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Human papillomavirus DNA in premenopausal and postmenopausal women

Abstract

Introduction: Papillomavirus strains can be practically classified by their risk of causing cervical cancer into low-risk (type 6 and 11) and high-risk (HPV 16 and 18) types. Therefore, it is necessary to investigate Papillomavirus DNA in different age groups.

Methods: This was a cross-sectional study, we determine the frequency of the papillomavirus in 50 premenopausal and 50 postmenopausal patients admitting Kahramanmaras Sutcu Imam University School of Medicine, Gynecology and Menopause outpatient clinics for follow-up, Kahramanmaras/Turkey for examination from December 2008 to December 2009. Inclusion criteria were patients had no other gynecological cancer history. After endocervical swab specimens reached to Medical Microbiology laboratory, we cut the tips of endocervical swab specimen and stored as frozen at -20 degrees centigrade in phosphate buffer in eppendorphs until studying. Real Time PCR was used for extraction of DNA and sequencing was done for genotyping.

Information about patients (Menopause/Gynecology patients, age, menopause age, marital status, education, income, marriage age, pregnancy age, number of pregnancy, number of sexual partners, history of using OCS/HRT, history of sexual transmitted disease, smoking/drinking, diet) was taken with patient information form.

Results: Six patients out of 100 (6%) were determined to be papillomavirus positive. Four of these papillomavirus DNA positive patients were at postmenopausal group and two of them were at premenopausal group. Two were type 6 (33.3%), two were type 45 (33.3%), one was type 16 (16.6%) and one was type 67 (16.6%). In this study, we couldn't determine statistically significant difference between positive results and being in premenopausal or postmenopausal period ($p>0.05$).

Conclusion: In our study, we evaluated papillomavirus prevalence and type distribution in two periods of life of woman in a local population. Further studies would be beneficial in different groups and to determine nonhospital based papillomavirus prevalence in our country.

Keywords: human papilloma virus, menopause, real-time PCR

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Abbreviations: BPVs, bovine papillomaviruses; HPV, human papilloma virus; EV, epidermodysplasia verruciformis; HGSIL, high grade squamous intraepithelial lesion; HRT, hormone replacement therapy

Introduction

Papillomaviruses are small, non-enveloped, epitheliotropic, double-stranded DNA viruses that cause cellular proliferation, infecting mucosal and skin epithelium in species-specific manner. It is known that only bovine papillomaviruses (BPVs) named type 1 and 2, infect mesenchymal tissues and show crossover between species. More than 100 species of human papilloma virus (HPV) have been identified, and about half of them infect the genital system. Many HPV types are found in cervical cancers, while others are rarely or nonexistent, leading to the designation of "high" (HPV 16 and 18) and "low risk risk (type 6 and 11) HPVs. Other types are associated with other anogenital and oropharyngeal cancers. In patients with epidermodysplasia verruciformis (EV), a number of HPVs have been found in skin cancers; these types are also found in non-melanoma skin cancers and normal skin.[1] There is a strong correlation between papillomavirus infection and cervical cancer. Recently the fourth most common cancer case in women is cervical cancer. Therefore, it is necessary to investigate papillomavirus DNA in cervical cancer and its precursor infections. ZurHausen received the 2008 Nobel Prize in Medicine detected 99.9% causal relationship between Papillomaviruses and cervical cancer.[2,3]

Mucosal high-risk HPVs such as HPV16 and 18 shows that both E6 and E7 play an important role in cervical cancer. They play a central role in carcinogenesis by interacting with cellular protein by cell cycle and apoptosis control. In addition to E6 and E7, HR HPVs encode a small hydrophobic oncoprotein of 90 amino acids, such as E5 also plays a role in carcinogenesis.[4]

Many studies have revealed the pattern of papillomavirus infection in different age groups. Zietkowiak et al. discussed patients in the perimenopausal (between 45-49 years) compared to postmenopausal group (56 years and over) in Poland; high papillomavirus infection rate was observed.[5] More than 20 million people and over 50% of sexually active adults infected in a period of life with an intense

papillomavirus infection in United States but many studies revealed similar prevalances of 27,5- 25,2-19,6 per cent seen in period of ages between 30-39, 40-49 and 50-59 respectively.[6] Papillomavirus DNA prevalence depending on continents and age groups shows that DNA detection in other regions except Asia is high with 30% rates in the young group.[7] Recently, prevalence of any genital HPV was found higher among men than women overall and among non-Hispanic white and non-Hispanic black adults.[8]

The reason for relative increase seen after menopause has been associated with the rate of HGSIL (High grade squamous intraepithelial lesion) at this age.[9] Brown et al. discussed immune system changes common in older age groups associated with these changes.[10] As explained by Sturgeon et al. increased positivity of papillomavirus as age progresses may also be due to use of HRT (Hormone replacement therapy). In particular, progesterone can increase papillomavirus gene expression, but the relationship with the incidence of cancer has not been defined yet[11] Infection can spontaneously resolve or may surge clinically. Identification and vaccination of all individuals at risk with the onset of sexual activity is an issue still being evaluated.[12]

Method

This is a cross sectional study based on women presenting for routine gynecologic care at a single center to examine the age and time interaction influencing papillomavirus prevalence.50 were premenopausal and 50 were postmenopausal in 100 patients included in our study. This study also examines the effect of the number of lifetime sexual partners, menopause/normal gynecology patient, age, menopause age, marrital status, education, income, marriage age, pregnancy age, number of pregnancy, number of partners, history of using OCS/HRT, history of sexual transmission, smoking/drinking and diet on papillomavirus prevalence.

Lab procedures

Endocervical samples were taken by a specialist physician from premenopausal and postmenopausal women in Kahramanmaras Sutcu Imam University Medical Faculty Hospital gynecology outpatient clinic. Sterile cotton swabs (dacron swab) were used for sample collection. Samples sent to the Medical Microbiology laboratory without the need for a cold chain. These specimens were kept in phosphate buffer in sterile ependorf at -20˚C until they are studied.

The specimens were sent in cold chain for grouping stages to IONTEK Central Laboratory (Istanbul). While studying first they must be melted and papillomavirus DNA extraction was performed. At the end of the purification, samples were loaded on to the Real-Time PCR for HPV detection. The Real time PCR device used in our study was named as Flourion detection system (Slam Samples found positive in real-time PCR undergo preliminary procedures for sequence analysis. First, post-PCR purification of each sample with High Pure (Roche) kit was done. Samples after purification; 1.5 minutes agarose gel at 170V for 15 minutes was conducted. Samples were compared with Gene Ruler DNA Ladder Mix (1000bp) marker.

Samples found positive in real-time PCR undergo preliminary procedures for sequence analysis. First, post-PCR purification of each sample with High Pure (Roche) kit was done. Samples after purification were conducted 1.5 minutes agarose gel at 170V for 15 minutes. Samples were compared with Gene Ruler DNA Ladder Mix (1000bp) marker. On the marker basis; the mean DNA concentration of the samples were determined and the volume (µl) required from the sample was determined. Each sample in PCR device; sequencing was performed in the presence of GP6 primer and sequence Reagent Mix. Sequencing was made with Sodium Acetate and Ethylene Hydroxide. Examples for sequence analysis installed on AB Prism 310 Genetic Analyzer. BLAST analysis was applied to sequence results and type determination was performed. Patients with positive risk were low risk (type 6, 11, 40, 42, 43, 44, 54, 61, 70, 72 and 81), moderate risk (26, 31, 33, 35, 39, 51, 52, 53, 55, 56, 57, 58, 59) and high risk (16, 18, 45, 56) and 67).

Patient's selection

In 100 patients evaluated, there was no history of cervical cancer and absence of warts in the genital area or skin of themselves and their first degree relatives. Patients with surgical menopause or without cervix were also included in the study. The aim is to determine the HPV transport in the genital system and not only in the cervix. Other facilities were ignored. Patients were informed with consent forms and approvals received prior to sample collection. Ethical approval of study was taken from ethics comitee of Kahramanmaras Sutcu Imam University Medical faculty.

Statistical analysis

Data analysis was performed with SPSS 8.0 package program. Complementary statistics were expressed as frequency (%). Fisher's exact X^2 test was used for categorical comparisons. All results were considered statistically significant for $p<0.05$.

Results

In 100 patients included, 59were under 49 years of age and other 41+20:61 were at menopause. Only one patient is in menopause under 49 years of age. The age limit was evaluated according to average age for the climacterium period of 49 years.

There were 6 specimen HPV-DNA positive and 94 were negative. HPV positivity was detected in two were in the premenopausal group (4% in the group), four were in the postmenopausal group. The HPV DNA positive samples were investigated in terms of HPV genotypes. 2 out of these 6 positive patients were type 6 (33.3%), 2 of them were type 45 (33.3%), 1 was type 16 (16.6%) and 1 was type 67 (16.6%). In this study, we couldn't determine statistically significant difference between positivity and being in premenopausal or postmenopausal period ($p>0.05$).

98 of the 100 patients were married and 2 were questioned as widows. Papillomavirus positive patients were married. One patient had more than one partner. Again, 78 (78%) of the patients were either not attending school (not literate) or primary school. 22 (22%) were graduated from secondary and post-secondary education. HPV was positive in four out of 78 (5.1%) patients having 5 years and under education. HPV with training time positivity relationship ($p = 0.610$) was not statistically significant. In our country, the first sexual intercourse age and the age of marriage questioned in patients in general; because of the parallelism between the two were included in the evaluation.

65 out of 100 patients (65%) were married under the age of 18 (as the first sexual intercourse age). Four of them were positive (6.2%). 2 out of 35 patients having first sexual intercourse age over 18 were positive (5.7%). First sexual intercourse age and HPV positivity relation was not statistically significant ($p=1.0$). 78 out of 100 patients had their first pregnancy before 22 years of age and 5 of them (6.4%)

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were positive; 21 of them had their first pregnancy over 22 years of age and 1 of them (4.8%) was positive. 1 patient had no pregnancy. HPV positivity relation with first gestational age was not statistically significant (p=1.0). Considering the relationship between HPV positivity and the number of pregnancies; 2 of 39 patients having two or less number of pregnancy (5.1%) had positive results. Four of 55 patients having 3 or more pregnancies were HPV positive (7.2%). This relationship was not statistically significant (p=1.0).6 out of 100 patients (6%) were smoking. One was HPV positive (16.7%). 5 out of 94 (94%) non-smokers was positive (5.3%). There was no statistically significant difference (p=0.317) according to the Fisher's exact test. All positive patients were in 81 out of 100 participants (81%) were on a diet rich of fruits and vegetables and realationship was not statistically significant (p=0.592).

Discussion

Papillomavirus infection is mainly a sexually transmitted disease and everyone may spread the infection as an asymptomatic carrier.[13] Accordingly, risk factors are closely related to sexual habits. For example, early onset sexual life, number of sexual partners may increase the risk, while circumcision and condom use in menmay reduce the risk of infection.[14]

Prevalence of papillomavirus in women worldwide estimated between 2% and 44%. The differences were present among studied groups. It is explained by the sensitivity of the method studied.[15] Papillomavirus infection in the majority of individuals is transient and asymptomatic, 70% of the individual's first infection with the virus within 1 year, 90%regresses in two years. In a study conducted among college students in the US, the mean duration of a new papillomavirus infection was 8 months. Persistence for more than 6 months may relate with high age, the presence of high-risk papillomavirus.[16] Data from the National Health and Nutrition Examination Survey showing that; during 2011–2014, prevalence of any oral humanpapillomavirus (HPV) foradultsaged 18–69 was 7.3%; high-risk HPV was 4.0%. Overall, prevalence of any and high-risk oral HPV was lowest among non-Hispanic Asian adults ; any oral HPV washighestamongnon-Hispanicblackadults. Prevalence of anyandhigh-risk oral HPV washigher in men thanwomenexceptforhigh-risk HPV amongAsianadults. During 2013–2014, prevalence of any and high-risk genital HPV for adults aged 18–59 was 45.2% and 25.1% in men and 39.9% and 20.4% in women, respectively. Prevalence of anyandhigh-risk genital HPV was lower among non-Hispanic Asian and higher among non-Hispanic black than both non-Hispanic white and Hispanic men and women.[17]

In a study conducted in 132 patients in our country, 27 (58.7%) of those who were HPV positive were under 37 years and 19 (41.3%) were over 37 years. The highest rate of HPV-DNA positivity was found in 9 patients (19.6%) in the 33-37 age range. In this study, 6 patients between the ages of 18-37 and 3 patients between the ages of 38-57 found high-risk HPV-DNA positive. Differently, in our study, HPV positivity was not observed in 14 patients between the ages of 20-34, while 2 of the 37 participants aged between 35-48, 3 of 33 people aged between 49-54 and 1 of 15 participants aged 55 and over were found HPV positive. The risk factors mentioned in many HPV infection studies include early marriage or early sexual intercourse. In the study, 51.5% of the patients had first sexual intercourse age below 20 years were found to be HPV positive and 10% of those over 20 year age were found to be HPV positive. According to this study, the first sexual experience under age of 20 increases HPV positivity by9.45 times.[18]

In large-scale studies on different continents, the type distribution varies. In a study conducted in Africa, type 16, 33, 58, 18, 31 and type 52 were found most frequently. In the same study, the prevalence of HPV type 16 found higher in cervical cancer in Europe compared to other continents; it would be explained by HPV 16 is less affected by reduced cellular immunity (due to malnutrition, HIV, etc.).[19] In our study we found only one type 16 and one type 67; two were type 6 and two were type 45.

Testing for high-risk humanpapillomavirus DNA (HPV test) has gained increasing acceptance as an alternative method to cytology in cervical cancer screening.[20] In our unpublished study; 81 patients were under 49 year old and 20 were older than 49 and in menopause. 4 patients were type 6, 9 of them were type 45, 31 sample was type 16, 2 sample was type 67, 15 were type 31, 3 were type 58, 12 were type 51, 1 were type 28, 5 were type 18, 8 were type 52, 7 were type 39, 6 were type 33, 17 were type 56, 4 were type 59, 5 were type 58, 7 were type 35, 8 were type 68, 4 were type 66, 1 of them was type 35. We determined type 16 was seen higher than other types in group. These 31 patients with type 16 were all in premenopausal group. Following most seen types were type 56 and type 31. Relative predominance have seen in menopausal group having type 31,56,16 but was not statistically significant.

Despite these high rates of infection at an early age, most of the HPV-infected women spontaneously heal. Viral type, persistent infection and viral load per cell and integration of viral DNA into cellular DNA have been recognized as important factors in disease progression. Neoplastic differentiation is associated with HIV association, long-term OC use, high parity and smoking.[21] Multiparity is one of the factors that increase the incidence of HPV infection, as supported by previous studies.[22] In the study by Franceschi et al., Factors such as high parity and early menopause were found to be significantly associated with HPV infection and thus cervical in situ carcinoma.[23] In our study, 55 of the 94 patients interviewed were multiparand 4 (7.2%) of the positive samples were included in this group. In our study, the first pregnancy age was questioned, and 78 out of 100 patients had their first pregnancy at 22 and lower ages than five of them (6.4%) were found to be HPV positive.

Although the strong relationship between HPV infection and having more than one sexual partner has been emphasized in various publications; our study included only one woman who reported having multiple sexual partners, and this patient was found to be HPV DNA negative. 98 of the 100 patients were married and 2 were questioned as widows. Papillomavirus positive patients were married. In a study; total of 2225 female and 1140 male patients were evaluated. The risk increases as the number of partners of the spouses of monogamic women increases, and the risk increases again if the number of partners of monogamic women increase.[24]

It has been reported that OCS can induce cervical cancer development in patients with long-term HPV positivity. Ten of our participants gave a history of using OKS between 0-5 years and 2 of them (20%) were found to be HPV positive. No statistically significant correlation was found between the use of OCS and detection of HPV. Previous studies have shown that the use of HRT, therefore progesterone, has a positive effect on HPV expression. Increase in HPV detection rates observed in postmenopausal women using HRT but the duration of use was not considered.[25] In our study, 1 of 50 postmenopausal patients was using HRT and this patient was negative for HPV.

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It has been reported that coinfection with sexually transmitted diseases is effective in the progression of HPV.[26] Castellsague and Bosch have concluded that Chlamydia trachomatis infection supports cellular atypia caused by HPV and chronic inflammatory process. They also reported that bacterial vaginosis was inversely proportional to HPV infection and thus to cellular atypia development.[27] In our study, HPV positivity was found in 1 of 3 patients who had a history of undiagnosed genital infection, and this was HPV type 16.

HPV DNA positivity was found to be significantly higher in smokers compared to non-smokers.[28] In our study, HPV positivity was found only in 1 (16.6%) of 6 patients who smoked, which was not statistically significant.

The importance of genotyping in HPV studies is increasing and targeting;

a. To determine strong relationship between certain types of cervical and other genital cancers,

b. Necessity in some infections with many genotypes and to identify these types,

c. Determining the geographical distribution of HPV types and creating HPV vaccination programs

New studies that have attempted to address whether serum antibodies developed following natural papillomavirus infection show protection against reinfection have shown inconsistent results. The purpose was to estimate the protective effect of naturally acquired anti-HPV16 serum antibodies against incidentalanogenital infection with HPV16 in females aged 20–64 years and to assess whether antibodies influence the persistence/clearance of anogenital HPV16 infection. Protection from reinfection among seropositive individuals has been detected in three studies of college-aged women[29] and in one of three population-based studies with average age greater than 30 years. Differences in the serological assay between studies may explain some of this inconsistency.[30,31] However, a recent analysis of papillomavirus incidence among baseline seropositive versus seronegative women in the placebo arm of the trial of the quadrivalent vaccine Gardasil (Merck) in mid-adult women showed direct evidence of protection in younger, but not older, women.[32] Women aged 26–34 years showed a lower rate of new type-specific detection among the seropositive compared with seronegative women.[33]

Conclusion

Despite the evidence described above, human studies are unable to directly demonstrate establishment of latency and induction of reactivation from the latent state. In our study, we evaluated papillomavirus prevalence and type distribution in two periods oflife and prevalance was similar to that reported worldwide. We evaluated local population in here Kahramanmaras so our data would not represent Turkey's prevalence. Further studies would bebeneficial in different groups and to determine nonhospital based papillomavirus prevalence in ourcountry.

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Conflicts of interest

The author and co-authors have no conflicts of interest relevant to this article.

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