

Hormonal effects behind the development of oral cancer

PhD Theses

Dániel Takács MD DMD

Semmelweis University

PhD School of Pathology



Consultant: József Tímár MD DSc

Opponents: József Blazsek DMD PhD

Jenő Czigner MD DSc

President of Examination Committee:

Péter Nagy MD DSc

Members of Examination Committee:

Zsolt Németh MD PhD

Dezső Tanka MD PhD

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Summary

The oral cancer morbidity and mortality in Hungary is the worst in all Europe. This worrying statistic is accompanied by new epidemiological phenomena, such as the increasing prevalence of cases free of classical risk factors (tobacco and alcohol consumption) and changes in the male to female ratio.

We have investigated the metabolic status of 224 inpatients with confirmed salivary gland tumors, and have found a close connection between the occurrence of tumors and insulin resistance.

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Surveying the alcohol consumption habits of 608 non-smoker oral cancer patients resulted in the recognition of cancer protective potential of moderate alcohol consumption among post menopausal women.

We have investigated the hormonal statuses, tumor localizations and connections with classical oral cancer risk factors among 2660 OC patients, and have found low estrogen levels to be a strong risk factor for oral cancer. Thus we have found answer to the significant male dominance among cancer cases, also we have clarified why female OC patients are older than male patients.

In two 2-years long phases, first between 01st January 1985 and 31st December 1986, second between 01st January 2005 and 31st December 2005 we have evaluated the data of 550 oral cancer inpatients and their controls to register changes in Hungarian OC epidemiology. We have come to the conclusion, that the dramatic increase in numbers of Hungarian OC cases is not likely to be caused by the increasing magnitude of classical risk factors, rather we find new risk factors behind the changes.

Immunohistochemical analysis of the samples from 15 male and 24 female OC patients we have found correlation between Estrogen receptor Alpha and Beta expression, and clinical behavior of the tumors. Our results indicate, that oral cancer cells respond to physiological Estrogen signals. As long as solely Beta receptors are found on cancer cells, the Estrogen effect is unchanged, however the emergence of additional Alpha receptors indicate a pathologic estrogen effect and a decline in prognosis.

Analyzing the occurrence of oral tumors among children, we found that OC does not occur among patients prior puberty. Benign jaw tumors were more frequent among girls.

Introduction

Epidemiology and significance of Oral Cancer in Hungary

Hungary is leader in Oral Cancer (OC) mortality among European countries, followed by other post-communist states. It is not only the mortality and morbidity statistics that require attention, but also the worrying fact, that OC cases show an elevation in occurrence during the past decades. The ratio of smoking and alcohol consumption among Hungarian male and female population shows only 15-16% difference, that can hardly explain the 4-5 folds male dominance among OC patients.

Properties of the male to female ratio

Oral Cancer shows a significant male dominance in most countries. It is also relevant, that OC occurs at higher ages among women than among men. Non-smoker non-drinker female cases are also surprisingly common.

According to our findings, the male to female ratio shows a declining tendency among elderly OC patients.

Risk factors of oral cancer

Classical risk factors

Oral Cancer is a multi-causal disease, but the etiologic factors are closely connected. Environmental hazards (such as tobacco, alcoholic beverages, high carb diet) are the classic risk factors for Oral Cancer.

New Risk Factors

No classical risk factors are present among young OC patients. Recently systematic metabolic disorders (Metabolic syndrome, type 2 diabetes mellitus) were found to be in connection with oral and other cancers.

Insulin resistance

Diabetes and its cardiovascular complications share a common background, that is insulin resistance. Metabolic syndrome (also known as: insulin resistance syndrome, pre-diabetes) is a well-defined group of symptoms. It is based on disorders in carbo-hydrate metabolism, dyslipidaemia, elevated blood pressure and obesity. These symptoms are all risk factors for cardiovascular diseases, but together the risk is even higher.

Hormonal disorders

It is widely accepted, that ovarian and endometrial cancers are connected to female sexual hormones. Hormone Replacement Therapy (HRT) of post-menopausal women is common in western countries.

Advantageous effects of HRT was reported in cases of oral- esophageal- gastric- colon- cervix- lung- and hepatic cancers. HRT was found to be protective against smoking-related cancers, such as Oral Cancer among post-menopausal smoker women.

Based on epidemiological findings, it is possible, that not estrogen, but its missing effects could provoke malignant transformation. This new theory could explain the contradictions surrounding estrogen effects on malignant tumors.

Aims

Clinical epidemiology

In the database of the Clinic of Oral and Maxillofacial Surgery and Dentistry of Semmelweis University Budapest

- We analyzed the connection between salivary gland tumors and insulin resistance (type 2 DM, metabolic syndrome) during a retrospective epidemiologic study.
- We examined the connection between Oral Cancer and alcohol consumption by analyzing the records of non-smoker male and female patients and their control.
- We examined the connections between elevated fasting glucose levels (IFG), hormonal effects, and Oral Cancer risk.
- We analyzed the changes in Oral Cancer risk factors in 20 years period.
- We examined the estrogen receptor expression of oral cancer tissue samples using immunohistochemical methods.
- We analyzed the occurrence of oral tumors among children prior puberty.

Risk research

During our research we were looking for answers on the following questions:

1. Is there an explanation for the male dominance among Oral Cancer cases?
2. Why are the female OC patients older than the males?
3. Is there a connection between the hormonal status of female OC patients and cancer risk?
4. Why is the number of Non-Smoker Non-Drinker patients continuously increasing?

Methods

Histological methods

During our research we examined the data of histologically confirmed Oral Cancer patients and their controls. All patients were treated at the Clinic of Oral and Maxillofacial Surgery of Semmelweis University Budapest. We obtained the histological diagnosis from surgically removed tumors, where it was possible. Regarding inoperable cases we examined the biopsy tissue samples.

Immunohistochemistry

We processed all tissues samples using routine diagnostic protocols. However in some cases we introduced additional methods. Estrogen hormone effects on Oral Cancer was a key element of our research, thus we measured the Estrogen Receptor Alpha and Beta expression in selected tissue samples using immunohistochemistry.

To enhance the weak signal obtained from the samples, we used a specific binding streptavidine-biotine complex, that connected large amount of peroxidase enzyme to each detected estrogen receptor. The presence of peroxidase was detected using the strong color reaction of diamino-benzidine (DAB). The traceable marker was brown.

Epidemiological methods

During our retrospective, case control studies we analyzed the data collected from patients records and survey sheets obtained solely at the Clinic of Oral and Maxillofacial Surgery of Semmelweis University Budapest.

Biometrical methods

During our research we recorded biological and environmental risk factors. For biological data we used laboratory methods, data on environmental factors was collected using survey-sheets.

Results

Epidemiology

Connection between insulin resistance and salivary gland tumors

224 histologically confirmed salivary gland tumor patients and 214 tumor free control patients from the same period was included in the study. Out of the 224 tumor patients 54,1% (121 cases) turned out to be insulin resistant. Among the controls this was only 14,5% (31cases). The difference was significant (Chi-square, $p<0,001$).

Tumors of other regions of salivary gland tumor patients was significantly more common than among controls (17,8% vs. 8,4%, Chi-square $p<0,01$). Malignant tumors of other regions among salivary gland tumor patients also showed a significant increase compared to controls (8,9% vs. 2,8%, Chi-square $p<0,05$).

48,2% of salivary gland tumor patients were smokers, while among controls smoking was only 36,9% (Chi-square $p<0,01$).

There was no significant age-difference between the tumor and control groups.

Connections between moderate alcohol consumption and Oral Cancer

We examined 608 newly diagnosed Oral Cancer patients, 466 men and 142 women. The male to female ratio was 4,38:1. The average age of female OC patients was significantly higher than that of males ($63,6\pm14,5$ years vs. $56,6\pm12,0$ years; Mann-Whitney $p<0,01$).

Almost half of the male OC group reported excessive alcohol consumption (41,8%), moderate drinkers were in minority (7,1%). Among male controls there were significantly more non-drinkers (76,5% vs. 51,1%; Chi-square $p<0,001$), but among consumers excessive drinkers were in majority. We found Excessive alcohol consumption to be a strong risk factor for Oral Cancer (OR:2,2). Moderate drinking was a weaker risk factor (OR:1,4) among men.

In the female OC group regular alcohol consumption was significantly less common, than among men (15,5% vs. 48,9%; Chi-Square $p<0,01$). Female OC patients were excessive drinkers on significantly larger scale, than their controls (12,7% vs. 2,1%; Chi-Square $p<0,05$). We found excessive alcohol consumption to be a strong risk factor for Oral Cancer (OR:3,6) among women as well. However moderate drinking was no risk factor at all, it had advantageous effect on OC risk for women (OR:0,7).

Hormonal effects and Oral Cancer risk

We included 2660 newly diagnosed and histologically confirmed squamous cell Oral Cancer cases in this study. The male to female ratio was 4:1 (2130 men and 530 women). Female OC patients were significantly elder than male patients at the time of diagnosis. The highest average age was found among female gingival cancer patients ($66,9 \pm 11,4$ years). The youngest patients were found among sublingual cancer cases, for both male and female groups ($54,7 \pm 10,9$ years and $56,5 \pm 10,1$ years).

The male to female ration for young (under 30 years old) patients was 2:1, thus male dominancy was significantly lower in this subgroup. The characteristically high, 4:1 male to female ratio was found between 31 and 55 years. After 50years of age (mean for menopause) female cases start to show a relative incline compared to male cases.

Regarding tumor locations, extensive alcohol consumption was a strong risk factor for sublingual cancer in both sex. Among OC patients (of both sex) non-smoker non-drinker patients were significantly less frequent than among controls. Regarding tumor location, the most non-smoker non-drinker patients were found among gingival cancer cases for both sex (29,4 of males, 54,5% of females).

Among male OC patients elevated blood sugar levels (impaired fasting glucose, IFG) were similar to that of controls. On the contrary, IFG proved to be a significant OC risk factor for women (OR=1,51-1,71).

Almost all female OC patients were post-menopausal, while among age-matched controls 25% of the patients were still active hormonally.

Changes in OC epidemiology in a 20 years period.

In two 2-yers long phases, first between 1st of January 1985 and 31st of December 1986, second between 1st of January 2005 and 31st of December 2005 we have evaluated the data Oral Cancer inpatients at the Clinic of Oral and Maxillofacial Surgery of Semmelweis University and their controls to register changes in OC epidemiology. In the first phase we examined the data of 460 confirmed squamous cell OC cases and 350 tumor free controls. In the second phase we examined the data of 550 confirmed squamous cell OC cases and 450 tumor free controls.

The male to female ratio dropped from 5,8:1 to 3,7:1 during the 20 years (Chi-Square $p < 0,05$). In both phases, female OC patients were a significantly higher age than males.

In the first phase, lower lip was the most frequent tumor location for male OC cases (35,0%). In the second phase, sublingual localization showed a strong dominance among men

(41,6%), almost doubling in 20 years. Gingival cancer (13,0%) stayed relatively rare among male OC cases.

In the first phase, gingival tumor location (23,9%) was the most frequent among women, significantly higher than that of men (Chi-Square $p<0,05$). In the second phase, gingival cancer stayed the dominant location for women, and showed a steady increase (28,3%).

Smoking habits also changed. Among male control patients smoking declined significantly (57,5% first phase, 50,7% second phase). Smoking was significantly more frequent among male OC cases than among controls (77,5% first phase, 73,5% second phase), but showed a declining tendency.

Smoking and alcohol consumption were significantly more frequent among OC cases, than among the controls in both gender, however they showed a declining tendency over the 20 years. These classical risk factors also became less frequent among control patients.

ER immunohistochemistry analysis of OC samples

We performed immunohistochemical detection of Estrogen Receptors on selected samples from 15 male and 20 female OC patients treated at the Clinic of Oral and Maxillofacial Surgery of Semmelweis University Budapest. Male patients were significantly lower age than females. ($59\pm7,6$ years, vs. $73\pm11,5$ years; Mann-Whitney $p<0,01$). We used a semi-quantitative method and a scale of 1-4 for recording receptor status. ERA was undoubtedly present in the samples (males 2,26; females 1,95). ERB showed a significantly stronger expression in both sex (males 3,07; Mann-Whitney $p<0,05$; females 3,0; Mann-Whitney $p<0,05$), however there was no significant difference among the two genders.

Oral tumors without sexual hormone effects

Analyzing the occurrence of oral tumors among children, we found that Oral Cancer does not occur among patients prior puberty. We presented three typical benign jaw tumor cases from the Clinic of Oral and Maxillofacial Surgery of Semmelweis University Budapest.

Discussion

Epidemiology

Connection between insulin resistance and salivary gland tumors

Metabolic Syndrome is a progrediating, complex metabolic disorder. As the number of severity of its components increase, it can cause the onset of different diseases (type 2 DM, cardiovascular disease or tumors). According to our findings, both type 2 DM and Metabolic Syndrome was significantly higher among salivary gland tumor patients than among their controls. This finding indicates a connection between salivary gland tumors and insulin resistant metabolic disorders.

It is a new finding, that not only type 2 DM, but other insulin resistant states of Metabolic Syndrome are connected to salivary gland tumors.

Both DM and Metabolic Syndrome were more frequent among our tumor patients than among their controls, regardless of the level of insulin resistance.

Examining other tumor locations, we found that both malignant and benign tumors of other sites were more frequent among salivary gland tumor patients, than their controls.

Connections between moderate alcohol consumption and Oral Cancer

Alcohol consumption is a well known risk factor for Oral and Esophageal cancers. However moderate alcohol consumption is known to lower the risk of type 2 DM and insulin resistance.

According to recently published studies, moderate alcohol consumption can be advantageous for post menopausal women by increasing insulin sensitivity and estrogen levels. Examining solely non-smoker patients, we proved that moderate alcohol consumption lowers the risk of Oral Cancer among women, contrary the classical theory, that alcohol intake is always a strong risk factor for OC. We found moderate alcohol consumption to be a weak OC risk factor for men, but protective for women. Excessive alcohol intake was found to be strong OC risk factor for both gender. Elevated blood glucose (Impaired Fasting Glucose, IFG) was a significant OC risk factor for women, but was not risk factor for men.

Hormonal effects and Oral Cancer risk

Besides the known harmful effect of excessive drinking and smoking, elevated blood glucose level and postmenopausal hormonal changes are found to be OC risk factors for women.

Examining the male to female ratio of OC cases in the perspective of age, our theory indicates a higher OC risk for hormonally inactive (pre- and post menopausal) women. This would mean that healthy women of reproductive age are somewhat protected against Oral Cancer. Examining female OC cases, we found more frequent cases of premature menopause or gynecological treatments (hysterectomy, ovariectomy) resulting in lower estrogen levels.

It is well known, that gingiva is a hormone-sensitive site. Type 2 DM is often accompanied by gingivitis and periodontitis in both gender. Gingiva was found to be the most frequent tumor location among female OC cases (28,3%). We didn't find classical OC risk factors (smoking and drinking) in the anamnesis of 30% of male and more, than 50% of female OC patients.

Our results indicate, that low estrogen levels accompanied by insulin resistance are in a strong connection with gingival cancers among post menopausal women.

Changes in OC epidemiology in a 20 years period.

The male to female ratio of OC cases showed a significant decline in a 20 years period.

Analyzing tumor locations of male and female OC patients, we found significant changes in 20 years. Gingival cancers showed significant difference between men and women. Gingival location was dominant among women in both phases, and its frequency showed an increase in 20 years. On the contrary gingiva was far behind other sites among men, and there was no significant increase in frequency.

Based on our results, the ratio of smokers among both patients and controls showed a decline. Smoking is still a major risk factor for OC, as there were significantly more smokers among cancer patients than among controls for both gender, in both phases.

We found drinking to be an important OC risk factor, mostly among men, but the decreasing tendency of overall alcohol consumption doesn't answer the increase in OC morbidity. Alcohol consumption habits didn't change significantly among women.

ER immunohistochemistry analysis of OC samples

Estrogens are held responsible in the development of several, mostly gynecological tumors. These new results and the male to female ratio of other, classically smoking dependent cancers, such as Oral Cancer, suggest an important role of estrogen in these cases.

Using immunohistochemical methods we found Estrogen Receptor expression in Oral Cancer tissue samples both among men and women. There was no significant difference of ER expression between the two genders. We found that the ERB expression, present also in

normal gingiva, was significantly stronger than ERA expression, the latter is not normally found in oral tissue samples.

Hungarian scientists suggest a possible role for anti-estrogen chemotherapy in ER positive Oral Cancer cases. Chinese scientists found ERB expression to be beneficial among small cell lung cancer patients, that is similarly to Oral Cancer, a smoking dependent tumor. Based on these findings, we assume, that physiological estrogen effects emerging on ERB can be beneficial, but pathological estrogen effects arise on ERA expressed in tumor cells. This mechanism can answer the high male to female ratio and elevated cancer risk among post-menopausal women.

Oral tumors without sexual hormone effects

Oral tumors among children and pre-puberty patients are mostly benign jaw tumors, Oral Cancer does not occur in this group of patients. Between 1997 and 2007 33 benign odontoma cases were treated at the Clinic of Oral and Maxillofacial Surgery of Semmelweis University Budapest, among those 14 boys and 19 girls. The male to female ratio was 1,36:1.

The ratio of adult male and female patients is not consistent through the literature, the female dominance is not obvious.

Considering the changes in sex ratio of children and adult patients with benign jaw tumors, and the complete lack of Oral Cancer cases among pre-puberty patients, one can assume, that sexual steroid hormones are somehow connected to the development of OC.

Conclusions

Epidemiology

Connection between insulin resistance and salivary gland tumors

Based on our results, it is clear that salivary gland tumors have epidemiological correlations with insulin resistance. It is also noteworthy, that among insulin resistant patients salivary gland tumors are often accompanied by tumors of other sites. According to previously published data and our findings, lifestyle changes that lower insulin resistance share beneficial effects on cardiovascular risk and tumors.

Connections between moderate alcohol consumption and Oral Cancer

Our results contradict the former theory, that women are especially vulnerable to drinking in terms of cancer risk. Local harmful effects of alcohol can be lowered or even turned backwards by the beneficial effects of moderate alcohol consumption on metabolism and endocrine profile, especially among women. Higher insulin sensitivity and increased estrogen levels can explain the beneficial effects of moderate alcohol intake among women.

Alcohol consumption is still considered a major risk factor for Oral Cancer, when it exceeds a very limited daily amount. Recommending alcohol consumption as a preventive method should not be a routine prescription for the patients. All beneficial and harmful effects must be taken in consideration.

Hormonal effects and Oral Cancer risk

According to our results, the hormonal differences between men and women can explain the high male to female ratio of Oral Cancer, and the significantly higher age of female OC patients. Our hypothesis, that elevated blood sugar connected with estrogen deficiency increases Oral Cancer risk can provide new strategies for screening and prevention of Oral Cancer.

Changes in OC epidemiology in a 20 years period.

Based on our results it is clear that the dramatic increase of Oral Cancer morbidity and mortality in Hungary cannot be explained by the increase of smoking and alcohol consumption. Changes in male to female ratio and the significantly higher age of female OC patients show that sex differences are important factors for Oral cancer risk. Striking

differences in tumor locations between men and women suggest an increasing role of non classical OC risk factors.

ER immunohistochemistry analysis of OC samples

We found that Oral Cancers, similarly to other smoking dependent cancers, such as small cell lung cancers, express Estrogen Receptors, that proves estrogen effect on these cells. The two Estrogen Receptor subtypes (Alpha and Beta) have different roles. ERB, also present in healthy gingiva, seems to transfer physiological estrogen effects, but ERA expression of Oral Cancer cells can be considered pathological. Hungarian scientists suggest a possible role for anti-estrogen chemotherapy in ER positive Oral Cancer cases. Chinese scientists found ERB expression to be beneficial among small cell lung cancer patients, but this is yet to be confirmed in Oral Cancer cases.

Oral tumors without sexual hormone effects

We found that oral tumors among children and pre-puberty patients treated at Clinic of Oral and Maxillofacial Surgery of Semmelweis University Budapest are mostly benign jaw tumors. We found that Oral Cancer does not occur in this group of patients, the male to female ratio of benign odontomas was 1,36:1. The ratio of adult male and female patients is not consistent through the literature, the female dominance is not obvious.

Considering the changes in sex ratio of children and adult patients with benign jaw tumors, and the complete lack of Oral Cancer cases among pre-puberty patients, one can assume, that sexual steroid hormones are somehow connected to the development of OC.

Risk research

During our research we found answers to the most striking questions of OC epidemiology:

1. The high male to female ratio cannot solely be explained with higher alcohol consumption and smoking of men, because oral mucosa is a hormone sensitive tissue. Physiological estrogen effect shows to be preventive against Oral Cancer.

2. Female OC patients are elder than males, because women are somewhat protected against Oral Cancer during their reproductive years.

3. Estrogen Receptor status of Oral Cancer tissue samples also indicates a beneficial estrogen effect on these tumors.

4. Estrogen sensitivity and increasing trends in insulin resistance can explain the significant increase in Oral cancer morbidity among non-smoker non-drinker patients.

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Summary

Number of publications:	11
Hungarian:	4
Hungarian Journal in English:	1
International Journal in English:	6
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All impact factor:	9,978