Unique database study linking gingival inflammation and smoking in carcinogenesis

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We investigated statistical association between gingival inflammation and cancer in a group of patients followed up for 26 years with the hypothesis that gingival inflammation affects carcinogenesis. Altogether, 1676 30- to 40-year-old subjects from Stockholm were clinically examined in 1985. In 2011, we compared the baseline oral examination and follow-up data with cancer diagnoses sourced from the Swedish national hospital register databases. Of 1676 individuals, 89 (55 women, 34 men) had got cancer by the year 2011. Women were found to be at higher risk for cancer than men. Smoking (expressed in pack-years) had been more prevalent in the cancer group than in those with no cancer diagnosis. Gingival index, marker of gingival inflammation, was higher in the cancer group than in subjects with no cancer. There were no significant differences between the groups regarding age, education, dental plaque and calculus index scores, or in the number of missing teeth. In multiple logistic regression analysis with cancer as the dependent variable and several independent variables, pack-years of smoking appeared to be a principal independent predictor with odds ratio (OR) 1.32 while gingival inflammation showed OR 1.29. Hence, our present findings showed that together with smoking, gingival inflammation indeed associated with the incidence of cancer in this cohort.

1. Introduction

Gingival inflammation (gingivitis) is the physiological response to oral microbial infection. If gingivitis is not resolved, the response becomes chronic. In chronic gingivitis, the adaptive immune response is activated with involvement of cellular and non-cellular mechanisms. These play further roles in the resolution of inflammation and in the healing process, including the repair and regeneration of lost or damaged tissues [1].

Gingival inflammation often leads to periodontitis characterized by destruction of the bone surrounding the teeth owing to immune-inflammatory reactions and, ultimately, to tooth loss [2–5]. It is estimated that 15 to 35% of the adult population in the industrialized countries suffers from this multifactorial disease [4]. Although microbes are required to initiate the pathological process, smoking is an important risk factor for the development of periodontitis; smoking also increases the severity of the disease [6,7]. In individuals with constitutional pro-inflammatory traits, the reaction to bacteria may lead to an excessive host response, resulting in systemic inflammatory reaction [8,9]. The presence of chronic gingivitis and periodontitis may reflect underlying weakness of the host defence systems and increased pro-inflammatory reactivity in the affected individuals. The persistent inflammatory and microbial burden present in periodontitis and other oral infections may further predispose these individuals to systemic complications such as cardiovascular diseases, and even to the development of cancer [10–12]. Recently, the history of dental infections was also shown to link statistically to the development of cancer [13]. Poor dental health was also shown to be a prognostic risk factor.
assessed for eligibility in 1985 subjects 30–40 years in Stockholm County (n = 105 798)

randomized subjects (n = 3273)

clinical examination in 1985 (n = 1676)
838 women, 838 men

cancer in 2011 (n = 89)
55 women, 34 men

Figure 1. Study profile.

for liver transplant patients [14]. These and respective studies emphasize the vast systemic health consequences derived from gingivitis and periodontitis.

Cancer is a multifactorial disease, being one of the leading causes of death worldwide. In 2008, of all deaths 13% were due to cancer, and its burden will continue to increase in the next decades [15]. The most frequent types of cancer differ among genders. Breast cancer leads in women and prostate cancer in men [16]. In Sweden where this study was made, cancer is the second largest cause of death after cardiovascular disease for both men and women.

We were the first to observe a statistical association between periodontitis and breast cancer, supporting the concept of chronic infection/inflammation in cancer [17]. The result from another study from our group has further shown that poor oral hygiene, as reflected in the amount of dental plaque, was statistically associated with increased cancer mortality [18]. This study addresses the issue of possible associations between gingival inflammation and cancer in a cohort of 1676 individuals followed up since 1985. Our hypothesis was that the chronic low-grade gingival inflammation associates with increased cancer risk. We aimed to compare baseline oral examination data with cancer diagnoses sourced from the Swedish national hospital register databases.

2. Material and methods

(a) Study participants

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 registry file is a unique file from Sweden. The subjects were informed about the purpose of the study and they were offered a clinical oral examination in 1985. In total 1676 individuals (838 men and 838 women) underwent a detailed clinical oral examination, including plaque index [19] and gingival index (GI) [20].

Gingival inflammation was recorded around every tooth using the GI. 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). The original inclusion and exclusion criteria of the patients have been given in our earlier publications [18,21].

(b) Cancer data

The cancer data were obtained 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, O¨ rebro, Sweden. The data for both the cancer incidence as well as the 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. The study profile is shown in figure 1.

(c) Statistical analysis

We used multiple logistic regression analysis to compare the incidence of cancer diagnoses 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 dental plaque index, gingival index and dental calculus index, and periodontal disease record. The outcome variable was the incidence of cancer. Two-tailed p-values were used and odds ratios (OR) and confidence intervals (CIs) were calculated at the 95% level. All statistical analyses were performed using the PASW Statistics software package, v. 21 (PASW Inc., Chicago, IL, USA).

Table 1. Demographic clinical oral health data of 1676 subjects at baseline examination in 1985 with and without cancer by the year 2011.

<table>
<thead>
<tr>
<th></th>
<th>cancer (n = 89)</th>
<th>no cancer (n = 1587)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n, mean ± s.d.</td>
<td>n, mean ± s.d.</td>
</tr>
<tr>
<td>gender (women/men)</td>
<td>55/34</td>
<td>783/804</td>
</tr>
<tr>
<td>age in 2011 (years with s.d.)</td>
<td>61.8 ± 2.8</td>
<td>61.6 ± 2.9</td>
</tr>
<tr>
<td>smoking (pack-years)</td>
<td>3791.3 ± 4339.2</td>
<td>3179 ± 4037</td>
</tr>
<tr>
<td>education (compulsory/higher)</td>
<td>98/210</td>
<td>197/941</td>
</tr>
<tr>
<td>income (Swedish crowns)</td>
<td>455 ± 501</td>
<td>502 ± 500</td>
</tr>
<tr>
<td>plaque index</td>
<td>0.69 ± 0.47</td>
<td>0.71 ± 0.49</td>
</tr>
<tr>
<td>gingival inflammation</td>
<td>1.30 ± 0.54</td>
<td>1.26 ± 0.53</td>
</tr>
<tr>
<td>calculus index</td>
<td>0.41 ± 0.45</td>
<td>0.46 ± 0.59</td>
</tr>
<tr>
<td>no. missing teeth</td>
<td>0.45 ± 0.49</td>
<td>0.44 ± 0.49</td>
</tr>
</tbody>
</table>
3. Results

From the study group of 1676 clinically examined subjects in 1985, 89 individuals (55 women and 34 men) had got cancer by the year 2011. Demographic and clinical oral health data of the patients with and without cancer showed that women were at higher risk for cancer than men (table 1). Smoking had been more prevalent in the cancer group than in those with no cancer diagnosis. At baseline examination in 1985, 412 patients were ex-smokers (205 women and 207 men), 581 were current smokers (292 women and 289 men), while 594 patients (286 women and 308 men) were non-smokers. GI score was also higher in the cancer group. There were no differences between the groups with or without cancer regarding age, education, dental plaque score, calculus index score or in the number of missing teeth (table 1). The first cancer diagnoses for the 89 patients are given in table 2, the total number of cancer diagnoses were 518. As expected, the most frequent cancer diagnoses were breast cancer in women and prostate cancer in men. Of the 89, 45 women (50.56%) and 33 men (37.07%) had got breast and prostate cancers, respectively.

We also conducted a subgroup analysis of 99 patients from the cohort with respect to gingival inflammation 26 years after baseline. These results showed that the GI score in the eight patients with cancer of this subgroup showed slightly higher score (1.60) compared with the 91 patients who had not got cancer (1.56). It should also be pointed out that compared with their GI score (1.30) in the 1985 examination, the cancer patients in the subgroup showed a higher score in 2008 (1.60).

In the multiple logistic regression analysis with cancer as the dependent variable and the several independent variables, smoking (OR 1.32) and GI (OR 1.29), respectively, associated significantly with the incidence of cancer. The results are given in detail in table 3.

4. Discussion

This study addressed the issue of statistical association between gingival inflammation and cancer by analysing the relationship between the clinically recorded GI and malignancies 26 years after baseline examination. Of our subjects, 89 got a cancer diagnosis during the follow-up. Gingival inflammation indeed appeared to associate with cancer. GI score associated with OR 1.29 with cancer in the cohort. This result thus supports our study hypothesis. According to statistics from the Swedish Cancer Registry our patients were diagnosed with cancer 10 years earlier than expected, when the age groups are taken into account, i.e. 30–40 years at baseline [22].

In the year 2011, when the cumulated register data of this study were collected, altogether 57,764 cancer diagnoses were reported to the Swedish Cancer Registry, with the following gender distribution: 52% men, 48% women. During the last two decades, the average annual increase in the number of cases has been 2.1% in men and 1.5% in women, respectively. The increase in cancer cases can be partly explained by the ageing population, and also by the introduction of screening programs and improvements in diagnostic practices.

<table>
<thead>
<tr>
<th>neoplasms</th>
<th>ICD-10</th>
<th>per cent*</th>
<th>men (n)</th>
<th>women (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>malignant neoplasm of stomach, unspecified</td>
<td>151X</td>
<td>0.58</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>malignant neoplasm of small intestine, including duodenum</td>
<td>153A</td>
<td>0.58</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>malignant neoplasm of colon, hepatic flexure</td>
<td>153B</td>
<td>0.19</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>malignant neoplasm of prostate</td>
<td>C61</td>
<td>6.37</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>malignant neoplasm of sigmoid colon</td>
<td>153D</td>
<td>2.70</td>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td>malignant neoplasm of cecum</td>
<td>153X</td>
<td>1.54</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>malignant neoplasm of liver, primary</td>
<td>153E</td>
<td>0.39</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>malignant neoplasm of larynx</td>
<td>161A</td>
<td>1.16</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>malignant neoplasm of middle lobe, bronchus or lung</td>
<td>162D</td>
<td>0.96</td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>malignant neoplasm of lower lobe, bronchus or lung</td>
<td>162E</td>
<td>0.39</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>malignant neoplasm of other parts of bronchus or lung</td>
<td>162F</td>
<td>0.58</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>malignant neoplasm of bronchus or lung, unspecified</td>
<td>162X</td>
<td>1.54</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>melanoma of skin, other and unspecified parts of face</td>
<td>172.39</td>
<td>0.77</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>malignant melanoma of skin, unspecified parts of face</td>
<td>172.81</td>
<td>0.19</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>malignant melanoma of ear and external auditory canal</td>
<td>172C</td>
<td>0.19</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>malignant melanoma of upper limb, including shoulder</td>
<td>172F</td>
<td>0.19</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>malignant melanoma of lower limb, including hip</td>
<td>172G</td>
<td>1.35</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>malignant melanoma of skin in other unspecified parts of face</td>
<td>172C</td>
<td>0.19</td>
<td></td>
<td>1</td>
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<tr>
<td>malignant melanoma of ear and external auditory canal</td>
<td>173.21</td>
<td>0.58</td>
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<tr>
<td>malignant melanoma of female breast, upper-outer quadrant</td>
<td>174E</td>
<td>1.16</td>
<td></td>
<td>6</td>
</tr>
<tr>
<td>malignant neoplasm of female breast, upper-inner quadrant</td>
<td>174.02</td>
<td>7.53</td>
<td>39</td>
<td></td>
</tr>
</tbody>
</table>

*aSome patients had multiple cancer diagnoses. The total no. of cancer diagnoses was 518.*
Table 3. The results of multiple logistic regression analysis of the relationship between cancer in 1676 subjects clinically examined, cancer as the dependent variable with several independent variables (age, gender, number of dental visits, education, income, socioeconomic status, working status, pack-years of smoking, dental plaque index, calculus index, gingival inflammation, periodontal disease and missing teeth). Cox & Snell $R^2 = 0.014$; Nagelkerke $R^2 = 0.020$.

<table>
<thead>
<tr>
<th>dependent variable</th>
<th>explaining variable</th>
<th>$\beta$</th>
<th>$\chi^2$</th>
<th>$p$-value</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>cancer</td>
<td>smoking</td>
<td>0.28</td>
<td>5.56</td>
<td>0.018</td>
<td>1.32 (1.05 – 1.67)</td>
</tr>
<tr>
<td></td>
<td>gingival inflammation</td>
<td>0.25</td>
<td>3.89</td>
<td>0.049</td>
<td>1.29 (1.00 – 1.65)</td>
</tr>
</tbody>
</table>

The most frequent cancers were breast cancer in women (30.3% of all cases in women) and prostate cancer in men (32.2% of all cases of men) [22]. Compared with the result of this study, 50.56% of the women were diagnosed with breast cancer and 37.07% of the men were diagnosed with prostate cancer; as said, these cancers were also the most common in our study.

Regarding the reliability of the results, our subjects were randomly chosen to avoid selection bias. The large subject pool was representative of the ethnically homogeneous Swedish adult population, with age range of 10 years to limit the influence of age differences. The study had a longitudinal prospective design with a cohort of subjects whose oral health status was documented at baseline 26 years earlier. Gingivitis was recorded based on the characteristic signs of inflammation, namely redness, oedema and glazing of the gingival tissue. It can be argued that the gingivitis healed as a result of later visits to a dentist. However, it should be borne in mind that the patients in fact already had suffered from gingivitis for a long time and also had a documented smoking history in 1985. Both these factors may increase the risk for cancer development later in life. Nevertheless, no causal conclusions can be drawn from the current results.

Knowing that smoking is one of the most important risk factors for cancer [15], it is important to emphasize that in our study population pack-years of smoking were higher in the development later in life. Nevertheless, no causal conclusions can be drawn from the current results.

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Knowing that smoking is one of the most important risk factors for cancer [15], it is important to emphasize that in our study population pack-years of smoking were higher in the cancer group than in those with no cancer diagnosis. In Sweden, in 2011, about 1 million people still smoked, despite a decline in smoking in the last few decades [23]. In the earlier mentioned subgroup analysis, of the eight patients with cancer four were still smokers at the follow-up examination. In the 91 patients who did not have cancer, 44 patients were smokers and 47 non-smokers.

Smoking is also the most important risk factor for periodontal health, and the epidemiological and clinical consequences of this have been extensively reviewed in Ryder [24]. The negative effects of smoking on the immune response have also been extensively studied and will not be commented on further here [25].

Gingivitis is one of the major public health problems all over the world. Hence, our present results are worth considering also in the context of global health programs. Maintaining proper daily oral hygiene may thus be emphasized also in the light of preventing systemic diseases. As we have shown, even malignancies might link to poor daily oral hygiene habits which, in turn, cause chronic dental diseases such as gingivitis. In the perspective of the role of the inflammatory pathways in carcinogenesis, this may then result in poor outcome [26]. But further evidence is certainly needed to back up this conclusion.

Ethics statement. 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 Helsinki Declaration.

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References


