здана коллекция из 10000 образцов, определение вирусного генотипа проводилось методом $SPF_{10}$-PCR/$LiPA_{25}$ технологии.

Были выявлены доминантные HPV генотипы, ассоциированные с плоскоклеточным раком шейки матки: HPV 16, 18, 45, 33 and 31 и с аденокарциномой шейки матки: HPV 16, 18 и 45 типа.

Комбинированная атрибутивная фракция генотипов HPV 16, 18, 45, 31 и 33 составила 83,2 % в развитии плоскоклеточного рака и 95,3% в развитии цервикальной аденокарциномы.

Ключевые слова: HPV-обусловленные раки, доминантные типы вируса папилломы человека.

Cervical cancer is a major global concern, with the vast majority of the disease burden carried by the developing world, and is predicted to increase dramatically over the next decade without significant intervention. HPV 16/18 vaccines have the potential to significantly reduce the worldwide burden of cervical cancer, although several challenges to successful vaccine implementation remain in the developing world.[1] Cross-protective efficacy against non-vaccine HPV types may increase the impact HPV 16/18 vaccines have on cervical cancer mortality.

The latest data from the Catalan Institute of Oncology (ICO) study on the relative contribution of different HPV types to cervical cancer will be presented and the contribution of single and multiple HPV infections and their interpretation will also be discussed. The ICO study included over 10,000 cases of cervical cancer in over 35 countries and used a centralized laboratory protocol and $SPF_{10}$-PCR/$LiPA_{25}$ technology, which is considered the reference testing method for paraffin preserved tissue specimens. The most common HPV types associated with cervical cancer and squamous cell carcinoma worldwide are HPV 16, 18, 45, 33 and 31. HPV 16, 18 and 45 are the HPV types associated with adenocarcinoma. When multiple infections were taken into account in a hierarchical mode (i.e. all cases including HPV 16 were considered as caused by HPV 16 and equally for other types in descending order of frequency) the combined attributable fraction of HPV 16, 18, 45, 31 and 33 was of 83.2 % of squamous cell carcinomas and 95.3 % of cervical adenocarcinomas. Data on the relative contribution of HPV types to cervical cancer will allow us to predict and compare the impact of HPV 16/18 vaccines with and without cross-protective efficacy against non-vaccine HPV types, including types 31, 33 and 45. The ICO study provides important data for the development of second-generation HPV vaccines and for the development of management protocols, which include HPV testing, for cervical cancer screening programmes.[1]

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## GLOBAL BURDEN OF HPV ASSOCIATED CANCER

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## МЕЖДУНАРОДНОЕ ЗНАЧЕНИЕ ВПЧ-АССОЦИИРОВАННОГО РАКА

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В статье рассмотрена роль вируса папилломы человека в развитии злокачественных опухолей различных локализаций: рака шейки матки, вульвы, влагалища у женщин; пениса у мужчин; анального отдела прямой кишки, полости рта и гортани у мужчин и женщин. Вирус папилломы человека является вторым по значимости канцерогенным фактором для человека, вызывая 5 % злокачественных опухолей: 10 % случаев рака, обусловленного этим фактором, у мужчин и 15 % случаев у женщин в развивающихся странах.

Ту часть злокачественных новообразований, которые связаны с HPV 16 и 18 типов возможно предупредить посредством профилактических вакцин, это составляет порядка 550 000 новых случаев в год.

Ключевые слова: HPV-обусловленные раки, доминантные типы вируса папилломы человека

### *Cervical cancer*

Cancer of the cervix uteri has been historically the number one cancer in women. In spite of the opportunities offered by screening programs still is the second most common cancer among women worldwide, with an estimated 493,000 new cases and 274,000 deaths in 2002. Cervical cancer clusters in developing countries, where 80 % of the cases occur and account for at least 15 % of all female cancers. In some of these populations the cumulative risk of developing cervical cancer is estimated in the range of 1.5 to 3 %, while in developed countries it accounts

for 3.6 % of all new cancers in women with a cumulative risk of 0.8 % up to 65 years of age.

In general, the lowest rates (less than 15 per 100,000) are found in Europe, except in many of the Eastern European countries, North America, and Japan. The incidence is particularly high in Latin America (age-standardized incidence rates; ASR 33.5 per 100,000) and the Caribbean (ASR 33.5), sub-Saharan Africa (ASR 31.0), and South-Central (ASR 26.5) and Southeast Asia (ASR 18.3). Moreover, within the developed countries, cervical cancer also clusters in the lower socioeconomic strata, signaling the lack of appropriate screening as one of the major determinants of the occurrence of the invasive stages of the disease. Predictions based on the passive growth of the population and the increase in life expectancy indicates that the expected number in 2020 will increase by 40 % corresponding to 56 % in developing countries and 11 % in the developed parts of the world.

Mortality rates are substantially lower than incidence. Worldwide, the ratio of mortality to incidence is 55%. The 5- year survival rates vary between regions with good prognosis in developed countries (73 % in US registries and 63% in European registries). Because cervical cancer affects relatively young women, it is an important cause of years of life lost. One recent estimate concluded that cervical cancer is the biggest single cause of years of life lost (YLL) from cancer in the developing world. In Latin America, the Caribbean and Eastern Europe, cervical cancer makes a greater contribution to YLL than diseases such as tuberculosis or Acquired Immune Deficiency Syndrome (AIDS). It also makes the largest contribution to YLL from cancer in the populous regions of sub-Saharan Africa and South-Central Asia.

***Other cancers linked to HPV: Vulva, vagina, penis, anal, oral cavity and oro-pharynx / larynx***

Cancers of the vulva and vagina are rare tumors that jointly account for 6–9 % of cancers of the genital tract. Although the majority are squamous cell keratinizing carcinomas (80+%), two distinct histological subtypes are recognized. The morphologically warty or basaloid type, which is associated with HPV infection, is diagnosed at relatively younger ages, are often concurrent with precursor lesions of vulvar intraepithelial neoplasia (VIN 2/3) and tends to follow the epidemiological patter of a sexually transmitted origin (related to larger number of partners and a record of previous cervical lesions). In contrast the keratinizing squamous cell vulvar cancers are diagnosed at older ages, and often relate to chronic degenerative epithelial conditions such as liquen sclerosus.

Cancers of the vagina is consistently rarer that vulvar cancer. The majority of cases are preceded by vaginal intraepithelial neoplasia (VAIN 2/3) and HPV, mostly HPV 16, has been implicated in over 90 % of the cases.

Cancer of the penis is a rare cancer, accounting for less than 0.5 % of cancers in men. The incidence in Jewish populations is particularly low. The importance of circumcision in determining the risk of penile cancer has been evident for many years. Case-control studies estimated that the risk of penile cancer is reduced about threefold among circumcised men. Circumcision also protects against other sexually transmitted infections, like HIV, and recently it has been shown that husband's circumcision also protects women from HPV infections and cervical cancer.

Cancers of the anus are those arising in the anal canal, largely in a zone of transition epithelium similar to the one encountered in the cervix. In most populations, anal cancer is twice as common in females as in males and the incidence is particularly high amongst homosexual males. HPV DNA, notable HPV 16 is found in 85–95 % of the cases and other risk factors include co-infections with HIV, cigarette smoking, frequency of anal intercourse, and the number of lifetime sexual partners.

Current research is actively investigating the role of HPV infections, notably of HPV 16, in cancers of the oro-pharynx (averaged estimates of 35 %) and of the oral cavity (averaged estimates of 20 %)

***Burden of HPV and relative importance of HPV 16 and 18***

HPV infections are the commonest of the sexually transmitted infections. Among women with normal cytology within the age ranges typical included in screening programs, the average HPV DNA prevalence has been estimated at 10 % with significant geographical variation. Among women with normal cytology and cervical HPV infections, one can often find multiple HPV types, a great variability in the HPV type distribution including a significant presence of low risk types. HPV 16 is the dominant type in most studies. In contrast as cervical lesions develop the global HPV DNA prevalence increases to 75–85 % in LSIL and to 85–100 % in HSIL and invasive carcinomas. In cervical cancer cases, the number of types is restricted to 12–15 types, the vast majority of cases harbour only one type and a clear type distribution pattern is found. On worldwide estimates, HPV 16 is consistently the most common type, accounting for some 50% of all cases followed by HPV 18 and 45. Some variability in the ranking thereafter has been described.

For the subgroup of cervical adenocarcinomas, HPV 16 and 18 are found in similar proportions followed by HPV 45. The three HPV types combined account for close to 75 % of the squamous cell carcinomas and close to 90 % of the adenocarcinomas.

In summary HPV is now considered the second most important human carcinogen accounting for 5 % of human cancer 10 % of cancer in women and 15 % of cancer in women in developing countries. The fraction linked to HPV 16 and 18 that are potentially preventable with current HPV vaccines account for close to 550,000 new cases per year worldwide.