

Comparison of Human Papilloma Virus Results in Women with and without Atopic Disease

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ABSTRACT

Objective: Virus infected cells are destroyed by the natural immune system. However, HPV genotype and concomitant diseases are effective in HPV persistence. The aim of the study is to compare HPV screening results between patients with and without atopic disease.

Methods: This cross-sectional controlled study was conducted between August 2019 February 2020 in a tertiary research hospital. Patients between the ages of 30-65 with allergic complaints were diagnosed "atopic disease" by same clinician. HPV test results were compared to healthy controls. Subgroup atopic disease diagnoses, duration of illness, treatments regimes and treatment time of the patients in the study group were also questioned and recorded.

Results: A total of 239 women were recruited (121 study and 118 controls). Of recruited 121 atopia diagnosed women, 65 had rhinitis, 9 had urticaria, 20 had asthma and remaining 27 had both rhinitis and asthma. 9 patients in control group and 7 patients in study group were HPV positive. No cervical carcinoma was reported. The mean duration of atopia was 50 months (12-360). 78 patients were treated medically while 43 were vaccinated during medical therapy

Conclusion: HPV test results of groups were similar. No extra screening schedules are needed for patients with atopic diseases such as asthma, rhinitis or urticaria.

Keywords: Human papilloma virus, screening test, atopic diseases, asthma, rhinitis, urticaria

INTRODUCTION

Cervical cancer is an important health problem in women. Human papillomavirus (HPV) is considered the primary etiological agent of cervical cancer worldwide (1). Cervical cancer screening methods are proved one of the few screening methods that are thought to decrease invasive cancer incidence and mortality (1-3). In our country, HPV screening is carried out free of charge by public health to women between the ages of 30-65 (4,5). Abnormal results, in cases where the HPV test is positive or abnormal cells are seen in the Pap-smear, the individual is directed to obstetricians at advanced centers (5). HPV screening is repeated every five years.

As with all virus infections, the cellular and humoral response of the immune system is very important in defense against the virus (6). Usually virus and virus infected cells are destroyed by the natural immune system (6). HPV genotype and concomitant diseases are effective in HPV persistence (7). Urticaria, Hepatitis B or C infection, chronic obstructive pulmonary disease and asthma are some examples for concomitant diseases (8). In some studies, systemic lupus disease and rheumatoid arthritis have also been shown to be associated with HPV infection (7,8).

Atopia causes tendency to develop allergic asthma, allergic rhinoconjunctivitis and atopic dermatitis due to creating type I hypersensitivity to certain antigens under the influence of environmental factors in individuals with genetic predisposition (9). The best known of atopic or allergic diseases are asthma, hay fever and eczema (9,10). T helper-1 (Th-1) response decreased and T-helper-2 (Th-2) response increased in atopic patients (10,11). There are studies investigating the relationship between atopic dermatitis and HPV in the literature ¹⁰⁻¹¹. Moreover, it has been shown that a history of childhood atopic dermatitis may play a role in an increased risk of cervical cancer (12). Although mechanisms are not clarified (probably changes in T cell responses), patients with atopic disease may have tend to persistence of HPV or late cleansing. Our aim is to compare HPV screening results between women diagnosed with atopic disease and healthy women without a history of atopy. To our knowledge, it is the first study investigating HPV relationship under the title of atopic disease (allergic dermatitis, urticaria, atopic asthma, allergic rhinitis). If HPV is detected more frequently in patients with atopy, it may be recommended to follow more closely in vaccination and screening programs. Therefore, our study was designed to evaluate whether HPV positivity is common in atopic women.

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METHODS

This cross-sectional controlled study was conducted between August 2019 February 2020 at a tertiary referral research and education hospital. Informed written consent was received from all participants and ethics committee of City Education and Research Hospital approved the study with the number 494/2019.

Patients between the ages of 30-65 with allergic complaints (sneezing, itching, runy nose, respiratory distress) were diagnosed "atopic disease" by same clinician in Immunology and Allergy Department. The HPV results of the screened patients were noted retrospectively through the result reports of the patients, and those who were not screened were directed to Gynecology Department and HPV results were followed. Healthy women without allergic complaints applied for routine gynecologic examination occurred control group. Similarly, the HPV results of the control group were recorded. Pregnancy, immunosuppressive therapy history (including chemotherapy and chronic corticosteroid therapy), HIV positivity, cancer and hysterectomized patients were excluded.

Patients' height, weight, demographic features (age, marital status, income level), obstetric histories (gravida, parity, mode of delivery), contraception methods and smoking status were noted. Subgroup atopic disease diagnoses, duration of illness, treatments regimes and treatment time of the patients in the study group were also questioned and recorded. Leukotriene receptor antagonists and histamine receptor antagonists were the main treatments for study group and all therapies were designed by the same clinician. Routine allergic skin tests were performed to all atopic patients during diagnosis.

Statistical Package for Social Sciences (SPSS) for Windows, version 18.0 (SPSS Inc. IL, USA) was used to compare the clinical features of groups. Normality of data distribution was tested with Kolmogorov-Smirnov test. Data was shown as means \pm SD for continuous variables and the independent t test was used to assess the differences in variables between groups. Kruskal-Wallis, Mann-Whitney U-test and Bonferroni correction were used for values with non-normal distribution. P Values below 0.05 ($p < 0.05$) was accepted as statistically significant.

RESULTS

A total of 239 women were recruited. Among patients, 121 were diagnosed atopia and 118 healthy women occurred control group. The baseline characteristics of the all patients were shown in

Table 1. There was no significant difference between in mean scores of age, body mass index (BMI), age at first marriage. No other significant differences in frequency of smoking status was reported. The two groups were comparable in terms of gravidity, parity and abortion. Regarding delivery mode among groups; cesarean section was the highest in the study group, while normal delivery was the highest in the control group. Nulliparity rate was similar between groups. Income per month was found statistically higher in study group ($p=0.002$). The most common contraception method was condom in both groups (57.9 %, 38.1%, study and control group respectively.) while patients with no contraception was the highest number (30.6 %, 49.2%, study and control group respectively). 9 patients in control group and 7 patients in atopic group were HPV positive. One patient had HPV type 16 while remaining 8 patients had other types of HPV in the control group. No cervical carcinoma was reported.

Clinical diagnosis and treatment history of study group were shown in Table 2. Of recruited 121 atopia diagnosed women, 65 had rhinitis, 9 had urticaria, 20 had asthma and remaining 27 had both rhinitis and asthma. The mean duration of atopia was 50 months (12-360). 78 patients were treated medically while 43 were vaccinated during medical therapy. The median treatment time after diagnosis was 28 months. There was no patients with atopic dermatitis.

DISCUSSION

This study reports that there was no significant difference in terms of HPV positivity. Between groups (controls and atopic diseases such as asthma, allergic rhinitis and urticaria).

In a recent retrospective study, Garritsen et al. (10) searched Pap smear results of 189 atopic dermatitis diagnosed patients medicating oral immunosuppressive drugs such as azathioprine, methotrexate and other similar drugs for more than 2 months between 1989 and 2014. They found no cervical carcinoma and suggested that extra screening for patients using oral immunosuppressive drugs was unnecessary for patients with atopic dermatitis (10). Additionally, although transplant patients have used more than one immunosuppressive drug for a long period of time, some studies revealed low prevalence of cervical HPV infection in renal transplant recipients (13,14). This might be explained by being monogamous or sexual inactivity among that patient population. Moreover, HPV vaccine may have an impact on decreased incidence in the future, although it is not yet widely available.

Orrigoni et al. (15), enrolled solid organ transplanted 48 patients prospectively for 10 years and they checked Pap smear and HPV tests each year during follow up time. Compared to control group there was no statistically significant higher incidence of HPV infection or high-grade cervical dysplasia in transplant received patients (15). On the other hand, Meeuwis et al (16), reported high number of anogenital tract malignancies and detected high-risk HPV (especially type 16) in 91.7% of investigated lesions among 1023 patients who were performed renal transplantation between 1968 and 2008. Also, they suggested periodically screening before and after the transplantation (16). There has been no consensus in literature on this issue.

Main Points:

- Cervical cancer screening methods are proved one of the few screening methods that are thought to decrease invasive cancer incidence and mortality.
- It is the first study investigating HPV relationship under the title of atopic disease (allergic dermatitis, urticaria, atopic asthma, allergic rhinitis).
- There is no need to different and extra screening schedules for patients with atopic diseases such as asthma, rhinitis or urticaria.

Table 1. Basic Characteristics Of Groups

	Control group n= 118	Study group n= 121	P value
Age (y)	42.9±7.5	41. 3±7.3	0.1
BMI (kg/m2)	27.0±4.7	26.8±4.5	0.2
Age of first marriage (y)	21.3±4.9	21.8±3.7	0.3
Smoking (yes) N, (%)	30	26	0.47
Gravidy	2.9±1.9	3.4±2.0	0.06
Parity	2.3±1.2	2.6±1.5	0.07
Abortion *	0 (0-7)	0 (0-13)	0.4
Type of delivery, N, %			
No delivery	7 (59)	6 (5)	0.009
Vaginal birth	66 (55.9)	45 (37.2)	
Cesarean section	45 (38.1)	70 (57.9)	
Income (tl)*	2000 (1000-10.000)	2600 (700-24000)	0.002
HPV positivity	9	7	0.56

BMI: body mass index, y: year, n:number, OCT: oral contraceptives, IUD: Intrauterine device,

*: median (min-max)

Table 2. Clinical Diagnosis And Treatment History Of Study Group

Study Group N=121	
Type of Atopia	
Rhinitis	65
Asthma	20
Rhinitis+ Asthma	27
Urticaria	9
Time of Atopia (month)*	50 (12-360)
Type of treatment	
Medical	78
Medical+ vaccine	43
Time of treatment (month)*	28 (2-360)

*: median (min-max)

In another study, they investigated the risk of cervical dysplasia and cervical cancer in women with systemic inflammatory diseases such as inflammatory bowel disease (IBD) and systemic lupus erythematosus (SLE), psoriasis and rheumatoid arthritis (RA) (17). They concluded that SLE and RA patients had 1.5 times higher cervical dysplasia and cervical cancer compared to patients with non-systemic diseases (17). This result was thought to be related with different severity of inflammation and doses of systemic immunosuppressive drugs. It was also reported that asthma, chronic rhino-sinusitis, atopic dermatitis, eosinophilic esophagitis, and IBD had similar tight junctions leading pathogenic mechanisms of these diseases (18). T-helper 2 (Th2) cells play one of the major role in the pathogenesis of the allergic

asthma and allergic dermatitis through pro-inflammatory cytokines (9,19). Moreover, HPV infection was well known to promote Th2 cells while reducing Th1 cells (20). Therefore, we chose to screen HPV positivity in atopic diseases including asthma, allergic rhinitis, atopic dermatitis or urticaria. Morgan et al. (11) compared the characteristics of patients with HPV infection to negative controls. As a result, they found that atopic dermatitis was statistically significantly high in HPV positive ones. However, allergic rhinitis or patients who had both allergic dermatitis and rhinitis were similar between groups. It was thought that difference of Th1 and Th2 balance may be related to results of the study. Cellular immunity declines due to reduced Th1 response (21). In our study, allergic patients were selected first and then

HPV results were checked. We preferred to compare the atopic and non-atopic patients results regarding HPV tests. The main significant difference was monthly income between groups. Allergic patients had higher income. It was well known that patients who had more income pay more attention to their allergic or cosmetic problems. The rates of contraception methods and delivery modes were also different between groups. Study group had higher cesarean rates and higher condom usage which may be in parallel with high income and may affect the HPV results. On the other hand, we had no patients with atopic dermatitis. It was thought to be related with preference of those patients to dermatology department mainly in our country.

In another different relationship between asthma and HPV was genetic control mechanism via serine/arginine rich splicing factors (SRSFs) (22,23). Those studies showed that SRSF2 and SRSF3 were important modulators of HPV16 for protein expression and maintenance of cervical tumor (22,23). Interestingly linked, SRSF6 was reported a trigger of asthma in horses and they also claimed that new therapy methods could be tried due splicing factors in asthma (24). The relationship between HPV and asthma seems complicated and larger, future studies are needed.

In a recent study, they analyzed the expression of HPV capsid protein by immunohistochemistry, for presence of HPV DNA via polymerase chain reaction in placenta specimens with villitis of unknown etiology (VUE) and chronic deciduitis with plasma cells (CD) (25). VUE and CD in miscarriage, preterm delivery, and adverse pregnancy outcome are supposed to be non infectious placental lesions caused by a pathologic immune reaction similar to a host versus graft mechanism and the frequent detection of autoimmune diseases in the VUE was 21% with atopic disease, 15.5% with other autoimmune disease, 10.5% with thrombophilia (25). Finally, the results show that a causal role for HPV in the development of VUE and CD is unlikely. A pathologic immune reaction is more probable since clinical signs of infection are usually not seen in association with the mentioned chronic inflammatory lesions (26). Therefore, the inflammation caused by autoimmune disease are not correlated with HPV in line with our smear test results.

As for the limitations, it was not a long follow-up study. The mean ages of the all participants were between 41 and 42. Therefore, HPV reports may change in years due to immune system and treatments. Second, patient population was small compared to retrospective studies.

A major strength of the present study was being the first study evaluating HPV results in women regarding "atopia" title that involves allergic asthma, rhinitis or both.

CONCLUSION

The significance of human papilloma virus as an etiologic factor in cancers among immun suppressive treated patients is known but for atopic disease it is unclear and still subject of debate. Our results showed that HPV positivity in smear test was not associated with atopic disease. Although HPV vaccination should still be encouraged to prevent carcinoma of the cervix, there is no

need to different and extra screening schedules for patients with atopic diseases such as asthma, rhinitis or urticaria.

Ethics Committee Approval: Ethics committee approval was received for this study from the Clinical Trials Ethics Committee of City Education and Research Hospital (decree number: 494/2019).

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REFERENCES

- 1- Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *CA Cancer J Clin.* 2019; 69:7-34. [\[Crossref\]](#)
- 2- Schiffman M, Bauer HM, Hoover RN, Glass AG, Cadell DM, Rush BB, et al. Epidemiologic evidence showing that human Papillomavirus infection causes most cervical intraepithelial neoplasia. *J Natl Cancer Inst* 1993; 85:958-64. [\[Crossref\]](#)
- 3- Wang R, Pan W, Jin L, Huang W, Li Y, Wu D, et al. Human papillomavirus vaccine against cervical cancer: Opportunity and challenge. *Cancer Lett.* 2020; 471:88-102. [\[Crossref\]](#)
- 4- Yıldırım D. Gökaslan H. Serviks kanseri taramasında HPV DNA testinin yeri. *Türk Jinekolojik Onkoloji Dergisi* 2015; 1:1-6.
- 5- Ozgul N, Tuncer M, Abacioglu M, Gultekin M. Estimating Prevalence of Genital Warts in Turkey: Survey among KETEM-affiliated Gynecologists across Turkey. *Asian Pacific J Cancer Prev*, 2011;12:2397-440. [\[Crossref\]](#)
- 6- Sheu BC, Chang WC, Lin HH, Chow SN, Huang SC. Immune concept of human papillomaviruses and related antigens in local cancer milieu of human cervical neoplasia. *J. Obstet. Gynaecol*, 2007; 33:103- 13. [\[Crossref\]](#)
- 7- Raposo A, Tani C, Costa J, Mosca M. Human papillomavirus infection and cervical lesions in rheumatic diseases: a systematic review. *Acta Reumatol Port* 2016; 41: 184-90. [\[Crossref\]](#)
- 8- Shi LH, Huang JY, Liu YZ, Chiou JY, Wu R, Wei JCC. Risk of systemic lupus erythematosus in patients with human papillomavirus infection: a population-based retrospective cohort study. *Lupus* 2018; 27: 2279-83. [\[Crossref\]](#)
- 9- Eyerich K, Novak N. Immunology of atopic eczema: overcoming the Th1/Th2 paradigm. *Allergy.* 2013; 68:974-82. [\[Crossref\]](#)
- 10- Garritsen F.M., Verheijen R.H.M., Gerestein C.G., Van Zuilen A.D., Oosterhaven J.A.F., Van Dijk M. et al. Is there an in-

- creased risk of cervical neoplasia in atopic dermatitis patients treated with oral immunosuppressive drugs? *J EADV* 2018; 32:271-75. [\[Crossref\]](#)
- 11- Morgan TK, Hanifin J, Mahmood M, Larson B, Baig-Lewis S, Long T, et al. Atopic Dermatitis Is Associated With Cervical High Risk Human Papillomavirus Infection? *J Lower Gen Tract Dis* 2015;19: 345-59. [\[Crossref\]](#)
 - 12- Montgomery S, Ehlin A, Sparen P, Bjorksten B, Ekborn A. Childhood indicators of susceptibility to subsequent cervical cancer. *Br J Cancer* 2002; 87:989-93. [\[Crossref\]](#)
 - 13- Morrison EA, Dole P, Sun XW, Stern L, Wright TC Jr. Low prevalence of human papillomavirus infection of the cervix in renal transplant recipients. *Nephrol Dial Transplant*. 1996; 11:1603-06. [\[Crossref\]](#)
 - 14- Pietrzak B, Mazanowska N, Ekiel AM, Durlik M, Martirosian G, Wielgos M, et al. Prevalence of high-risk human papillomavirus cervical infection in female kidney graft recipients: an observational study. *Virology*. 2012; 9:117.
 - 15- Origoni M, Stefani C, Dell'Antonio G, Carminati G, Parma M, Candiani M. Cervical Human Papillomavirus in transplanted Italian women: a long-term prospective follow-up study. *J Clin Virol*. 2011; 51:250-54. [\[Crossref\]](#)
 - 16- Meeuwis KA, Melchers WJ, Bouten H, van de Kerkhof PC, Hinten F, Quint WG, et al. Anogenital Malignancies in Women After Renal Transplantation Over 40 Years in a Single Center. *Transplantation*. 2012; 93:914-22. [\[Crossref\]](#)
 - 17- Kim SC, Glynn RJ, Giovannucci E, Hernández-Díaz S, Liu J, Feldman S, et al. Risk of high-grade cervical dysplasia and cervical cancer in women with systemic inflammatory diseases: a population-based cohort study. *Ann Rheum Dis*. 2015; 74:1360-67. [\[Crossref\]](#)
 - 18- Sugita K, Kabashima K. Tight junctions in the development of asthma, chronic rhinosinusitis, atopic dermatitis, eosinophilic esophagitis, and inflammatory bowel diseases. *J Leukoc Biol*. 2020 Feb 28. [\[Crossref\]](#)
 - 19- Brusselle GG, Maes T, Bracke KR. Bedside to bench: eosinophilic airway inflammation in nonallergic asthma. *Nat Med* 2013; 19: 977-79. [\[Crossref\]](#)
 - 20- Deligeoroglou E, Giannouli A, Athanasopoulos N, Karountzos V, Vatopoulou A, Dimopoulos K, et al. HPV infection: immunological aspects and their utility in future therapy. *Infect Dis Obstet Gynecol* 2013; 2013: 540850. [\[Crossref\]](#)
 - 21- Ong PY, Ohtake T, Brandt C, Strickland I, Boguniewicz M, Ganz T, et al. Endogenous antimicrobial peptides and skin infections in atopic dermatitis. *N Engl J Med*. 2002; 347:1151-60. [\[Crossref\]](#)
 - 22- McFarlane M, MacDonald AI, Stevenson A, Graham SV2. Human Papillomavirus 16 Oncoprotein Expression Is Controlled by the Cellular Splicing Factor SRSF2 (SC35). *J Virol*. 2015; 89:5276-87. [\[Crossref\]](#)
 - 23- Klymenko T, Hernandez-Lopez H, MacDonald AI, Bodily JM, Graham SV. Human Papillomavirus E2 Regulates SRSF3 (SRp20) To Promote Capsid Protein Expression in Infected Differentiated Keratinocytes. *J Virol*. 2016; 90:5047-58. [\[Crossref\]](#)
 - 24- Issouf M, Vargas A, Boivin R, Lavoie JP. SRSF6 is upregulated in asthmatic horses and involved in the MYH11 SMB expression. *Physiol Rep*. 2018; 20:13896. [\[Crossref\]](#)
 - 25- Feist H, Hussein K, Stucki-Koch A, Wohlschlaeger J, Hager T, Blöcker T, et al. Villitis of unknown etiology and chronic deciduitis are not associated with human papilloma virus and enterovirus infection. *Virchows Arch*. 2020; 1:73-81. [\[Crossref\]](#)
 - 26- Kim CJ, Romero R, Chaemsathong P, Kim JS. Chronic inflammation of the placenta: definition, classification, pathogenesis, and clinical significance. *Am J Obstet Gynecol*. 2015; 4:53-69. [\[Crossref\]](#)