Poor Oral Hygiene Associates with Prostate Cancer - A 28-Year Follow-Up Study from Sweden

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Abstract
The objective of this study was to investigate whether there is an association between the amount of dental plaques and incidence of prostate cancer in patients followed up for 28 years. We hypothesized that dental plaque reflects infection and affects carcinogenesis via the inflammation pathway. This was a database incidence study on 838 30-40-year-old men of 3273 randomly selected subjects from Stockholm area, clinically examined in 1985. Prostate cancer incidence was registered during 28 years from the Center of Epidemiology, Swedish National Board of Health and Welfare, Sweden, according to WHO International Classification of Diseases. We compared baseline clinical data with prostate cancer diagnoses. Twentyeight men of the 838 were diagnosed with prostate cancer up to year 2013. Descriptive statistics and logistic regression were used for analyses. Results showed that dental plaque index (PLI), as indicator of poor oral hygiene and potential source of infection, was higher in men with than without prostate cancer (1.04±0.63 vs 0.78±0.52; p<0.01). This also reflected in higher number of missing molars (p<0.02) which appeared as principal independent predictor with odds ratio 2.4 (95% confidence interval 1.11 – 5.12) in multiple logistic regression analyses with prostate cancer as dependent variable and several independent variables. No significant differences were seen between the groups regarding age, smoking, education, gingival index, calculus index, periodontal pockets, and social status. To our knowledge these data are the first in showing the potential risk of poor oral hygiene for prostate cancer. Result may be explained by low-grade systemic inflammation of oral origin that affects carcinogenesis.

Keywords: Oral hygiene, dental plaque, prostate cancer, inflammation.

Introduction
Prostate cancer is the most prevalent malignancy in men and also an important cause of death in industrialized countries. In autopsy reports it is a frequent finding presenting 30% in >50 year olds and up to 80% in >80 year olds. The principal risk factor for prostate cancer is high age [1]. In addition to age, the American Cancer Societists the following prostate cancer risk factors: race and ethnicity (in particular African-American men), geography (most common in North America, Europe and Australia), family history, gene changes (especially BRCA2 mutations), diet (high consumption of red meat and high-fat products), obesity, smoking, exposure to chemicals, and prostatitis [2].

Recently, Karan & Dubey reviewed the role of inflammation in the development of prostate cancer. Inflammation of the prostate, i.e. prostatitis has been extensively studied also in this respect but the results are contradictory [3]. For example, in a screening study conducted in Finland, where inflammation was analysed from prostate biopsy specimens in men with high serum prostate specific antigen values, failed to show that inflammation would link to the increased risk of prostate cancer [4]. Nevertheless, inflammation in and around the prostate tissue may affect carcinogenesis. The role of tissue specific inflammasomes has been recently discussed in this perspective. These protein molecules are major regulators of inflammation leading to up-regulation of a number of cytokines and inflammatory mediators such as interleukin (IL)-1β and IL-18 [5]. In general, inflammation has been associated with many kinds of cancers; even 20% of cancer deaths have been estimated to link to chronic infections and persistent inflammations [6].

Infections in the mouth are highly prevalent in populations. Periodontitis, for example, affects 15 – 35% of the adults in industrialized countries [7]. This long-term infection leads to continuous low-grade bacterial invasion in the blood stream with subsequent systemic up-regulation of cytokines and inflammatory mediators that may have consequences in other organs [8]. Oral infections have indeed been statistically linked to cancer [9].

With this background we set out to investigate in a Swedish population cohort of subjects, with and without periodontitis, the incidence of prostate cancer during 28 years. We hypothesized that periodontitis in particular would emerge as a risk factor in this regard.
Materials and Methods
The baseline cohort was selected in 1985 using the registry file of all inhabitants (n = 105,798) of the Stockholm metropolitan area and consisted of a random sample of 3273 individuals aged 30–40 years and born on the 20th of any month from 1945 to 1954. The cohort has been described in detail by Söder, et al. [10]. The registry files include data for persons born on the 20th of any month from 1985 and on-going. This kind of register is uncommon in other countries.

In the present database study 838 randomly selected men from the cohort of 3273 subjects were studied. At baseline clinical examination in 1985 they had been 30-40-year old. The clinical oral examination included assessing plaque index (PLI), gingival index (GI), calculus index (CLI); number and depth of periodontal pockets and gingival crevices were measured using a periodontal probe [11-13]. Pockets were recorded to the nearest higher millimetre for six sites of each tooth.

Background variables such as socioeconomic status, education, regular dental visits and use of tobacco were recorded. Smoking was assessed in pack-years (number of cigarettes per day multiplied by 365 days, divided by 20 [number of cigarettes in a pack] = the number of packages per year multiplied by the number of years smoked).

Prostate cancer incidence was registered during 28 years according to WHO International Classification of Diseases. In 2013 we compared baseline clinical data with prostate cancer diagnoses sourced from the Center of Epidemiology, Swedish National Board of Health and Welfare, Sweden. The data were classified according to the WHO International Statistical Classification of Diseases and Related Health Problems (ICD-9 and ICD-10). Socioeconomic data were obtained from the National Statistics Centre, Örebro, Sweden.

Ethical considerations
The study was approved by the Ethics Committee of the Karolinska Institutet and Huddinge University Hospital in Sweden (Dnr 101/85 and revised in 2012/590-32). The study is in accordance with the Declaration of Helsinki.

Table 1: Demographic and clinical oral health data of 838 subjects at baseline examination in 1985 with and without prostate cancer by the year 2013.

| Age, in 2013 (years) | Prostate cancer (n=28) Number, (Mean ± SD) | No prostate cancer(n=810) Number, (Mean ± SD) | p |
|---------------------|------------------------------------------|---------------------------------------------|---|
| Smoking (pack-years) | 3285.0 ± 3192.9                          | 3685.8 ± 4534.4                             | NS |
| Education (compulsory/higher) | 6/22                                       | 149/661                                     | NS |
| Income (Swedish crowns x 1000) | 2145.74 ± 872.12                   | 2118.61 ± 1161.84                         | NS |
| Plaque index (PLI)# | 1.04 ± 0.63                             | 0.78 ± 0.52                                 | 0.01 |
| Gingival index (GI)° | 1.30 ± 0.49                             | 1.37 ± 0.55                                 | NS |
| Calculus index¤    | 0.63 ± 0.63                             | 0.53 ± 0.62                                 | NS |
| Number of missing molars | 0.43 ± 0.50                           | 0.24 ± 0.43                                 | 0.02 |
| Snuff use (cans/year) | 1260.0 ± 849.8                   | 1592.7 ± 942.5                             | 0.06 |
| Periodontal pockets | 0.25 ± 0.70                             | 1.04 ± 3.20                                 | NS |

# Plaque index by Silness & Loe 1964
° Gingival index by Loe & Silness 1963
¤ Calculus index by Greene & Vermillion 1964

Statistical analysis
Unpaired t-test, chi-square test, and multiple logistic regression analysis were applied when appropriate. We used multiple logistic regression analysis to compare the incidence of prostate cancer according to the state of oral health at baseline, while simultaneously controlling for several potential confounding variables. We included in the model the variables of age, gender, education, income, socioeconomic status, working status, smoking (pack-years of smoking), number of dental visits, scores of PLI, GI, CLI, and periodontal disease record. The outcome variable was the incidence of prostate cancer. Differences between data sets with a probability of <0.05 were regarded as significant. Two-tailed p-values were used and confidence intervals (CIs) calculated at the 95% level. All statistical analyses were performed using the SPSS Statistics software package, version 22 (SPSS Inc., Chicago, Illinois, USA). The study profile is shown in Fig 1.

Results
Of the 838 men, 28(3%) were diagnosed with prostate cancer by the year 2013. Demographic and clinical oral health data at baseline in 1985 of the subjects with and without prostate cancer at the 28-year follow-up are given in Table 1.
Of the oral health variables PLI differed significantly between the men with and without prostate cancer (scores: 1.04±0.63 vs. 0.78±0.52; p<0.01). This also reflected in higher number of missing molars (0.24±0.43 vs. 0.43±0.50; p<0.02). However, subjects without prostate cancer showed less numbers of periodontal pockets and reported fewer cans of snuff use per year (p<0.06). There were no significant differences between the groups regarding age, smoking, education, income, gingival index and calculus index scores, respectively.

In the multiple logistic regression analysis with prostate cancer as the dependent variable and several independent variables, namely, social status, dental plaque, dental calculus and gingival index scores, snuff use and number of missing molars, respectively, the missing molars appeared to be a principal independent predictor associated with 2.4 times the odds of prostate cancer (p = 0.02). The results are given in detail in Table 2.

Table 2: Results of multiple regression analysis of the relationship between incidence of prostate cancer as the dependent variable and independent variables social status, smoking, snuff use, dental plaque index, calculus index, gingival index and the number of missing molars.

| Dependent variable | Explaining variable | β   | x2     | p      | OR (95% CI) |
|--------------------|---------------------|-----|--------|--------|-------------|
| Prostate cancer    | Missing molars      | 0.868 | 4.936  | 0.026  | 2.4 (1.11-5.12) |

Cox & Snell 0.006 square, Nagelkerk 0.22 square

Discussion

In Sweden like in many countries prostate cancer is the most common cancer in men, representing 30.5% of the male cases in 2013. On average, the incidence has increased by 1.3 per cent annually over the last 20 years. In 2013 malignant diagnoses of prostate cancer were 9,678 in Sweden, which corresponds to 202 cases per 100,000 men. The increase in prostate cancer from the late 1990s is likely linked to the wide use of the prostate specific antibody (PSA) screening. But the past five years the incidence of prostate cancer has slightly decreased [14].

Our results confirmed the study hypothesis by showing significant difference in PLI scores between men with and without prostate cancer. PLI is an indicator of poor oral hygiene and reflects the oral cavity as a potential source of infection. Poor oral hygiene, reflected in the accumulation of dental plaque, is the main risk factor for periodontitis. Hence in our patients, originally examined 28 years earlier, bacterial burden of the mouth had putatively caused a low-grade inflammation in the periodontium with potential detrimental systemic consequences. From the oral biofilms microbial cells, toxins and enzymes are released through the epithelium, particularly in the gingival crevice, where the microbes and their metabolites may enter the blood circulation and spread all over the body [15].

Our observation that men with prostate cancer had more missing molar teeth when compared with those with no prostate cancer also supports the oral infection theory. Namely, missing teeth indicate earlier infections in the teeth in question, mostly due to caries and/or periodontal disease [16,17]. Extruded or extracted molars were used in our analyses as indicators of past dental infections. Subjects with prostate cancer showed less periodontal pockets compared with subjects without prostate cancer diagnosis which may reflect eradication of the worst foci by tooth extraction.

Smoking is one of the most important risk factors for cancer [18]. It is important to emphasize that in our study population no significant difference in pack-years of smoking was found between those with and without prostate cancer. Pack-years of smoking were lower in men with prostate cancer. Smoking is also the most important risk factor for periodontal health, and the epidemiological and clinical consequences of this have been extensively reviewed [19].

Regarding use of snuff, men with prostate cancer reported less cans of snuff use per year than men with no prostate cancer (p<0.06). The results of sniffing are in agreement with the results of a systematic review by Lee & Hamling, where in the USA the meta-analysis estimates for cancer risk in general were predominantly greater than 1.0, while in Scandinavia below 1.0, respectively. The results thus do not indicate that snuff as used in Scandinavia has any effect on cancer risk [20].

Finally, the current results indeed support the hypothesis of infection vs. cancer, by showing that long-term infection burden may affect carcinogenesis; in this case the incidence of prostate cancer. However, in a register study like here presented causality cannot be assessed. Whether or not periodontitis, or its prerequisite the accumulation of bacterial plaque on teeth, is an independent risk factor for prostate cancer would require sequential evaluation. There, controlling a number of other factors such as occurrence of other inflammations, nutrition, and genetics is not an easy task, however [21].

Conclusion

To our knowledge these data are the first in showing eventual risk of poor oral hygiene for prostate cancer. Result may be explained by low-grade systemic inflammation of oral origin that affects carcinogenesis.

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