Classification of Diseases and Related Health Problems ICD-7, ICD-9 and ICD-10. Socioeconomic data were obtained from the National Statistics Centre, Örebro, Sweden. The data for cancer incidence as well as socioeconomic status were obtained from the registry files including data for persons born on the 20th of any month from 1985 and ongoing. This kind of register is uncommon in other countries and indeed unique for Sweden.

2.4 Statistical Analysis

Analysis of variance, chi-square tests, Fisher´s exact t-test and multiple logistic regression analysis were applied when appropriate. Multiple logistic regression analysis

was used to compare the incidence of cancer in relation to the state of oral health at baseline, i.e. the number of teeth, missing teeth and other oral health variables, while simultaneously controlling for confounding variables, here including age, gender, education, income, socioeconomic status, smoking habits, and dental visits as confounders. Smoking was expressed in pack-years of smoking. The model with the confounders was associated to cancer. A backwards elimination method was used to control for multicollinearity (correlation between confounders). The statistical model was tested according to Cox & Snell [22] and Nagelkerke [23]. Bonferroni correlation was used for multiple comparisons in **Table1**.

3. RESULTS

In the study group of 286 individuals clinically examined in 1985 and who had been suffering from periodontal disease, 6.3% got cancer by the year 2009 (18 subjects: 10 women and 8 men). Demographic and clinical oral health data of patients with and without cancer 2009 are given in **Table 1**. According to Bonferroni correlation for multiple comparisons we divided the P-value (0.05) with the number of tests. The result 0.00454 showed that the significant values in the table still are significant after the Bonferroni test. The groups did not differ significantly from each other except those patients who had periodontal disease and characteristic tooth loss, the lower mandibular first (tooth 46) and second molar tooth (tooth 47) extruded or extracted.

Table 1. Demographic clinical oral health data of 286 subjects with periodontal disease at baseline examination in 1985 and with and without cancer in 2009

	Cancer (n=18) number, mean ± SD	No Cancer (n=268) number, mean ± SD	*p**
Gender (women/men)	10/8	115/153	NS
Age in 2009 (years)	60.7±2.8	60.4±2.8	NS
Education (compulsory school/higher)	7/11	66/202	NS
Smoking (pack-years)	6673.42±5397.31	5323.88±4726.19	NS
Income (Swedish Crowns x 1000)	175.17±78.68	187.24±90.07	NS
Plaque index	1.00±0.53	0.89±0.53	NS
Gingival index	1.77±0.46	1.76±0.55	NS
Calculus index	0.53±0.48	0.82±074	NS
Missing teeth	2.23±3.43	1.51±2.32	NS
Missing molars	1.33±1.88	0.73±1.40	NS
Missing tooth 46	0.39±0.50	0.12±0.32	<0.001
Missing tooth 47	0.28±0.46	0.08±0.27	=0.004

* Fisher´s exact t/test or Student´s t-test for unpaired samples as appropriate

Data are expressed as mean ± SD

No significant difference was found for gival pocket depth between subjects with and without cancer.

In the multiple logistic regression analysis with cancer as the dependent variable and several independent variables (age, gender, dental visits, education, income, socioeconomic status, working, pack-years of smoking, dental plaque, calculus, gingival inflammation, periodontal disease indicated by extruded or extracted teeth, cancer appeared to be a principal independent predictor associated with 8.43-times the odds of the first missing molar (tooth 46) in the mandible and 6.11-times the odds of the missing second molar (tooth 47) in the mandible. The result is given in detail in **Table 2**. Other

factors considered in the model exerted no significant independent the development of cancer.

The different diagnoses of cancers according to the ICD-7, ICD-9 and ICD-10 classifications of the malignant neoplasms registered are given in **Table 3**. In women the predominant malignancy was breast cancer (50%). In men the malignancies were more scattered where lung cancer and malignant neoplasm of the trunk represented the majority of malignancies in men. The ten women who got the diagnosis of cancer were in the mean 46.3±5.03 years of age, and the eight men in the mean 49.7±5.6 years of age, respectively, at the time of diagnosis.

Table 2. The results of multiple logistic regression analysis of the relationship between cancer in 286 subjects with periodontal disease and cancer as a dependent variable and several independent variables (age, gender, dental visits, education, income, socioeconomic status, working, pack-years smoking, dental plaque, calculus, gingival inflammation, periodontal disease with extracted or extruded teeth, excluding third molars)

Dependent Variable	Explaining variable	Beta	Chi-Square	p-value	OR (95% CI)
Cancer	First molar in the right mandible is missing (tooth number 46)	2.13	7.65	0.006	8.43 (1.86-38.16)
	Second molar in the right mandible is missing (tooth number 47)	1.81	5.24	0.022	6.11 (1.30-28.73)

Cox & Snell R^2= 0.030; Nagelkerke R^2 = 0.069

4. DISCUSSION

This study addressed the issue of statistical association between periodontal disease and cancer. Extruded or extracted teeth were used as indicators of past dental infections. Our hypothesis was based on the paradigm that chronic infection and inflammation may link with malignant transformation practically in all tissues [24]. Hence, also infections of the teeth might associate with malignancies in remote tissues [25]. Our results clearly identified loss of specific missing molars in the mandible as independent predictors of cancer. Consequently, our study hypothesis was confirmed. Namely, it can be reliably anticipated that among our subjects tooth extractions had been made or the teeth because of periodontal infection since the subjects remained periodontitis patients throughout the 24-year follow-up.

Nevertheless, some comments should be made concerning the reliability of the results. Our subjects were randomly chosen at baseline to avoid selection bias. The subject pool was representative of the ethnically homogenous Swedish adult population, with an age range of 10 years to limit the influence of age differences. The study was of longitudinal prospective design, with a group of subjects with periodontal disease documented 24 years earlier. The subjects in our study who had lost their molars in the mandible had already in 1985 been suffering from periodontal disease which is known to take years to manifest. Thus missing molars in the mandible indeed indicate the presence of preceding chronic inflammation for many years and we subsequently used these markers in our analyses as a proxy for specific long-lasting dental infections. However, the loss of teeth in young individuals signals not only a long history of chronic inflammatory and microbial burden of dental diseases but may also reflect an underlying weakness of the host defence system. Knowing that tobacco is one of the most important risk factors for cancer [15], it is important to emphasize that in our study population the difference between the patient and control groups as expressed in pack-years of smoking was statistically not significant.

Earlier studies have shown that chronic inflammations indeed may link with cancer which, as said, was the background of the present investigation. For example long-term inflammation of the gastrointestinal tract, such as in inflammatory bowel diseases, has shown a clear association with colorectal cancer [26], [27] and also with thromboembolic events [28]. The well-known association between periodontal disease and diabetes shows how local oral infection and inflammation is systemically modified such as with alteration in the innate immune response by the activation of toll-like receptors (TLRs) [29]. The TLRs have also been shown to have an important role in the initiation and progression of cancer but they may also have antitumor effects. Genetic polymorphisms of the TLRs receptors have even reflected in higher susceptibility to chronic periodontal disease [30], [31] as well as in the susceptibility to different cancers [32], [33]. Pyrosequencing technology has revealed a previously unappreciated large diversity of bacterial species inhabiting the oral cavity [34]. The impact of the oral and gut microbiotaon the innate immunity of the host is still poorly understood [35]. Nevertheless, it is conceivable that subjects with propensity for chronic periodontal disease may have altered compositions of their oral metagenome like that reported for caries [34]. In the presense of selected TLR specificities such variations in the oral microbiota may contribute to chronic inflammation.

In general, the present study showed that periodontal disease indicated by missing molars in the mandible associated statistically with cancer which in our patients was diagnosed 10 years earlier than expected. Further studies should explore the eventual role of specific oral microorganisms and the frequency of bacteraemia of oral origin in cancer development in general. Bacteraemia of oral origin is highly prevalent even in normal daily activities and in particular so in cases with dental infections such as periodontal disease [36], [37].

Table 3. Cancer diagnosis in ICD-7, ICD-9, ICD-10 and age at the diagnosis

	Men	Women	Age
ICD-7			
Malignant neoplasm of lips, 172.0		1	38
ICD-9			
Malignant neoplasm of trunk, except scrotum, 172.5	1		42
Malignant neoplasm of breast, upper-inner quadrant, 174.2		1	40
Malignant neoplasm of testis, unspecified, 186.9	1		45
ICD-10			
Malignant neoplasm of colon, C18.9	1		48
Malignant neoplasm of bronchus or lung, unspecified, C34.9	1		51
Malignant neoplasm of bronchus or lung, unspecified, C34.9	1		54
Malignant neoplasm of trunk, C43.5	1		57
Malignant neoplasm of breast, upper-inner quadrant, C50.2		1	49
Malignant neoplasm of breast, unspecified, C50.9		1	45
Malignant neoplasm of breast, unspecified, C50.9		1	49
Malignant neoplasm of breast, unspecified, C50.9		1	53
Malignant neoplasm of cervix uteri, unspecified, C53.9		1	44
Malignant neoplasm of prostate, C61.9	1		56
Malignant neoplasm of pituitary gland, C75.1		1	48
Malignant neoplasm of brain, unspecified, C71.9		1	44
Acute myeloid leukemia, C92.0		1	53
Multiple myeloma, C90.0	1		45

Nevertheless, our present results indicate that similar to what has been observed in the association between dental infections and the development of atherosclerosis [38] and myocardial infarction [39] oral infections may also associate with the development of cancer [40]. The present results thus open a new field of research.

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