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ARTICLE

Gender-Related Hormonal Risk Factors for Oral Cancer

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Oral cancer (OC) is a neoplasm with fairly high male to female ratio in most populations. The conspicuously lower incidence of this tumor among women than man is suggestive of certain endocrine involvement in its development. The aim of the present case-control study was to clarify the origin of this gender-specific risk of OC incidence. 2660 inpatients (530 females and 2130 males) with squamous cell OC at the Department of Oral and Maxillofacial Surgery were included in a case-control study. Smoking, alcohol consumption, elevated fasting serum glucose level and menopausal histories of female cases were registered. Smoking and excessive alcohol intake proved to be strong risk factors for OC both in the male and female group. However, moderate alcohol consumption was a weaker risk factor for male patients, and it presented no risk for female cases. Elevated fasting glucose level was not a demonstrable OC risk factor among males, however, it proved to be strong risk factor for OC among female patients, especially in gingival cancer cases. The almost exclusively postmenopausal state of female OC patients and the long mean interval (17 years) between their menopause and OC diagnosis suggested an important role of estrogen deficiency in OC epidemiology. The significantly younger mean age at menopause and the significantly higher rate of hysterectomy among female OC cases in comparison with their controls also support the estrogen deficiency hypothesis. This novel hypothesis of estrogen deficiency and elevated fasting glucose as risk factors for OC in postmenopausal women may provide new insights into the etiology of oral malignancies. (Pathology Oncology Research Vol 13, No 3, 195–202)

Key words: oral cancer, fasting glucose, insulin resistance, estrogen deficiency, gender difference

Introduction

Oral cancer (OC) is a neoplasm with a fairly high male to female sex ratio in most populations.[1-4] Moreover, OC develops in older age in females in comparison with males, and the ratio of non-smokers, non-drinkers among elderly female OC cases is surprisingly high.[4] The conspicuously lower incidence of this tumor among women than among men is suggestive of certain endocrine involvement in its development. This gender-specific risk for OC raises two different assumptions. First, there are noxious factors affecting selectively only male patients, and second, common risk factors affect both sexes, but females have some defense mechanisms owing to their special hormonal and metabolic features. There are no available literary data as yet which would give an explanation to the gender-specific incidence rate of OC.

Hungarian morbidity and mortality rates for OC are the worst in Europe among both men and women, with the trends becoming quite disadvantageous during the last decades.[2,5] The exceedingly high rates of OC in the majority of central European countries and especially in Hungary are attributed to the excessive smoking and alcohol consumption habits.[2,6] However, the rates of these bad habits show a 15-16% difference between the Hungarian male and female population, which can hardly justify a four-to-six-fold excess of male patients among oral cancer cases.[7]

OC is a multi-causal disease and there are close interrelationships among the etiologic factors. Till now the exogenous harmful noxae (tobacco, alcohol consumption and energy-rich diet) were overemphasized in OC epidemiology.[2-6] Recently, however, internal metabolic changes, e.g. metabolic syndrome and type-2 diabetes also seem to be risk factors for oral tumors.[8,9] Nevertheless,

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exogenous dietary factors, tobacco and alcohol consumption have not only local carcinogenic effect in the oral cavity, but also induce systemic changes by means of metabolic and hormonal pathways. Inflammation, atrophy and hyperplastic processes on the epithelial surface of the oral mucosa caused by external, internal factors or both, may enhance the vulnerability of the squamous epithelial cells and may provoke disturbances in their regeneration.[10]

Nowadays, data in the literature have revealed interrelationships among the effects of smoking, alcohol consumption, insulin resistance and alterations of the sex hormone milieu.[11-14] With full knowledge of these correlations, isolated investigations of exogenous risk factors may be misleading, without yielding correct results.

The present case-control study was planned to answer the following questions. (i) What is the explanation of the conspicuous excess of male OC cases? (ii) Why are the female OC patients markedly older than the male patients? (iii) Is there any correlation between the reproductive factors of women and their OC risk? (iv) Could there be any gender-related association between elevated fasting glucose and OC risk?

Materials and methods

Patients

2660 inpatients (530 females and 2130 males) with histologically confirmed squamous cell OC at the Department of Oral and Maxillofacial Surgery were included into a case-control study between l January 1997 and 30 June 2006. The controls were complaint-free adults (530 females and 2450 males) who volunteered to participate in stomato-oncological screening in the same period. The data of the oral cancer patients and their controls were collected by means of questionnaires and from case reports of the inpatients. All these patients gave their informed consent to participate in the study. Eighteen tumor patients and 42 controls refused to participate.

The age of female patients was especially important in this study. For each female OC case a female control was chosen who matched the patient's age (within 5 months) at the time of cancer diagnosis. The mean age of control male patients was chosen so as to be within 1 year of the mean age for the male OC cases. The mean ages of the male and female OC patients and the ratio of young (45 years and under) cases at the time of OC diagnosis were registered. Mean ages of the male and female OC cases in the groups of the prevailing tumor locations were also recorded. Frequencies of the different tumor locations among the male and female OC cases were compared.

Smoking habits and alcohol consumption

The ratio of smokers among the male and female OC cases and their controls were assessed. Mean ages of the smokers and non-smokers among the male and female patients at OC diagnosis were evaluated. The ratios of smokers were determined in the groups of the prevailing OC locations for both the male and female OC cases.

Regular alcohol consumption was registered among the OC and control men and women, moderate and excessive drinkers evaluated separately. A regular <30 g daily alcohol intake was regarded as moderate, and a >30 g/daily intake as excessive alcohol consumption. The correlations of drinking and tumor locations were also evaluated separately in both the male and female OC groups.

Determination of the ratio of elevated fasting glucose (EFG) level

The ratio of EFG among the male and female OC and control cases were investigated. Fasting blood glucose levels were determined repeatedly within 4 days. All determinations were made by means of Hitachi 717/912 automatic analyzers (Roche Diagnostics, Boehringer Mannheim, Germany). The level was regarded as elevated only if it was repeatedly >5.5 mmol/l. These EFG groups comprised symptom-free insulin-resistant cases, newly diagnosed and known, treated or untreated type-2 diabetes cases. The correlations of the EFG ratios and the tumor locations were also studied in the male and female groups.

Menopausal history of female control and OC cases

The ratios of the postmenopausal cases and the mean age at menopause in the OC and control groups were determined. The ratio of early menopause (<45 years) cases due to either unidentified ovarian failure or hysterectomy/ovariectomy and of late menopause (>51 years) were also registered in both the OC and control female groups. The mean time intervals between menopause and OC diagnosis (M-OC) were established in the group of all female OC patients, in the early and in the late menopausal female groups. M-OC intervals were assessed both in the smoker and non-smoker groups of women with OC. Ratio of postmenopausal hormone replacement therapy and its length were registered.

Statistical methods

The associations of OC incidence with various risk factors were obtained from conditional logistic regression analysis by means of odds ratios and their 95% confidence intervals (CI).

The chi-square and Fisher exact tests were also used for statistical analysis. The mean ages of the different groups were compared by means of two-sided Student's t-test. A probability level of 5% was taken as limit of statistical significance.

Table 1. **Mean age of oral cancer (OC) cases at the time of tumor diagnosis and ratio of young OC patients**

	Males	*Females*	*p*
OC cases (year)	55.1±10.8 (range:33-85)	63.5±10.9 (range:36-91)	p<0.001
Gingival cancer (year)	56.9±11.1	66.9±11.4	p<0.01
Sublingual cancer (year)	54.7±10.9	56.5±10.1	p>0.05
Ratio of young OC cases (<45 years)	16.5%	4.6%	p<0.001

Results

Distribution of gender, age and tumor locations of the OC cases

Of a total of 2660 newly diagnosed and histologically verified oral squamous cell carcinoma cases, 2130 were males and 530 females, with a male to female ratio of 4:1. The mean age of female OC patients upon admission was significantly higher as compared with the male OC patients (*Table 1*). Concerning tumor site, the highest mean age was registered among the female gingival cancer cases. In the male gingival cancer group mean age was moderately elevated as compared with all male OC cases. The lowest mean ages were observed in the sublingual cancer groups both among males and females. Young oral cancer patients aged 45 years and under were significantly more frequent among men as compared with women.

Regarding the male OC patients, the most common tumor site was the sublingual region (41.6%). This was followed in decreasing order by the tongue (24.6%), lower lip (15.3%), gingiva (12.9%), palate (2.5%), bucca (2.1%) and other rare locations (1.0%). In respect to the female patients, the site prevalence was quite different. The most common OC location was the gingiva (28.3%), followed in decreasing order by the sublingual (26.4%), the tongue (18.3%), lower lip (8.4%), bucca (7.1%) palate (6.1%), and other rare locations (5.4%).

Smoking and drinking habits of OC patients and controls

Both in the male and female OC group, the summarized ratio of active and earlier smokers was significantly higher as compared with the smoking histories of the male and female controls (*Table 2*). Considering the age of the patients at the diagnosis of OC, both in males and females smokers had a significantly lower mean age (54.2 and 56.1 years, respectively) as compared with the non-smoker male and female cases (62.9 and 68.5 years, respectively. In the female OC group the combination of postmenopausal hormone deficiency and smoking resulted in a lower mean age as compared with the non-smoker cases. In regard to tumor location (*Table 2*), the rate of smokers was the highest in the sublingual cancer subgroups both among the male and female OC cases. The rate of smokers was lower in the gingival cancer groups, especially among the female cases.

In the male OC group near the half of the cases were regular alcohol consumers, within which a small part were moderate drinkers, whereas the majority were excessive drinkers (*Table 3*). A significantly lower regular alcohol consumption rate was registered in the male control group, however, the great majority of them were excessive drinkers. In men alcohol consumption proved a strong risk

Table 2. **Prevalence of smoking in OC and control cases**

	Males			*Females*		
	Ratio of smokers	*p*	*OR*	*Ratio of smokers*	*p*	*OR*
Controls	53.0%			38.3%		
All OC	75.1%	<0.01	3.67	57.2%	<0.01	2.15
Sublingual cancer	84.5%	<0.01	4.80	75.9%	<0.01	5.04
Gingival cancer	68.2%	<0.05	1.89	45.4%	>0.05	1.33

Table 3. **Correlations of alcohol consumption and OC incidence**

	Frequency of alcohol consumption		*p*	*OR*
	Control cases	*OC cases*		
Male cases				
All alcohol consumers	21.0%	47.7%	<0.01	3.26
Moderate alcohol consumers	3.4%	6.6%	<0.05	2.02
Excessive alcohol consumers	17.6%	41.1%	<0.01	3.44
Female cases				
All alcohol consumers	5.5%	12.0%	<0.05	2.36
Moderate alcohol consumers	2.7%	2.8%	>0.05	1.00
Excessive alcohol consumers	2.8%	9.2%	<0.01	3.72

factor for OC, although the risk was lower among moderate compared to excessive drinkers.

In the female OC group, the rate of regular alcohol consumption was significantly lower as compared with the male OC group ($p<0.01$). Among the female drinker OC patients the excessive alcohol intake predominated. Regarding the female control cases, the regular alcohol consumption rate was significantly lower, and a near equal distribution of moderate and excessive drinking was registered. Regular excessive alcohol consumption proved to confer a high risk, however, regular moderate alcohol consumption was not an OC risk factor in women.

Considering tumor location, alcohol consumption proved to confer a higher risk for sublingual cancer in both genders when compared with all OC cases (*Table 4*). Among males with gingival cancer the rate of regular drinkers was similar as compared with all male OC cases. Among female gingival cancer cases, drinking proved to be slightly weaker risk factor, as compared to all women with OC.

Both in the male and female OC groups the ratios of non-smoker, non-drinker (NSND) cases were significantly lower as compared with their control groups (*Table 5*). Considering the tumor locations, the highest rates of NSND cases were found in the gingival cancer groups both among males and females. Nearly one third (29.4%) of the male and more than half (54.5%) of the female gingival cancer group were registered as NSND cases.

Table 4. **Prevalence of alcohol consumption in OC and control cases**

	Males			*Females*		
	Ratio of alcohol consumers	*p*	*OR*	*Ratio of alcohol consumers*	*p*	*OR*
Controls	21.0%			5.5%		
All OC	47.7%	<0.01	3.26	12.0%	<0.05	2.36
Sublingual cancer	58.1%	<0.01	5.22	20.4%	<0.001	4.46
Gingival cancer	46.7%	<0.01	3.30	11.3%	>0.05	1.93

Table 5. **Ratio of NSND cases in OC patients and controls**

	Males			*Females*		
	Ratio of NSND cases	*p*	*OR*	*Ratio of NSND cases*	*p*	*OR*
Controls	44.1%			60.0%		
All OC	20.1%	<0.01	0.33	42.8%	<0.05	0.48
Sublingual cancer	14.3%	<0.01	0.21	24.1%	<0.05	0.21
Gingival cancer	29.4%	<0.05	0.52	54.5%	>0.05	0.80

Table 6. **Prevalence of EFG in OC patients and controls**

	Males			*Females*		
	Ratio of EFG	*p*	*OR*	*Ratio of EFG*	*p*	*OR*
Controls	52.5%			43.5%		
All OC	51.9%	>0.05	0.97	55.4%	<0.05	1.61
Sublingual cancer	51.6%	>0.05	0.96	53.7%	<0.05	1.51
Gingival cancer	56.8%	>0.05	1.19	56.9%	<0.05	1.69

Table 7. **History of menopause of female OC patients and controls**

	Controls	*OC patients*	*p*	*OR*
Postmenopausal cases	74%	98%	<0.001	
Mean age at menopause	50.9 years	43.5 years	<0.01	
Early menopause cases (<45 years)	16.0%	31.4%	<0.05	2.36
Late menopause cases (>51 years)	23.1%	14.3%	<0.05	0.78
Hysterectomy or ovariectomy cases	18.4%	35.1%	<0.05	1.69

Correlations of elevated fasting glucose level and OC incidence

In the male OC group elevated fasting glucose (EFG) rate was quite similar to that of control men (*Table 6*). However, among female OC cases EFG rate was significantly higher than among female controls, so EFG proved to be an OC risk factor among women. In men, the EFG rate in the group of sublingual cancer cases was similar to both that of the controls and of all OC cases, while it was found slightly higher in the gingival cancer group. EFG did not prove to be a risk factor for sublingual or gingival cancer in men. In contrast, in women the EFG rate was not significantly higher in sublingual cancer cases than in controls, while in the gingival cancer group it was significantly elevated as compared with the controls and moderately elevated in com-

parison with all female OC cases. EFG was a demonstrable risk factor for sublingual cancer and proved to confer an especially high risk for gingival cancer in women.

History of menopause in the group of female patients and controls

Almost all female OC patients were postmenopausal, whereas among control women in the same age group a quarter of them were premenopausal (*Table 7*). Mean age at menopause was significantly lower among the female OC patients as compared with the female controls. The rate of early menopause (<45 years) was significantly higher among OC patients as compared with controls. Hysterectomy and/or ovariectomy occurred significantly more frequently in the history of female OC cases as compared to controls. The mean time interval between menopause and OC diagnosis (M-OC) among the female OC patients was 16.9 years (range: 3-35 years). The mean M-OC interval in the female OC group with early menopause was significantly lower (13.4 years) and with late menopause was significantly longer (23.5 years) as compared with all female OC patients ($p<0.05$, and $p<0.01$, respectively). Separate evaluation of M-OC intervals related to smoker and non-smoker OC patients resulted in significant differences: 11.9 years for smokers and 19.2 years for non-smokers ($p<0.01$). Postmenopausal hormone replacement therapy was relatively rare both in the OC group (8.4%) and in the control group (10.5%), and showed no significant difference ($p>0.05$). The hormone therapy was relatively short; the mean length was 1.6 years in the OC group, and 1.9 years in the control group ($p>0.05$).

Discussion

Separate analysis of the well-known exogenous and the suspected endogenous OC risk factors in male and female patients yielded striking differences. Apart from the well-known risk imposed by tobacco and alcohol, elevated fasting glucose and postmenopausal sex hormone deficiency in women proved to be strong factors affecting OC incidence.

Controversial associations between female sexual steroids and cancer. Nowadays, a prevailing concept is the positive correlation between female sexual steroid hormones and risk for ovarian, breast and endometrial cancers.[15-17] Hormone replacement therapy (HRT) in postmenopausal women is fairly widespread in the Western countries, and it is regarded as a causal factor of increased prevalence of cancers.[16,18]

However, clinical studies on HRT use in postmenopausal women yielded unexpected and fairly controversial associations with malignancies.[19] Unexplained, beneficial anticancer effects of HRT use were reported against esophageal, gastric, colorectal, cervical and liver cancer[17,20-22] and there are also many contradictions concerning the associations of HRT and hormone-dependent cancers.[19,23]

A protective role of HRT against smoking-associated cancers, such as OC, was justified among smoker postmenopausal women.[24] The authors supposed that HRT postpones smoking-associated cancers by a transitory maintenance of epithelial thickness and integrity in the upper aero-digestive tract.

Correlations of estrogen deficiency and cancer risk. The results of the present study raise a new concept concerning OC initiation. It is a fairly heretical idea that not estrogen but its deficiency may provoke malignant transformation. This new theory may explain many controversial associations of female sexual steroids and malignancies.

Data in the literature support that a physiological estrogen milieu during the reproductive period of healthy women is fairly protective against cardiovascular diseases and total mortality.[25-27] However, an abrupt decrease of estrogen hormone levels either after a natural or an artificial menopause may cause gene regulation disturbances. As cancer initiation requires many years, the longer the postmenopausal estrogen deficiency period the higher the possibility of cancer development.

In the present study, the significantly higher mean age of female OC patients as compared with male OC patients, and the significantly lower ratio of young (<45 years) female OC patients as compared with male ones may allow the assumption that women are protected against OC in their reproductive period. The almost exclusively postmenopausal state of the female OC patients and the long mean interval (17 years) between their menopause and tumor diagnosis also suggest an important role of estrogen deprivation in OC epidemiology. The significantly younger age at menopause and the considerably higher rate of hysterectomy and/or ovariectomy among the female OC patients in comparison with the control women also support the estrogen deficiency hypothesis.

Similarly to our observations, a statistically significant increase of bladder cancer was associated with the postmenopausal state and the early menopause in females.[28] An increased risk for renal cell carcinoma was also reported among women who had been submitted to a hysterectomy with or without oophorectomy.[29] Unfortunately, menopausal history of the cases was not reported in this study. Similar gynecological surgeries were significantly more frequent in our group of female OC cases when compared with the control women. These observations also support a correlation between estrogen deficiency and cancer.

Correlations of estrogen deficiency and insulin resistance. The postmenopausal state is an excellent physiological model to study the hormonal and metabolic effects of

estrogen deprivation in women.[25] On the other hand, estrogen deficiency in males occurs in extremely rare cases.[30] Nevertheless, it is a well-known fact that estrogen deficiency has a close association with insulin resistance both in males and females.[30]

All phases of insulin resistance (hyperinsulinemia, hyperglycemia, metabolic syndrome and type-2 diabetes) are proven risk factors for cancers of the pancreas, liver, colon, urinary bladder, prostate and the oral cavity[8,9,31-35] and even for malignancies of highly estrogen-dependent tissues.[36-38]

Elevated fasting glucose is an easily accessible mirror to reflect the different stages of the glucose metabolism disorder. The results of the present study underline that EFG is a strong risk factor for OC in estrogen-deficient postmenopausal women, especially in gingival cancer cases. In contrast, among male OC patients EFG is not a marked risk factor.

Results of clinical and experimental investigations suggest that pre- or postmenopausal decrease in female sexual steroid hormone levels enhance the prevalence of insulin-resistant states.[39-42] Polycystic ovarium syndrome (PCOS) in young, premenopausal women is a pathologic example of the correlations between estrogen deficiency and insulin resistance.[40] Its cardinal symptoms are anovulation, infertility, hirsutism and obesity, and predict the risk of type-2 diabetes. In PCOS cases hyperinsulinemia overregulates ovarian androgen production at the expense of reduction of estrogen synthesis.[14]

Premenopausal or postmenopausal decrease in the estrogen level, relative excess of androgens, hyperinsulinemia and elevated IGF-I bioavailability exert a crossfire at cellular level and may induce serious gene alterations, even malignant transformation.

Estrogen deficiency, insulin resistance and cancer risk of hormone-sensitive organs. Endometrial and ovarian cancer frequently occurs in young women with long menstrual cycles or unexplained infertility.[38] In young PCOS cases the combination of estrogen deficiency and insulin resistance is also in close association with cancer risk for the highly hormone-sensitive endometrium and ovary.[40,43] However, there are no available literary data concerning the correlations of breast cancer and estrogen deficiency, and at the same time insulin resistance is a well-known risk for breast tumors.[36,40] Clinical data on concomitantly elevated insulin and estrogen levels in breast cancer cases seems to be controversial.[37]

Oral mucosa and especially the gingiva are thoroughly affected by hormonal influences.[10] Type-2 diabetes is associated with increased prevalence of gingivitis and periodontitis in both genders. In postmenopausal women reduced estrogen level results in atrophic, desquamative gingivitis.

In the present study the conspicuous difference of the prevailing OC locations between male and female patients supplied a further key to reveal gender-specific risks. Among the female OC patients the gingiva was the most prominent tumor location (28.3%), however, in the male OC group gingival cancer incidence was significantly lower (13.0%). In the female gingival cancer group, EFG proved to be a slightly stronger risk factor as compared with all female OC patients. Exogenous carcinogenic noxae (alcohol and tobacco) were not demonstrated in almost one third of male and more than half of female gingival cancer cases.

The mean age of female gingival cancer cases was higher in comparison with all female OC cases, suggestive of the higher risk imposed by the long postmenopausal period in this group. On the contrary, the mean age among male gingival cancer cases was similar to that of all male OC cases.

The results of the present study suggest that combined estrogen deficiency and insulin resistance play an etiologic role in gingival cancer epidemiology among predominantly postmenopausal women.

Alcohol-derived metabolic and hormonal changes and oral cancer. Alcohol consumption is a well-known, strong risk factor for OC. However, alcohol consumption is associated with contradictory metabolic effects.[44] Mild to moderate alcohol intake is associated with improved insulin sensitivity, while the two extremes; complete abstinence and excessive drinking impose risk for insulin resistance in both genders.[12] In women who regularly consume alcoholic beverages, especially in postmenopausal cases, estrogen levels are elevated as alcohol mediates an increase of estrogen synthesis in the adipose tissue.[45]

Mild to moderate alcohol intake has a Janus-faced effect on the oral mucosa. The advantageous increase of insulin sensitivity, and the elevated estrogen level in postmenopausal women may oppose the local toxic effects of the carcinogenic metabolites.[13,27]

In the present study, excessive alcohol consumption proved to confer high risk for OC both in males and females. Among male patients moderate alcohol intake was a weaker OC risk factor as compared with heavy drinking. However, among the predominantly postmenopausal women involved in the study, moderate drinking was not an OC risk factor, which may be attributed to both increased insulin sensitivity and elevated estrogen level.

Local and systemic effects of tobacco and OC initiation. Smoking confers a double cancer risk for the oral mucosa by means of its local toxic and systemic metabolic effects.[11] However, Mediterranean dietary habits, such as high fruit, vegetable, fish consumption and red wine decrease the risk for oral cancer even in heavy smokers.[46] This protective dietary effect in smokers was also observed against breast, female genital tract, urinary tract and other epithelial neoplasms due to a systemic antioxidant effect of this advantageous diet.

The predominance of sublingual cancers among male OC patients may be explained by the higher rate of smoking and alcohol consumption as compared with female patients with OC. These well-known carcinogenic noxae are dissolved and concentrated in the saliva of the floor of mouth, which results in a strong local carcinogenic effect.[1]

In the present study smoking was a strong risk factor for oral cancer both among men and women in accordance with the results of earlier studies.[1-6] On the other hand, smoking seemed to be an anticipating factor for OC initiation in the group of both male and female OC patients as the mean age of smokers was significantly lower as compared with the non-smoker cases. Earlier epidemiological studies established that the majority of NSND cases of OC patients are elderly females.[3,4] Based on the results of the present study, the combination of postmenopausal estrogen deficiency and smoking with its local and systemic toxic effects exerts double carcinogenic capacity on the oral mucosa and results in earlier tumor manifestation.

In conclusion, the estrogen deficiency theory and the sexual hormone differences between the two genders may explain the conspicuously lower incidence of OC among females and the significantly older age of women with OC as compared with men. This novel hypothesis of estrogen deficiency and elevated fasting glucose as risk factors for OC may provide new insights into the etiology of oral malignancies and lead to new strategies for cancer prevention.

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