



## Full Length Research Article

### THE ROLE OF CHEMICAL COMPOUNDS USED IN NATURAL RUBBER PRODUCTION PROCESS ON THE ETIOLOGY OF NASOPHARYNGEAL CANCER

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#### ABSTRACT

**Introduction and Objectives:** Nasopharyngeal Carcinoma (NPC) has been shown to be highly associated with Epstein-Barr virus (EBV) infection. Its incidence is higher in Chinese populations living in southern China, Malaysia, and Indonesia due to particular ethnic genetic polymorphisms. Anyway, the cancerogenesis activation happens only after the exposure to some environmental factors. Large scale epidemiological studies proposed associations between various dietary habits and an increase in risk for nasopharyngeal cancer, mainly for salted fish consumption. Our work is to highlight, with the support of the literature data and direct observations, such as the exposure to compounds, particularly the formaldehyde, present in the different working conditions of the countries with the highest incidence, may be the real cause environmental able to establish the carcinogenic process.

**Materials and Methods:** The most recent publications regarding the impact of various external factors on Pub Med, Cochran Library, Google, TOXLINE, Chem., Abstract, were analyzed and Videos of YouTube

**Results:** The relationship between food consumption and nasopharyngeal cancer are not clear and statistically insignificant. The incidence data (ASR), Globocan published in 2012, indicate in Indonesia, Malaysia and the countries at greatest risk where the most dangerous environmental factor the carcinogenicity of the nasopharynx is the preparation of natural rubber, where the workers are exposed to various chemical compounds including formaldehyde, known carcinogen. Interesting fact about then the incidence of cancer in Chinese ethnic groups is resulting in decrease in the same populations when migrate from these Chinese districts, to other countries.

**Discussion:** The production of natural rubber is the most important industrial activity for Malaysia and Indonesia. Various steps of the preparation and production of the same, exhibiting a lot of people to, acids and formaldehyde. The coagulation phase, that of the stripping, the drying of the rubber sheet, takes place without eminently of environmental hygiene precautions. The Chinese districts where there is higher incidence of nasopharyngeal cancer, are those where is concentrated most of the world production of components for the electronics, welding, and other machining operations with a strong environmental impact, but it can be observed from the data of literature that in migrant populations and not more exposed to pollutants, the appearance of these tumors decreases.

**Conclusions:** The EBV is certainly a significant risk factor, but its activation in carcinogenesis process is likely to be associated with exposure to compounds such as formaldehyde, present in industrial workings of countries such as Indonesia and Malaysia, while in south China to many other characteristic pollutants of industrial activity cycles of this region and typical for the onset of cancer nasopharynx.

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#### INTRODUCTION

Nasopharyngeal carcinoma (NPC) arises from nasopharyngeal epithelium and is primarily localized in the Rosenmüller fossa (Chua *et al.*, 2016), where the cancer typically invades adjacent anatomical spaces and it is a rare disease, with a particular geographical distribution.

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Worldwide, 86.500 cases of nasopharyngeal carcinoma were reported in 2012, (GLOBOCAN, 2012), equal to 0.6% of all cancers diagnosed in that year. Most of them (70-80%) are reported in Malaysia, Indonesia, and some districts of southern China, such as Guangdong. The incidence, expressed as age standardized incidence rate (ASR) (GLOBOCAN, 2012), is 8.7 new cases for 100,000 inhabitants, for Indonesia, 9.2 for Malaysia, with values of 14.0 in southern China (Cao, 2011 and Zhang, 1997). In the regions where disease is endemic,

the undifferentiated subtype “non-keratinizing carcinoma” has an incidence higher than 95% (Cao *et al.*, 2011) and a strong association with the Epstein-Barr virus (EBV) is reported. EBV infection is perhaps the most widely studied etiological factor NPC. In situ hybridization for EBV-encoded ribonucleic acid (RNA), showed that the virus is detected in all cancer cells but not in normal nasopharyngeal epithelium, suggesting role for activating exogenous factors promoting cancer pathogenesis. Large-scale epidemiological studies proposed an association between different dietary and social practices and NPC risk. In particular, salted fish consumption reported as a common habit in NPC patients, specifically ingesting, N-nitrosamines, generated in fish conservation, (Zhang, 1987), thought to confer long-term increased risk for NPC. Some authors indicate that in these conditions the risk increases bent king times. Other risk factors are consumption of foods preserves, tea, alcohol, and smoking (Guo, 2009; Cheng Wang *et al.*, 2016; Xu,). However, also working conditions should be taken into consideration, especially subjects employed in the extraction or production of natural rubber. This is typical Malaysia and Indonesia (main world producers’ natural rubber), having extensive plantations of Hevea and using toxic chemical compounds and /or carcinogens such as formaldehyde clearly demonstrated to induce NPC formation. Conversely, removing equally dangerous work conditions as happened in southern China could reduce NPC incidence.

## MATERIAL AND METHODS

### Search strategy

We searched on Pub Med (MEDLINE) for articles published in English from Jan 1, 2000 to Dec 31, 2014. The following keywords were used: "nasopharyngeal carcinoma", "epidemiology", "traditional food habits", "environmental pollution", "industrial hygiene", "rubber production", and “migrants”. We also searched on the Cochrane library, Google, Pub Med Compound, Toxiline, and You Tube. The key words are used in the research in free text, and with cross-referencing method application

## RESULTS

Large-scale epidemiological studies proposed an associations between dietary or social practices and an increased NPC risk. Notably a history salted fish consumption has been reported to be common in NPC patients. Specifically, N-nitrosamines are believed to be the associated carcinogen, and long-term exposure to them was associated with a two-three folds increase in the risk of developing the disease. Other reported risk factors are consumption of preserved foods, herbal teas, slow-cooked soups, and alcohol, and smoking habits (Guo, 2009; Cheng Wang, 2016 and Xu). However, such associations were variable across studies, and even when reported, were weaker than that salted fish consumption and dissemination of this limited habit, especially in Indonesia and Malaysia. Epidemiology studies confirmed that the highest NPC incidences independent from ethnicity in both Malaysia and Indonesia. In these countries direct working personal experience and You Tube movies (8),(9) showed that during the production of natural rubber, workers are exposed to many toxic compounds, such as ammonia and formaldehyde, a well-

known carcinogen. Guangdong province, in particular the chief town part of the production area of the Pearl River Delta (PRD), is one of the most productive areas of Hong Kong. It has the highest industrial concentration and income level all over China. Some cities, or districts, are currently characterized by a high concentration of polluting productions such as furniture, clothing, leather goods, home and public lighting, small metal parts, household appliances, cosmetics, automotive, electronics and integrated circuits, computer industry products, eyewear, processing machines wooden, shoes (using toxic chemicals), leather, flooring and wall tiles, electrical and mechanical machinery, plastic products for the automotive industry and textiles. If workplace safety regulations are inadequate, exposure to pollutants is obvious, and relevant for those working processes associated with a high risk for NPC. Some examples are the regulations recently adopted in force in Italy for the same industrial process.

## DISCUSSION

Regarding the exposure to various chemical compounds during the natural rubber production, we have to examine the entire working cycle from latex extraction up, until packaging and storage. ([www.britannica.com/.../rubber-chemical-compound](http://www.britannica.com/.../rubber-chemical-compound)). Latex extraction is obtained by etching a thin and narrow cortex layer (excision) with a special knife along a path for the most part in a herringbone pattern, i.e. with a longitudinal centre line and various other lines converging from both sides. The latex runny by different cuts collect at the base of the vertical portion into a suitable container fixed to the frame. Freshly harvested, the latex is added with formic acid, acetic acid or ammonia or sodium sulphite to prevent it from clotting, and finally sent to the processing plant.

The final product to the market is the concentrated latex, and the dried gum. The concentrate, 60% rubber, is obtained by simple centrifugation and further addition of ammonia, boric acid and zinc diethyldithiocarbamate for preservation purposes. The 15% is derived from the dried rubber latex dilution and acidification with formic acid or acetic acid resulting in coagulation and precipitation to the bottom; a subsequent passage through a grille rotating cylinders (at equal or different speeds) imparts the form of plain or creped sheets (sheets and crepe) respectively. The product is rotating cylinders then sent to drying in stoves in the presence of wood smoke (ribbed smoked-sheet) or air (air-dried-sheet). It is evident that the aim of this study is to focus on the processes carried out in the various steps of the production of natural rubber (Jitladda, 2012).

In the various steps of this process, exposure to various chemical compounds is variable depending on everything from personal protective means and equipment that should remove the polluted air outside and enter it or absorb it in special direct filters. From a direct experience and as you can see by the various movies present for example also on You Tube, the possibility of exposure is high, and the reduction of it is almost never performed, and in particular, no precautions are applied for protecting workers from exposure to formaldehyde. Of note, data on formaldehyde as a high risk factor for NPC are publicly available since many years (<http://www.cancer.gov/about-cancer/causes-prevention/risk/substances/>

formaldehyde/formaldehyde-fact-sheet2009, IARC Monograph 2014 and [www.cancer.org/cancer/cancer-causes/other-carcinogens/in-the-workplace/formaldehyde](http://www.cancer.org/cancer/cancer-causes/other-carcinogens/in-the-workplace/formaldehyde)). The NPC incidence seems to decline in these last years probably due to replacement of the above-mentioned dangerous substances listed or due the adoption of new regulations and protection devices at workplaces. Moreover, the only way to avoid that EBV latency is not repeated exposure to carcinogens. A special must be dedicated to cancer incidence in the same populations after migration. Not surprisingly, it decreases sharply (Yu and Hussain, 2009) clearly confirming the influence of environmental factors. Other two studies showed the same type of risk, even though the populations under observation had a different ethnicity (Parkin, 1997; Jeannel *et al.*, 1993).

## Conclusions

In those regions where NPC is endemic, the non-keratinizing undifferentiated subtype had the highest incidence, closely associated with the EBV infection. However, other exogenous factors are necessary to activate the transformation of the infected cells into cancerous including compounds in foods, conservation, cigarette smoking. Formaldehyde involved in the production of natural rubber, especially in poor environmental hygiene conditions, should not be neglected, considering that, Malaysia and Indonesia have the world monopoly of natural rubber production. These countries have the highest ASR index for NPC. Similar considerations, can be applied apply to the districts of southern China, where the high number of industrial activities implies a large emission of dangerous pollutants. Notably, to further support this evidence, migration of these workers to other countries strongly reduces the NPC incidence.

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