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Crosstalk Between Human Papillomavirus and Cigarette Smoke Components for Cancer Development. Does it exist?

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In 1911, Peyton Rous discovered that some cell-free extracts from chicken sarcomas induce tumors when inoculated in other chickens, thus leading to the discovery of the Rous Sarcoma Virus (RSV). Since then, there have been four Nobel Prizes awarded to researchers whose investigations led to the discovery or characterization of the relationship between viruses and cancer. Only in 1966, 54 years after the aforementioned discovery, was the Nobel Prize awarded to Rous. In 1975 Dulbecco, Temin and Baltimore received the prize for the discovery of reverse transcriptase and other viruses related to cancer. In 1980, Bishop and Varmus received the prize for the discovery of cellular oncogenes, a very important finding for viral oncology. The most recent award went to Harald Zur Hausen in 2008, for the discovery that human papillomavirus is the causal agent of cervix-uterine cancer. Today it is accepted that about 15% of human malignancies are caused by viruses. However, it seems clear that other factors such as those related to the immune state, inflammation, genetic and environmental factors are involved in the development of virus-associated tumors. Thus viral infections are a necessary but not sufficient condition for the development of human malignancies.

Human papillomavirus (HPV) is a sexually transmitted virus with double-stranded DNA as genetic material, that is the recognized etiological agent of cervix-uterine and anogenital cancers. In addition, it is accepted that HPV is etiologically associated with a subset of oropharyngeal cancers. Even though a high percentage of people around the world will be infected with HPV during their lifetime, the infection is cleared in the vast majority of cases and only in a very small percentage of infected subjects is the virus able to persist in the tissue leading to cancer development. Thus, factors that allow HPV persistence are relevant in cervix-uterine carcinogenesis. Epidemiological studies have revealed that female smokers infected with HPV are more susceptible to cervix-uterine carcinogenesis compared to non-smokers. As a consequence, tobacco smoke is a very important cofactor in HPV-mediated carcinogenesis. Tobacco smoke is a complex mixture of carcinogenic and non-carcinogenic substances. More than 4,000 compounds have been identified; with more than 60 of them demonstrating carcinogenicity that are involved in the initiation, promotion or progression of tumors. One of the best known and important carcinogenic compounds present in tobacco smoke is benzo-α-pyrene, a polycyclic aromatic hydrocarbon. Functional studies demonstrated that this compound at some concentrations is able to increase the quantity of HPV virions or HPV genome copies in cervical keratinocyte raft-models. Therefore, tobacco smoke is a cofactor for HPV-mediated carcinogenesis; but is it possible that HPV could be a cofactor for tobacco-smoke mediated carcinogenesis?

Lung cancer and head and neck cancers are models of tobacco smoke-mediated carcinogenesis. It is known that cigarette smoking or tobacco smoke exposition is directly and strongly related to the development of a high percentage of these malignancies . However, only a very low percentage of smokers finally develop these cancers. Obviously other factors that are able to work cooperatively with smoking are involved in tobacco smoke-associated carcinogenesis. For instance, genetic susceptibility may be a very important factor related to the ability of some subjects to develop these kinds of tumors. In addition, a plethora of studies have reported the variable presence of high-risk HPV in lung cancer around the world. The same virus that is the causal agent of cervix-uterine cancer has been detected in lung carcinomas at variable frequencies in different geographical regions (0 to 70%). Up to now, the role of HPV in this cancer is frankly unknown. We need to remember that lung cancer is the first cause of death from cancer around the world. In addition, oral and oropharyngeal malignancies represent approximately 3% of all malignant tumors in males and 2% in females in the United States. It has been determined that approximately 25% of these tumors are HPV positive. For HPV in lung and oropharyngeal carcinomas it appears that this virus is prevalent in non-smoking subjects who develop lung or head and neck tumors. As a consequence, it has been suggested that HPV is a potential carcinogen in this population. However, it is now clear that there is crosstalk between HPV and tobacco smoke, at least for cervix-uterine carcinogenesis. The exact mechanisms for this crosstalk are unknown. In addition, in anatomical regions that are susceptible to direct tobacco smoke exposition or HPV infections such as those that occur in upper aerodigestive organs, a functional interaction for cancer development is plausible. These concerns warrant further investigation in the future.

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