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CLINICAL STUDY

Quality of food intake and spontaneous clearance of Human papillomavirus in women

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ABSTRACT
BACKGROUND. Human papillomavirus is known to be the main cause of cervical cancer. Given that cervical cancer is still one of the leading causes of death in women of reproductive age, it is very important to prevent HPV infection and its persistence.
OBJECTIVE. The aim of our study was to explore the quality of the diet in the spontaneous clearance of cervical HPV infection and its persistence. Furthermore, we have assessed the associations of overall diet quality and dietary components with HPV occurrence and clinical resolution of HPV over time.
METHODS. 200 women of age between 20 and 68 years were included in this prospective study. Patients were tested for the presence of HPV subtypes, and were given questionnaires about their dietary habits.
RESULTS. 43 patients were positive for HPV virus, and 157 patients were negative. Among the positive HPV patients, the mean value (±SEM) of the score was 12.88±0.6822 (min=7, max=21) with upper CI of mean 14.26 and coefficient of variation of 34.72%.
CONCLUSION. Various antioxidants have different abilities to influence the course of HPV-mediated cervical cancer. This study showed that women who did not consume fruits, and dark-green vegetables had a higher risk of HPV infection *(Tab. 2, Fig. 3, Ref. 40):* Text in PDF www.elis.sk
KEY WORDS. cervical cancer, human papillomavirus, folate, vitamin D3, dietary intake.

Introduction

Cervical cancer is considered to be one of the most preventable cancers in women and it is predominantly attributed to human papillomavirus (HPV) diagnosed infections. It is the second most common cancer and the third leading cause of cancer death among women especially in the developing and low-income countries (1, 2):

The causal role of oncogenic HPV infection in the pathogenesis of cervical cancer has been already established that is preceded by precancerous changes of the cervix that are known as cervical intraepithelial neoplasia (CIN) (3):

According to the World Health Organization (WHO), more than 12,000 new cervical cancers are registered each year in the United States as well as more than 570,000 worldwide. In 2020, more than 342,000 women died from metastatic advanced cervical cancer (4, 5): Nearly all cases of cervical cancer have in the background human papillomavirus (HPV) infection of the cervix. HPV infection clears spontaneously in 90% of cases, but persists in the remaining 10%, and it might lead to precancerous high-grade cervical intraepithelial neoplasia (CIN2+) and afterwards in cervical cancer (6):

Several studies have been able to prove that in women with higher serum levels of certain micronutrients including vitamin B12, C, α-carotene, β carotene, lutein, folate, vitamin D, zinc, lycopene, α-tocopherol as well as increased daily intake of whole fruits leads to reduced rates of high grade cervical intraepithelial neoplasia (7–17): In addition, patients who often consume papaya, dark green vegetables and yellow fruits and vegetables had reduced risks of persistent HPV infection (16, 18–20): Regression of neoplasia was higher in women with low-grade CIN, who in the period of 6 months received vitamin D or folic acid, compared with placebo group (21–22): Oxidative stress has also been considered to be associated with cervical cancer, being responsible for production of reactive oxygen species (ROS) resulting in DNA damage to cervical cells. Under these conditions, cervical cells are considered to be vulnerable to HPV infection and consequently leading to cervical cancer development.

In recent years, dietary supplements (vitamins, minerals) and food rich with antioxidants have gained attention in regards to their role in prevention of cancer. The proposed mechanism is that they can prevent free-radical damage to DNA by neutralizing free radicals and oxidants.

The aim of our study was to explore the quality of the diet in the spontaneous clearance of cervical HPV infection and its persistence. Furthermore, we have assessed the associations of overall diet quality and dietary components with HPV occurrence and clinical resolution of HPV over time.

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Materials and method

Study design and participants

Sexually active women of age between 20 and 68 years were included in this prospective study. The patients were recruited when visiting their gynaecologist for a routine check from August 2022 until November 2023. The targeted group counts 200 patients. The exclusion criteria were. patients with a history of hysterectomy, patients with a history of treatment for cervical and vaginal lesions and patients with diseases of the blood and digestive system. The participants were asked to fill out a questionnaire regarding their diet habits and supplement intake (Tab. 1): More specifically, the questionnaire was structured in a way to receive information in regards to the intake of carrots, green salad, citrus, fresh vegetables more than 100 g, fruit more than 100 g, vitamin D3 2000 IU and folic acid 10 mg. The responses were assessed by giving points on the scale from 7 to 21, 7 meaning no intake at all and 21 a daily intake. Their smoking habits were also considered. All participants have given consent.

Tab. 1. QUESTIONNAIRE – HPV infections and hygienic dietary regime.

Name and surname _____

Age _____

Are you a smoker? YES NO

How often do you eat each of the following foods and supplements?

1. Carrot (raw)
   - less than 3 times a week (1)
   - 3–4 times a week (2)
   - 5 or more times a week (3)
2. Onion and garlic (fresh)
   - do not consume at all (1)
   - once a week (2)
   - 2 or more times a week (3)
3. Citrus fruits
   - less than 3 times a week (1)
   - 3–4 times a week (2)
   - 5 or more times a week (3)
4. Vegetables (100g)
   - less than 2 times a week (1)
   - 2–4 times a week (2)
   - 5 or more times a week (3)
5. Fruit (100g)
   - less than 2 times a week (1)
   - 2–4 times a week (2)
   - 5 or more times a week (3)
6. Vitamin D3 (2000 IU)
   - do not consume at all (1)
   - 2–3 times a week (2)
   - 4 or more times a week (3)
7. Folic acid (as a supplement) or lettuce
   - do not consume at all (1)
   - 2–3 times a week (2)
   - 4 or more times a week (3)

HPV testing

In all patients HPV DNA testing was done. The analysis of the samples was done as described below. Briefly, samples were taken using endocervical cyto-brush, the swabs were collected in the lithotomy gynaecological position of the patient, then placed in sterile test tube with 0.5 mL of transport medium. Samples were stored at temperatures of 2–8 °C and Human Papilloma Virus (HPV) genotyping was analysed within 7 days by multiple Polymerase Chain Reaction (PCR) method.

The method was based on simultaneous real-time amplification (multiplex PCR) of DNA fragments of HPV genotypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68 and a DNA fragment of β-globin gene in one tube. Detection by polymerase chain reaction (PCR) was based on the amplification of pathogen genome specific region using special primers. The Fluorescent End-Point PCR, the amplified product was detected with the use of fluorescent dyes, which were linked to oligonucleotide probes that bind specifically to the amplified product during thermocycling. A multichannel rotor-type fluorometer was specially designed to detect fluorescent emission from the accumulating product without re-opening the reaction tubes after the PCR run.

Statistical analysis

Data analysis was performed using statistical analysis software GraphPad Prism 9.0 (USA) The subjects of the study were analysed according to their age, the presence of HPV type(s) and the score of the questionnaire. Differences between the groups were tested by using Fisher exact test. Differences were considered statistically significant if the level of significance was $p<0.05$. Descriptive statistics was used where it was necessary.

Results

Patients and HPV distribution

A total of 200 female patients between 20 and 68 years of age were included in this study. The average age of the participants was 35.3 years. The total number of patients and their distribution according to HPV positivity is shown in Figure 1.

Out of the total number of patients, 43 patients were positive for HPV virus, and 157 patients were negative. Among the positive HPV patients, the mean value (±SEM) of the score was 12.88±0.6822 (min=7 and max=21) with upper CI of mean 14.26 and coefficient of variation of 34.72%. The average age

Tab. 2. The distribution of HPV infection among women by age groups.

Age group	Positive	Negative	Total
20–30	23 (32.39%)	48 (67.60%)	71
30–40	11 (15.2%)	61 (84.72%)	72
40–50	7 (15.5%)	38 (84.44%)	45
>50	2 (16.6%)	10 (83.33%)	12

of the patients that were HPV positive was 32.72±1.591 (range 20–66 years): The distribution by age of the HPV is presented in Table 2.

From all participants, 27 patients were pregnant. 61 of the HPV negative patients declared themselves as smokers (or 38.85%), and the average value of the determined score for the hygienic-dietary regime was 16.8535. 22 (14.01%) of the HPV negative patients were pregnant. The average age of HPV positive patients was 32.72 years. 34 (79.06%) of them were smokers, and the average value of the score was 12.8837. There were a total of 27 pregnant women with an average age of 27.59 years. Five of them (18.51%) were positive, and as well five (18.51%) were also smokers. The average score among pregnant women was 19.9259.

HPV distribution and association between the score and the subtype

A low dietary score is associated with the presence of HPV infection. The low score at the HPV positive cases is most often associated with HPV types 16 and 18, as we see in Figure 2.

From the distribution of HPV genotypes, the most common in our case is HPV type 16, followed by 31 and 52, shown in Figure 3.

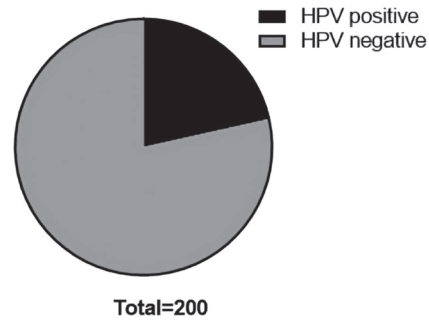

Fig. 1. Patient distribution according to HPV positivity.

Discussion

Patients positive for HPV infection had lower dietary score, similar to the patients included in Barchita et al, research, who established a correlation with Western diet characterized by high intake of red and processed meats, dipping sauces, chips and snacks with low intake of olive oil and higher risk of HPV infection (23): The dietary intake of carotenoids (lutein, zeaxanthin, β-cryptoxanthin), vitamin-C and papaya was associated with a reduced incidence of type-specific HPV persistence in 433 HPV-positive women by Giuliano et al (19): A Western diet has been reported to lead to increased inflammation, reduced infection control and increased risk of developing auto-inflammatory disease (24): Women with medium adherence to Mediterranean diet (MD) had a lower risk of HPV infection when compared to women who showed low adherence to the MD, which includes vegetables legumes, fruits and nuts, cereals, fish, and a high ratio of unsaturated to saturated lipids (23): On the other hand, the low consumption of whole vegetables (including dark green, dark yellow, and dark orange vegetables and cruciferous vegetables), fruits (including fruit juices), yogurt, tofu, fish and meat did not offer protection against HPV persistence (26): Feng et al. showed that the consumption of onion vegetables, legumes and nuts was associated with adjusted odds ratios (AORs) for the development of CIN2+ of 0.589, 0.591 and 0.635, respectively, according to the study conducted among 748 HPV-positive women. The consumption of these foods may reduce the risk of developing CIN2+. However, no associations were found between the risk of developing CIN2+ and the consumption of dark-coloured vegetables, light-coloured vegetables or eggs (27): The low intake of fruits and vegetables, especially fruits and dark-green and deep-yellow vegetables and smoking habits increase the risk of developing CIN3 according to Tomita et al (15):

Barchita et al. found a direct relationship between increased intake of Mediterranean Diet and the slowdown of progression of high-risk HPV infection, thus playing a protective role in the onset of neoplasia. Conclusion is that the adherence to Mediterranean Diet can provide a 60% reduction in cervical cancer (19):

All these patients, who were positive for HPV infection, were retested for HPV after 6 months, and spontaneous clearance of the virus was observed only in a very small percentage, in absence of change in dietary habits.

Most of the respondents were aged 30–40, but most of the positive HPV tests were among the respondents aged 20–30. While observing specifically the age-related prevalence of high-risk HPV, we noticed a peak in the age group from 14–25 years, in accordance with other European studies (28, 29): It's more likely for younger women to develop an HPV infection as they tend to have multiple partners (30) and less likely to have developed immunity to HPV given their recent exposure to the virus.

As lesions progressed to higher grades, the HPV prevalence increased, as expected. We noticed the same trend in hrHPV positivity in relation to cytological status. Looking at the results per age group, we observed that hrHPV infection dominated in 14–25 year old women irrespective of cytology. However it's less likely for younger women to develop cancerous lesions as in the most cases after 2-3 years the lesion regresses (31, 32):

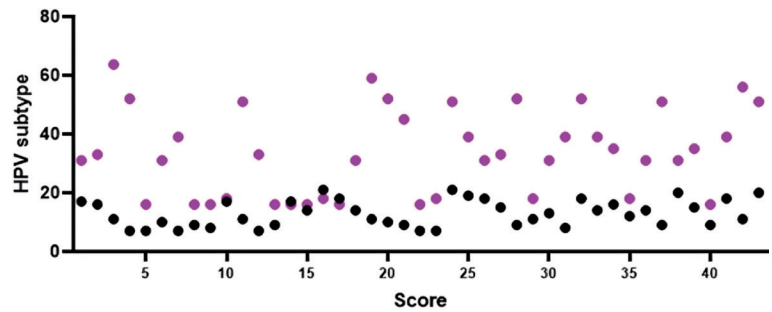

Fig. 2. Association between the dietary score and the HPV subtype. R2=0.6596, p<0.0001 (two-tailed t-test).

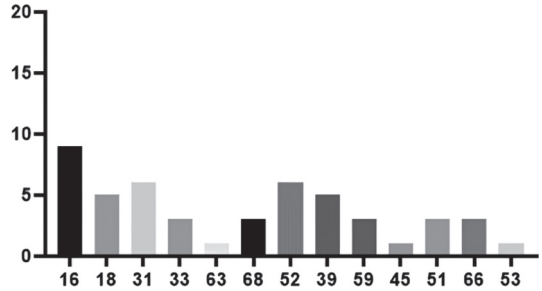

Fig. 3. HPV genotype distribution presented as number of patients.

Smoking increases the likelihood of HPV infection. Based on the fact that 70% of our positive patients are smokers, we can conclude that smokers have a higher chance of having positive HPV test.

Smoking may impair woman's antibody response (33–35): The diminished antibody response could be a consequence of an impaired immune system. Both cellular and humoral immune response are affected by smoking; it can reduce the levels of immunoglobulins, cytokines and natural killer cells (36): The diminished cellular response could lead to a persistent infection by inadequate clearance of HPV; while diminished humoral response could lead to a subsequent infection by inadequate antibody protection. It is unclear whether smoking increases the risk of subsequent HPV infection, despite the fact it is being associated with a lower antibody response.

Pregnant patients have the highest average score, understandably, due to the fact that they pay more attention to nutrition, taking care of themselves and the foetus during pregnancy, and consume a greater amount of fresh fruit, fresh vegetables, salads and, of course, additionally use supplements.

Every fifth patient who participated in the study was positive for HPV infection.

We can notice that in the majority of patients in whom HPV types 16 and 18 are isolated, they also have a low dietary score (Fig. 2):

In Mediterranean countries like Italy, Portugal, Spain, the high-risk HPV distribution (37–40) is similar to our data, with HPV 16 ranked as number one and HPV 51 ranking second or third.

Regarding the distribution of HPV genotypes, the most common is infection with HPV type 16, followed by HPV type 31 and HPV type 52 (Fig. 3):

Conclusion

Various antioxidants have different abilities to influence the course of HPV-mediated cervical cancer, regarding dietary nutrients. To be precise, each vitamin can have different suppressive effects at each stage of the development of cervical cancer (from HPV infection to the development of CIN and cervical cancer):

This study showed that women who did not consume fruits, and dark-green vegetables had a higher risk of persistent HPV infection. Taking into account the fact that persistent HPV infections are a cause of cervical cancer, we can conclude that increased intake of fresh vegetables, fresh fruit, as well as smoking cessation, reduce the risk of developing cervical cancer.

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