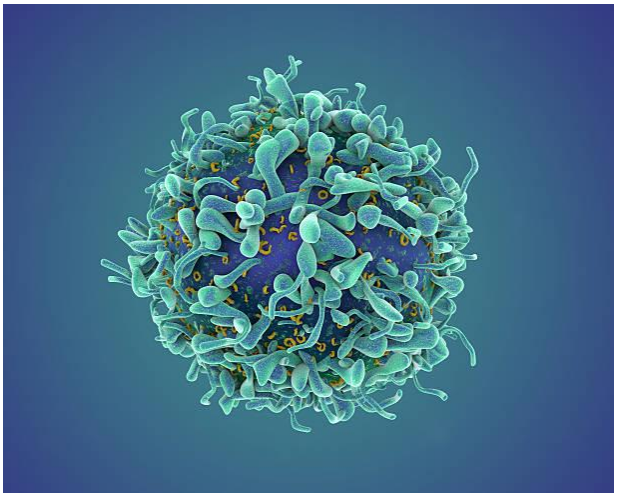
ONCORAL™



How to evaluate risk of oral cancer – ONCORAL testing procedure

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Oral cancer disease is the consequence of prolonged presence of specific carcinogenic molecules from alcohol/tobacco or cell integration of Human Papilloma Virus (HPV) into oral cavity.

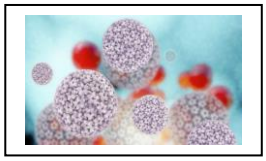
The prevalence of oral cancer is particularly high among men, the eighth most common cancer worldwide. Incidence rates for oral cancer in men vary from 1 to 10 cases per 100 000 population in many countries. In South-Central Asia, cancer of the oral cavity ranks among the three most common types of cancer. In India, the age standardized incidence rate of oral cancer is 12.6 per 100 000 population. What is noteworthy is the sharp increases in incidence rates of oral/pharyngeal cancers being reported for several countries and regions such as Denmark, France, Germany, Scotland, Central and Eastern Europe and to a lesser extent Australia, Japan, New Zealand and the USA (3, 4). The cancer epidemic in developed countries, and increasingly in developing countries, is due to the combined effect of the ageing populations and high or increasing levels of prevalence of cancer risk factors. The evidence that smokeless tobacco causes oral cancer was confirmed recently by the International Agency for Research on Cancer (6). At the same time as cigarette smoking declined in developed countries, the number of oral cancer augmented, Human Papilloma Virus (HPV 16 & 18) is identified as a new cause.

- ✓ **If detected at an early stage, survival from oral cancer is better than 90% at 5 years, whereas late stage disease survival is only 30%. Therefore, there is an obvious clinical utility for innovative metabolic markers that help to diagnose oral cancer at early stages and to monitor treatment response.**
- ✓ **Depending on the countries, about 50 to 70% of patients are diagnosed at an advanced stage.**
- ✓ **In the past 20 years, an increase of oral infected HPV patients has been observed.**
- ✓ **7% of the US adults are infected.**
- ✓ **HPV prevalence was identified in around 16% of tumor specimens collected between 1984 and 1989 versus approximately 72% of tumor specimens collected between 2000 and 2004, a trend affecting younger populations.**
- ✓ **It has now been established that the path to oral cancer contains at least two distinct etiologies; one through tobacco and alcohol and another via the HPV virus infection, particularly version 16.**
- ✓ **In general, it appears that HPV positive tumors occur most frequently in a younger group of individuals than tobacco related malignancies (Tobacco oral cancers occur most frequently in the 5th through the 7th decade of life). HPV positive tumors also occur more in white males and in non-smokers.**
- ✓ **Classifying the HPV status of the cancer can offer eligible patients less intensive treatment with reduced side-effects. "Get the most appropriate treatment for their cancer".**
- ✓ **HPV-positive oropharyngeal cancers have better outcomes and fewer relapses after treatment than HPV-negative cancers.**

A great number of cases could be diagnosed early with the use of biological risk assessment measures to guide clinical decision making.

Assessment tools definition:

- Patient history (age, tobacco, alcohol, bad oral hygiene, sexual life, HPV status)
- Clinical examination (oral and nasal)
- HPV and volatonomic analysis of saliva
- Biopsy of identified oral lesion



HPV

Human Papilloma Virus (also called HPV) is the most common sexually transmitted infection (STI) in developed countries. Most types of HPV are not harmful to people. There are more than 40 types of HPV that can infect the genital areas as well as the mouth and throat. Most people who become infected with HPV are unaware that they are infected. HPV-induced cancers arise when viral sequences are accidentally integrated into the DNA of host cells. Some of the "early genes" carried by the HPV virus, such as genes E6 and E7, act as oncogenes that promote tumor growth and malignant transformation. Furthermore, HPV can induce a tumorigenic process through integration into a host genome which is associated with alterations in DNA copy number.

What is oral HPV?

The same types of HPV that infect the genital areas can infect the mouth and throat. HPV found in the mouth and throat is called “oral HPV.” Some types of oral HPV (known as “high risk types”) can cause cancers of the head and neck area. Other types of oral HPV (known as “low risk types”) can cause warts in the mouth or throat. In most cases, HPV infections of all types go away before they cause any health problems.

What head and neck cancers can be caused by HPV?

HPV can cause cancers in the back of the throat, most commonly in the base of the tongue and tonsils, in an area known as the “oropharynx.” These cancers are called “oropharyngeal cancers.”

What are the signs and symptoms of oropharyngeal cancer?

Signs and symptoms may include persistent sore throat, earaches, hoarseness, enlarged lymph nodes, pain when swallowing and unexplained weight loss. Some persons have no signs or symptoms.

How common is oral HPV?

Studies in the U.S. have found that about 7% of people have oral HPV but only 1% of people have the type of oral HPV that is found in oropharyngeal cancers (HPV type 16). Oral HPV is about three times more common in men than in women.

How common are cancers of the oropharynx?

Each year, in the U.S., about 9,000 people are diagnosed with cancers of the oropharynx that may be caused by HPV. Cancers of the oropharynx are about four times more common in men than women.

How do people get oral HPV?

Only a few studies have looked at how people get oral HPV, and some of these studies show conflicting results. Some studies suggest that oral HPV may be passed on during oral sex (from mouth-to-genital or mouth-to-anus contact) or open-mouthed (“French”) kissing, while others have not. The likelihood of getting HPV from kissing or having oral sex with someone who has HPV is not known. We do know that partners who have been together a long time tend to share genital HPV—meaning they both may have it. More research is needed to understand exactly how people contract or pass on oral HPV infections.

Can the HPV vaccine prevent oral HPV and oropharyngeal cancers?

The HPV vaccine that is now on the market was developed to prevent cervical and other less common genital cancers. It is possible that the HPV vaccine might also prevent oropharyngeal cancers, since the vaccine prevents an initial infection with HPV types that can cause oropharyngeal cancers but studies have not yet been undertaken to determine if the HPV vaccine will prevent oropharyngeal cancers.

What is Volatolom analysis

Volatile organic compounds (VOCs) are organic chemicals that have a high vapor pressure at ordinary room temperature. VOCs are numerous, varied, and ubiquitous. They include both man-made and naturally occurring chemical compounds. Most scents or odors are of VOCs. Analysis of specific VOCs profiling from specific sample (saliva, liquid biopsies, breath) is call Volatolomics. VOCs are detected by Mass Spectrometry analysis.

Oral cancer and Volatonomics

VOC pattern analysis in exhaled breath in patients with head and neck squamous cell carcinoma (HNSCC) have been reported in 2014. Logistic regression showed a significant difference ($P < 0.05$) in VOC resistance patterns between patients diagnosed with HNSCC and the control group, with a sensitivity of 90% and a corresponding specificity of 80%. The target volatile molecules are derived from human cellular metabolism

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Institut clinident developed a new strategy for oral cancer risk measurement using stabilized saliva for HPV identification and saliva volatolomics analysis. The method and the volatolomics profile of saliva in relation with oral cancer has been patented by the laboratory.

Oral cancer symptoms and signs?

- ✓ Persistent mouth sore: A sore in the mouth that does not heal is the most common symptom of oral cancer
- ✓ Pain: Persistent mouth pain is another common oral cancer sign
- ✓ A lump or thickening in the cheek
- ✓ A white or red patch on the gums, tongue, tonsil, or lining of the mouth
- ✓ A sore throat or feeling that something is caught in the throat that does not go away
- ✓ Difficult swallowing
- ✓ Difficulty to move the jaw or tongue
- ✓ Numbness of the tongue or elsewhere in the mouth
- ✓ Jaw swelling that makes dentures hurt or fit poorly
- ✓ Loosening of teeth
- ✓ Pain in teeth or jaw
- ✓ Voice changes
- ✓ A lump in the neck
- ✓ Weight loss
- ✓ Persistent bad breath

Technical recommendations and Oncoral™ objectives:

It is advised to carry out an analysis in the following situations:

- Patient with any symptoms or signs
- Patient who smoke (more than 45 years old)
- Patient who drink (more than 45 years old)
- Patient with poor oral hygiene
- Patient with genital HPV or other HPV infection
- 6 months after the first positive oral saliva test
- Annually for all patients at risk

References: Specific requests of scientific publications could be provided to dentists via email. Please contact info@institut-clinident.com or visit the institute clinident webpages (www.institut-clinident.com) and request publications.

Oncoral Instructions for use & kit contents: collected stabilized saliva should be sent by express mail no later than 24H after collection.

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Instructions for Use

Kit Contents:
1 extraction solution tube (Blue Cap), 1 Beaker (Orange Lid), 2 sample tubes (Orange caps)

Hardware requirement not provided:
Clock or Stop watch to measure time

Storage and shelf life:
Storage: safe from the light, at a temperature ranging between 4°C and 25°C.
Shelf life: See the labels on tubes.
The extraction solution must be used immediately after opening. Once opened, the tube cannot be used later.

General recommendations concerning the saliva sampling:
No food or drink at least 30 minutes prior to saliva collection.

Procedure:

Open the **extraction solution tube** and **Rinse** the oral cavity with its contents **during 2 minutes**.

Open the **Beaker** and **spit in** all the contents of mouth.
Close the beaker.

Withdraw the round safety sticker on the beaker. **Place the beaker on a plane surface.** Take the **Sample tube** (**DO NOT OPEN IT**) and **firmly insert** it in the opening with the cap to the bottom. The sample tube fills automatically. **Bring out** the sample tube as soon as it is filled. Repeat the same operation with the second sample tube. If liquid remains in the beaker, the sample and the beaker must be eliminated. **Homogenize** the content of the sample tubes by inverting and preserve at **room temperature** until forwarding. After use, the cover in the lid of the **beaker** must be closed again using the round adhesive of safety.

Collected stabilized saliva should be sent no more than 24 hours after collection via express mail for reception at laboratory within 5 days.

Warning statements and precautions:
A not blocked nasal breathing represents the prerequisite for saliva sampling with the system.
Extraction solution tube : The Saliva Extraction Solution contains the food dye FD&C yellow n° 5 (tartrazine). If any saliva extraction solution is swallowed, there is no health risk, and a doctor need not be informed. Occasionally an allergic reaction to FD&C yellow n° 5 (tartrazine) may occur. Persons who do not tolerate aspirin and/or benzoic acid could be affected by this. Application is not recommended, if such cases of intolerance are known.
Beaker : The round safety sticker should only be removed when saliva is being transferred into tube 3. After transfer, the sticker should be replaced. Fingers should not be placed into the opening because there is risk of needlestick!
Sample tubes : The tube contain sodium azide, which is poisonous*. In case of accidental swallowing, doctor's advice should be sought immediately, with reference to the instructions.
* Special precautions for people and environment: R 28 is very poisonous if swallowed. R 32 produces poisonous vapours on contact. R 50/53 is very poisonous for water organisms and can cause long-term damage in waters.

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