

# Laryngeal carcinoma and laryngo-pharyngeal reflux disease

## *Il cancro laringeo e la malattia da reflusso gastro-laringofaringeo*

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### Key words

Acid and biliary reflux • Gastro-resection • Laryngeal carcinoma

### Parole chiave

Reflusso acido e biliare • Gastrosesezione • Carcinoma laringeo

### Summary

A correlation between laryngo-pharyngeal reflux and laryngeal carcinoma is currently debated. Chronic inflammation is a mutagen factor confirmed in the cancerogenesis of various tumours. Aim of the present study was to evaluate, in an objective and consecutive way, with 24h multi-electrode pH-metry the presence of proximal and distal oesophageal reflux in patients presenting pre-cancerosis or squamous cell laryngeal and/or pharyngeal carcinomas. From our data, a strict correlation emerged between laryngo-pharyngeal reflux and neoplasias of the upper airways, documented through multi-electrode pH-metry. Data emerging from this study would seem to support the theory that the protracted exposure (> 20 years) to biliary reflux would represent a statistically significant added risk factor in the precancerous lesions and squamous pharyngo-laryngeal carcinoma as it occurs at oesophageal level. Moreover, a significant statistical association ( $p < 0.0001$ ) emerged between laryngeal carcinoma and previous gastro-resection (odds ratio 3.8).

### Riassunto

*A tutt'oggi è dibattuta la correlazione tra reflusso faringolaringeo e carcinoma laringeo. Sicuramente la flogosi cronica è un noto fattore di cancerogenesi. Scopo del presente lavoro è stato quello di valutare attraverso la pH-metria multielettrodo la presenza di reflusso prossimale e distale in un gruppo di pazienti affetti da lesioni precancerose o da cancro laringeo. I nostri dati confermano questa correlazione, come pure la teoria che il reflusso biliare protratto possa essere un fattore aggiuntivo di rischio. Inoltre sembra emergere anche una correlazione statisticamente significativa tra insorgenza di carcinoma laringeo e una precedente gastrosesezione.*

## Introduction

Although widely studied in the literature, particularly throughout the last 10 years, the possible correlation between laryngo-pharyngeal reflux (LPR) and laryngeal carcinoma is currently debated.

In fact, although the high presence of LPR in patients affected by laryngeal carcinoma (between 68%<sup>1</sup> and 87%<sup>2</sup> in the world literature), the complex multi-factoriality of neoplastic transformation does not yet permit to establish a causal relationship between cancer and reflux<sup>3</sup>.

Among the possible cancerogenesis mechanisms, the most important are chronic inflammation, free radical action and the synergism with the well-known exogenous risk factors. Chronic inflammation, in particular, with the regular alternation of tissue damage and repair phases represents a mutagen factor in the cancerogenesis of many tumours. The chronic exposure of the laryngeal mucosa to reflux, that generally occurs during spontaneous reductions of continence

of the superior oesophageal sphincter, in post-prandial eructations, during decreases in sphincter pressure associated with deglutition, especially in the night in supine position<sup>4</sup>, could be at the root of the chronic inflammation mechanism.

However the damage induced by the gastric secretions would, be mediated by the its main components, HCl and pepsin, that act in a combined way (chlorhydro-peptic complex)<sup>5</sup>.

The damaging action of the chlorhydric-peptic complex occurs at the level of the junctional intercellular structures of the epithelium, with an increase in permeability and consequently an increase in the intercellular acidity, active ion and water recall inside the cell through the Na-K<sub>2</sub>-Cl co-transportation, alteration of the osmotic balance and, consequently, cellular death. Besides this classical mechanism that expects the alternation of the damage, cellular death and tissue repairing there is also the most modern one that considers the free radicals, products from the neutrophil leucocytes recalled in situ from the in-

flammation mediators as the main cause of cellular damage and necrosis<sup>6</sup>.

Finally, the direct action of the reflux on the laryngeal mucosa at the same time with other inflammatory factors (voice abuse, chronic cough, vomit, relapsing infections of the upper airways) would have a predisposing effect upon the mutagen action of the well-known cancerogenic exogenous factors (cigarette smoke and alcohol).

Moreover, over the last few years, besides the chlorhydric-peptic complex, considered the main damaging agent for oesophageal and laryngo-pharyngeal mucosa, also the involvement of the duodenal secretion components, has emerged in the damaging action of the reflux. In particular, the mixed duodenal-gastric reflux would present elements of both secretions; different investigations have shown how their combined damaging action could develop in particular conditions, related above all to the pH values of the environment<sup>7,8</sup>.

In particular, among all components of the biliary reflux able to damage the laryngeal mucosa, it is to mention: the trypsin, which, when it is not activated by pepsin, remains active for about one hour at various levels of pH favouring, with its proteolytic properties, the detachment of the surface cells from the epithelium, through the digestion of the intercellular connection necessary to intercellular<sup>9</sup> cohesion; the bile acids, that damage the mucosa solubilizing the membrane lipids on account of their detergent properties, and penetrating through it thanks to their lipophilic condition, causing disorganization of the membrane structure and alteration of the cell functions<sup>10,11</sup>.

Some Authors<sup>12</sup> have also suggested that, in the alkaline reflux, cancerogenic substances could form as a consequence of bacterial colonization of the stomach caused by the presence of the gastric-duodenal reflux or by decreased acid secretion. Some Authors have demonstrated a correlation between the entity of the reflux and the increasing bacterial growth<sup>13</sup>. In fact, bacteria would determine, first of all, the transformation of the saliva or diet nitrates in nitrites, that subsequently, would be conjugated with the amines or the amids, generating nitrose composed compounds as nitrosamine or nitrosamides, which are powerful cancerogenic substances on account of their DNA alkylating action<sup>14</sup>. The amines necessary for this process could come from swallowed food or from the same alkaline reflux, because the intra-gastric bile acids represent an excellent source of amid. Moreover, from the conjugation of the nitrites with the conjuncted bile acids, taurocholic and glycocholic, that are the bile acids the most represented in the alkaline reflux, N-nitrosotaurocholic and the N-nitrosoglycocholic acids could be formed, that have already shown in a cancerogenic and mutagenic action<sup>15</sup>.

The previous model well explains cancerogenesis in patients submitted to gastro-resection, but it is not valid in patients with primary reflux, in which the acid pH inhibits bacterial growth. In these cases the most probable models of cancerogenesis include: the chronic inflammation mechanism, with the consequent increase in oxidative stress and production of free oxygen radicals (involved in the tumouri genesis); the hyper-expression of the well-known tumoural markers such as EGFR<sup>16-18</sup> and Cox-2<sup>19</sup>.

## Personal experience

In our clinic, we conducted a study to evaluate with the use of 24h multi-electrode/pH-metry, the presence of oesophageal proximal and distal reflux in patients presenting pre-cancerous, or squamous cell laryngeal and/or pharyngeal carcinomas<sup>20</sup>. The study included 24 patients, 20 (18 men, 2 women) with laryngeal or laryngo-pharyngeal carcinoma (localisation was glottic n = 11, supra-glottic n = 4, hypo-pharyngo-laryngeal n = 4, glottic hypoglottic n = 1) and 4 patients affected by laryngeal leucoplakia. In this study population, 63.7% of patients didn't complain about typical symptoms of gastro-oesophageal reflux (GER); 21 out of 24 were smokers and 2 out of 4 patients affected by hypo-pharyngo-laryngeal carcinoma were heavy drinkers. In 20/24 patients studied (83.3%), the presence of a pathological proximal reflux was observed; in 4 patients (16.6%), with the anamnesis of a previous gastrectomy (Billroth II) or gastro-jejuno-anastomosis, an alkaline reflux was documented with total reflux time of 39.3%.

From our data, a strong correlation emerged between laryngo-pharyngeal reflux (LPR) and neoplasias of the upper airways, documented by multi-electrode pH-metry, also if it was not possible to establish a direct cause-effect relationship, because of the frequent concomitant presence of classical risk factors, such as cigarette smoking and alcohol.

Concerning the possible role of the alkaline/bile reflux as a highly irritable factor on the mucosa of the upper airways, we studied the possible damaging effect of other reflux components, such as bile acids and pancreatic enzymes in addition to the chlorhydric-peptic complex.

Therefore we evaluated, the incidence of pre-cancerous lesions and/or the laryngeal carcinomas in patients who underwent gastrectomy, so epidemiologically exposed to duodeno-gastro-oesophageal reflux or bile reflux<sup>10,11</sup>. We submitted to anamnestic and ENT clinical evaluation 93 patients gastrectomized more than 5 years ago (group I) and 93 age- and sex-matched patients who underwent digestive endoscopy in the Gastroenterology Unit (controls). In group I, a concomitant or previous malignant lesion

was documented in 7 patients (8%): 3 patients were submitted to cordectomy for a squamous cell carcinoma, 4 patients simultaneously presented a precancerous lesion (n = 3 moderate dysplasia, n = 1 severe dysplasia). Only one patient in the control group showed a cordal leukoplakia at laryngeal inspection. Data emerging from this study support the hypothesis that the prolonged exposure (> 20 years) to bile reflux would represent a statistically significant added risk factor for pharyngo-laryngeal precancerous lesions or squamous cell carcinoma as occurs at oesophageal level.

We also verified this hypothesis evaluating retrospectively the percentage of gastrectomized patients within a population of 828 patients affected by pharyngo-laryngeal carcinoma and admitted into our clinic in the period from 1987 to 2002<sup>8</sup>; these percentage was compared with a control group of 825 patients, matched for gender and age, admitted for myocardial infarction in the Cardiology Institute of our University in the same period, and, for this reason, exposed to the same risk factors (particularly cigarette smoking).

A previous gastro-resection was documented in 67 patients (8.1%) with pharyngo-laryngeal carcinoma and in 15 patients (1.8%) of the control group. In all cases, gastro-resection was performed for peptic ulcer and/or its complications.

The mean time between gastro-resection and diagnosis of the pharyngo-laryngeal carcinoma was 22.3 years. The multi-variate analysis, revealed a statistically significant association ( $p < 0.0001$ ) between laryngeal carcinoma and the previous gastro-resection (OR 3.8).

At present, in our clinica prospective study is underway from October 2004 on patients with ENT symptoms and signs indicative of LPR. All patients were submitted to ENT and gastroenterological investigation with endoscopy at high magnification, and other functional evaluations. Of the patients studied until the present day (n =61), 22 presented pre-cancerous lesions (leukoplakia of the vocal cord) and 5 laryngeal squamous cell carcinoma; 18/27 presented at gastro-enterological evaluation, endoscopic signs of

reflux-oesophagitis and/or hiatal hernia and/or bile reflux. Therefore, our data underline the importance of oesophago-gastro-duodenoscopy also in patients presenting symptoms and clinical signs exclusively localized at the level of the upper aero-digestive tract, since, in a considerable percentage of cases, the simultaneous presence of asymptomatic gastro-oesophageal disease was revealed.

## Conclusions

LPR appears to represent the main endogen co-factor involved in the pathogenesis of both chronic inflammatory and neoplastic laryngo-pharyngeal disorders. The development of new diagnostic techniques, the broader knowledge of the local micro-environment and individual susceptibility, as well as the randomized prospective studies, will contribute to clarify the present controversies, because the complex interactions between the airways and the upper gastrointestinal tract still need further clarification, despite the rich scientific production present in the literature. Another reference in our study is reserved to the so called paradox of the posterior commissure: in fact, the posterior part of the larynx, is near to the superior digestive tract but rarely involved as primary site of laryngeal carcinoma<sup>21</sup>.

On this subject, Johnston et al.<sup>22</sup> studied the reflux impact on the laryngeal epithelium and the existence of ultra-structural mechanisms of protection, at this level: one of these was represented by the metal enzymes of the carbonic anhydrase, that allow the cell to secrete bicarbonate into the extracellular fluid thus contributing to neutralisation of the intra-cellular protons. Other studies<sup>23</sup> showed that the posterior part of the larynx would express the higher level of carbon anhydrase than the supraglottic or anterior glottic regions, which are the most frequent sites of laryngeal carcinoma. These data confirm the necessity of studies on the local micro-environment to clarify those still shadow zones on the mechanisms and modalities of the mucosal damage due to LPR.

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