Association between Human papillomavirus infection and abnormal cytopathology of uterine cervix in Baghdad women

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ABSTRACT

Background: Human papillomavirus (HPV) is considered one of sexually transferred disease in the world and it is considered as one of the causative agents of cervical cancer. Cervical cytology is used widely as the initial tool in cervical cancer screening worldwide. **Objective**: The purpose of this study was to analyze the correlation between cytological findings from Papanicolaou (pap.)-stained cervical smears and cases of HPV infection of the uterine cervix as identified by Polymerase Chain Reaction (PCR) testing. **Methodology**: Between June 2021 and December 2022, retrospective study for cervical smears of 370 Baghdad women (attending to the Central Public Health Laboratory (CPHL)/Ministry of Health in Baghdad) were stained by the Pap procedure and categorized by the Bethesda classification system, High Risk-Human papilloma Virus (HR-HPV) detection was used to analyze the HPV status of the cervical samples that were collected **Results**: HR-HPV testing was done for 370 women (230 women that have shown Positive results for HR-HPV and 140 were negative for HPV). Our result showed highly significant differences at ($P \leq 0.01$) for HR-HPV genotype and abnormal Pap smear with High grade squamous intraepithelial lesion (HSIL) at 23.9 %, while it was at 41.3% with low grade squamous intraepithelial lesion (LSIL) Pap smear which represent the highest rate, in addition to 34.7% for abnormal Pap smear with atypical squamous cells of undetermined significance (ASCUS) classification **Conclusion**: This study has shown that molecular investigation for HR-HPV might be essential for diagnosis of patients with proven epithelial abnormality in their Pap smears.

Keywords: Human Papilloma virus (HPV), Pap smear, abnormal cervical findings (cytological changings).

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INTRODUCTION

One of the most prevalent cancers in women is cervical cancer, which represent 80 percent of new cases in developing nations (1). Effective screening and treatment programs could help lower the high global mortality rate of 52% from cervical cancer (2). Screening will continue to be crucial even with more research being done on the Human Papilloma Virus (HPV) and the advent of HPV vaccinations to prevent infection and the development of cervical cancer (3).

When identifying precancerous lesions, HPV testing is more frequently performed than the Pap test. The HPV test detects cancer-causing viruses. However, some gynecologists continue to employ Pap smears in addition to HPV tests because they think that HPV tests alone can miss unknown viruses that cause cancer (4). Nonetheless, the body of research favors adding HPV testing to screening; so, going forward, the fundamental decision is between contesting and primary HPV testing only (4). Given that HPV is recognized to be the cause of the majority of cervical malignancies, there is well-established evidence linking HPV to cervical squamous cell carcinoma (CSCC) (5).

Cytological screening, which includes doctor-administered cervical samples and directed inspections that are analyzed by a qualified cytopathologist, has successfully suppressed cervical cancer in developed nations. On the other hand, cervical cancer is most communal in low- and middle-income nations (6) .The placenta, trophoblasts, and/or cytotrophoblasts may get infected with a variety of human viruses following viremia or an ascendant infection, including the adenovirus, adeno-associated virus, dengue virus, cytomegalovirus (CMV), zika virus, and the herpes simplex viruses 1 and 2 (7). Pregnancy outcomes may be impacted by the human papillomavirus (HPV), according to prior research (8). The human papillomavirus, or HPV, is an established cause of cervical cancer. Small, double-stranded, circular DNA genome of the HPV virus is around 7900 bp long and contains eight overlapping open reading frames make up the more than 180 recognized HPV-types, which are divided into early (E) and late (L) reading frames. Genes as well as a lengthy untranslated regulatory region. The major and minor capsid proteins are encoded by the L1 and L2 genes. About 12 molecules of L2 and 72 pentamers of L1 are present in the capsid. Some of the early genes have the ability to change, and they regulate late viral replication (9).

There are more than 220 distinct varieties of the DNA virus known as HPV (10). HPVs can be classified into two separate groups based on their carcinogenic potential: (i) high-risk HPVs (HR-HPVs) and (ii) low-risk HPVs (LRHPVs). The most important oncogenic viruses linked to the development of anogenital and upper respiratory tract malignancies are HR-HPVs, which include HPV16–18 (11) .HPVs can be detected by qualitative polymerase chain reaction (PCR) of cervical samples to identify particular genotypes of viruses (12) after a positive Papanicolaou (PAP) test. HPV viruses are one of the most common sexually transmitted viral infections among men and women of reproductive age worldwide (13). These viruses were detected in cytological samples of healthy females international and have an occurrence of approximately 12% (14). Current evidence indicates that HPV might potentially impact productiveness, clinical pregnancy rates of medically aided reproductive technology (MAR), and pregnancy (15, 16).

HPV genotyping and koilocytic (sequamous epithelial cells with perinuclear cavitation and nuclear features) cytological changes, giving varying degrees of modifications that can be present in cells that are separate from abnormal cells (by cytological specialties) but are not clear and are considered in many cases as a sign of HPV infection. This change is called unspecified atypical squamous cells. Significance (ASCUS) in addition to dysplasia (an increase in abnormal cell growth or development), ranging from mild dysplasia/low-grade squamous cell injury (LSIL), moderate and severe dysplasia/high-grade squamous cell injury (HSIL) (17). Pap test results can be histologically described according to the classification system of cervical intraepithelial neoplasia (CIN) (developed in 1968: CIN I, CIN II, CIN III) concurring to the degree of expansion of atypical basal cells and the nearness of mitotic figures (17).

The goal of research was to analyze the relationship between Human Papillomavirus (HPV) infections of uterine cervix by (HPV typing) and cytopathology results of Papanicolaou (Pap.) stained cervical smears.

METHODOLOGY

1- Study design

The study design will be retrospective cross sectional with analytical component by analyzing results database from Central Public Health Laboratories (CPHL) in Baghdad, Iraq. During period from January 2021 to December 2022. Data will be collected during 2024 and about 370 patients (their ages range between (20-48 years)), Patient`s medical history and HPV test with pap smear results were collected from CPHL records from women whose complaining from many gynecological problems (post-coital bleeding, vaginal discharge and warts). Exclusion criteria included (Menstrual period and the use of any vaginal medication within the last 24 h)

- Ethical issues: All data concerning patient`s personal details were protected.
- Specimen collection techniques.

Two types of samples were collected from each patient (Females may be healthy or not) at the same time by trained laboratory personnel, First sample was taken by using cervical swabs, the cervix was exposed using a sterile disposable speculum, remove of excess mucus from the cervical canal and nearby ectocervix was done by using a sterile cotton swab, and a cervical swab was inserted 1.0-1.5 centimeters into the cervical canal and rotated 4 to 5 times in a counterclockwise direction to obtain a sufficient amount of cervical epithelial cells that was transferred into

viral transport medium (Citotest Labware Manufacturing, China) .

The second (cytological) sample was taken from exo-cervix and cervical canal using Ayre`s spatula and cytological smears were arranged by obsession on a microscope slide and stained using Pap technique. After staining microscopical analysis was performed by specialist pathologist (using Olympus BX41 microscope).

The characteristics of benign and malignant cervical cells and other pathological changes were observed based on the morphological characteristics of the cells, the results were presented according to the terminology of the 2001 Bethesda system as follows (18):

- Negative for Intraepithelial Lesion or Malignancy (NILM)
- Atypical Squamous Cells of Undetermined Significance (ASCUS)
- Low grade Squamous Intraepithelial Lesion (LSIL)
- High grade Squamous Intraepithelial Lesion (HSIL)

2- HPV Study (DNA preparation)

Viral DNA was isolated from cervical cells for molecular detection by using a DNA extraction kit (Sacace Biotechnologies, Italy). Samples on cervical swabs were eluted; 100µl of elution was transferred to a 1.5 ml Eppendorf centrifuge tube and added 300µl of Lysis solution, then vortex and incubate 5 min at 65ºC after that centrifuge for 5 min at 16000xg. Added 20µl of the sorbent to the tube, vortex for 5-7 sec, and incubated for 3 min at room temperature, then centrifuge at 5000xg/ 30 sec. After that added 500µl washing solution for each tube, vortex, and centrifuge for 30sec/10000xg then discard supernatant, repeated the wash step, and incubated tubes with an open cap for 5-10 min at 65ºC. Finally re-suspend the pellet in 100µl of DNA eluent, incubated for 5 min/65ºC and vortex periodically, then centrifuge tube for 1 min/12000xg, which were transferred the supernatant into new sterile 0.5 ml tubes (19).

3- High-risk HPV Genotype Amplification

For detection of High-Risk HPV genotype used RT-PCR (Multiplex PCR) was carried out by using specific HPV genotypes 14 Real-TM kit (SACACE biotechnologies® HPV 14 Screening & 16, 18, 45 Typing Real-TM Quant, Italy. For amplification, prepare 4 tubes for each clinical sample, 4 tubes for standards K1, 4 tubes for standards K2, 4 tubes for Negative control. The final reaction volume was 25µl containing: 10µl of specific primers (PCR-mix 1 “16,18,31, IC”, PRC-mix 2 “39,45,59, IC”, PRC-mix 3 “33,35,56,68”, PCR-mix 4 “51,52,58,66”) each PCR mix represent specific dye, 5µl of mix-PCR-Buffer-FRT and DNA-polymerase, 10 µl of extracted DNA sample).

The test used for quantitative or qualitative detection for the most widespread and oncogenic14 genotypes of human papillomavirus (genotype 16, genotype 18, genotype 31, genotype 33, genotype 35, genotype 39, genotype 45, genotype 51, genotype 52, genotype 56, genotype 58, genotype 59, genotype 66, and genotype 68) with a determination of clinical significance according to the manufacturer’s instructions that use. Amplification was performed using 7500 Applied Biosystems by Thermo Fisher Scientific PCR amplification instrument.

A specific program designed by the kit for optimal detection was performed using RT-PCR. Reaction conditions were: The DNA template was amplified in 5 cycles of programmed denaturation for 5 second at 95°C, primer annealing at 60°C programmed for 20 second and extension at 72°C for 15seconds and for 40 cycles of programmed denaturation for 5 second at 95°C, programmed primer annealing at 60°C for 30 seconds and extension at 72°C for 15seconds Fluorescence data were collected during every expansion step. This program is executed according to package guidelines for optimal target detection (19).

4- Statistical Analysis:

The Statistical Analysis System- SAS (2018) program was used to detect the consequence of different factors on study parameters. The chi-square test will be used to evaluate the association which significantly compare between ratios ($P \leq 0.01$probability) (20).

RESULTS

In this study 370 patients with abnormal Cytological findings have been included. Women`s mean age was (26) and the age range was 20 to 48 years. The results presented that 46% of the patient aged (20-30 years), 36% aged (31-40 years), whereas the remaining of the age group indicates 18% of aged (41-48 years).

Table (1) showed that there was significant association between HPV distribution from one side, and abnormal Pap smear in other side. This result revealed highly significant differences at ($P \leq 0.01$) for HR-HPV genotype and abnormal Pap smear with High grade (HSIL) at 23.9 %, while it was at 41.3% with low grade (LSIL) pap smear which represent the highest rate, in addition to 34.7% for abnormal pap smear with ASCUS classification (Figures (1,2,3).

Table (1): Distribution of HPV infection according to Cytological examination of Baghdad Women

Cytopathology	(HPV +)	Percentage (%)	(HPV-)	Percentage (%)
Ascus.	80	34.7 %	65	46.4 %
LSIL	95	41.3 %	45	32.1%
HSIL	55	23.9 %	30	21.4%
Total	230	--	140	--
Chi-square	--	10.783 **	--	13.361 **
P-value	--	0.0046	--	0.0003
** (P≤0.01).				

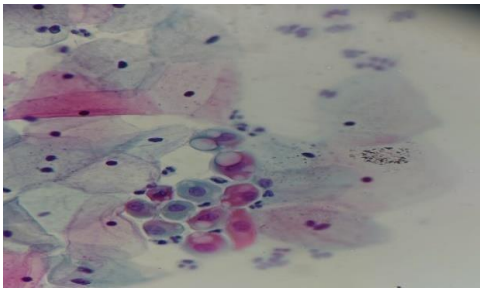

Figure (1): Cervicovaginal smear showing atypical squamous cells of undetermined significance (ASCUS) (Conventional Smear, Papanicolaou stain, ×Medium Power)

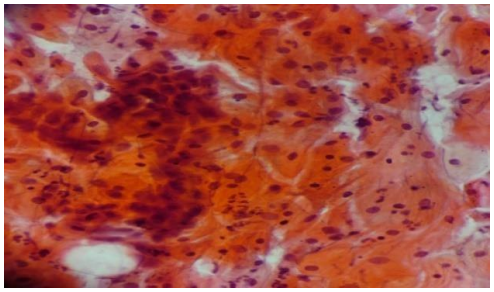

Figure (2): Cervicovaginal smear showing Low-grade squamous intraepithelial lesion (LSIL) (Conventional Smear, Papanicolaou stain, ×Medium Power)

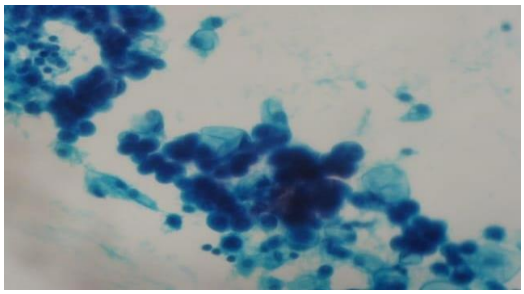

Figure (3): Cervicovaginal smear showing High-grade squamous intraepithelial lesion (HSIL) (Conventional Smear, Papanicolaou stain, ×Medium Power)

This finding showed significant differences in patients with abnormal cytopathological results with negative HPV genotyping. ASCUS gave the highest percentage (46.4%), while LSIL showed low percentage (32.1%) and the lowest percentage was in the HSIL category (21.4%).

Current study utilized Multiplex Real-Time PCR (7500 Applied Biosystems by Thermo Fisher Scientific) technique for identifying the qualitative detection of HR-HPV by targeting the E1-E7 early genes and L1-L2 late genes a particular set of primers is used to identify the HR-HPV region and specifically designed probe. The results showed that out of 370 patients undergoing HPV genotyping test, 230 of them were positive for HPV test. Channel FAM fluorophore was used (Figures 4 and 5), to detect the internal control gene for Epithelial cells in the samples (Internal control represent, specimen with DNA were introduced for PCR for human β-globin gene amplification, determined according to the dye that represent human β-globin gene)

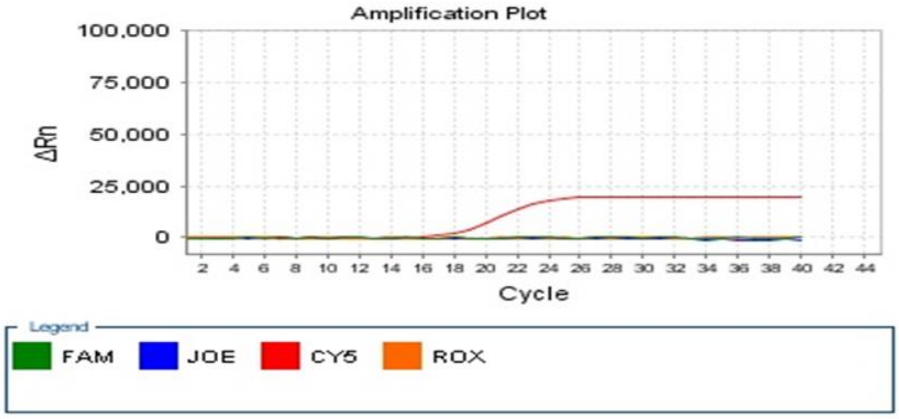

Figure (4): Amplification curves were obtained from the target DNA in semi-logarithmic view. The curve represents an internal control gene for epithelial cells in cervical swabs as general detection in Channel for CY5 fluorophore

The HPV Genotyping kit for HR-HPV detection was used for the qualitative detection and genotyping for 14 types (16 ,18 ,31 , 33 , 35 ,39 ,45 , 51 , 52 , 56 , 58 , 59 ,66 and 68) , taking into account that 16 & 18 genotypes were the utmost superabundant in cases extending from cervical variations from the normal to cervical carcinoma. The kit for HR-HPV Detection comprises two steps, isolation of DNA from tests and multiplex Real Time amplification of the specimen. The kit used four channels for interpretation four various kinds of dyes (FAM, ROX, CY5 and JOE) specific primers (PCR-mix 1 “16,18,31, IC”, PRC-mix 2 “39,45,59, IC”, PRC-mix 3 “33,35,56,68”, PCR-mix 4 “51,52,58,66”) each PCR mix represent specific dye to detect 14 HPV genotypes and the internal control gene Beta-Globin correspondingly.

As exposed in figure (5). Channels used for detection of HR-HPV types then the internal control gene include Fluorescence channel Color Target JOE (blue) HPV 31, FAM (Green) for HPV 16 and CY5 (red) Internal control, while in Figures (6) Fluorescence channel Color Target ROX (Orange) for HPV 18 and CY5 (Red) as Internal control, and in figure (7) appears JOE (Blue) for HPV45, ROX (Orange) for HPV 59 and CY5(Red) Internal control (The color of the internal control and HPV target can change according to instrument`s user but without change the target) . Then Cycle threshold (CT) values were measured through the of the device`s Thermal cycler report for each channel to approve the type of sample, as well as whether each data is positive or negative of HR-HPV. By examining the outcomes of real-time PCR for HPV16, , 18, 31, 45 and 59 genotyping and qualitative detection, it was shown that two detections of data were available for the cycling channels (Per dye figure) as presented in Figures (5,6,7).

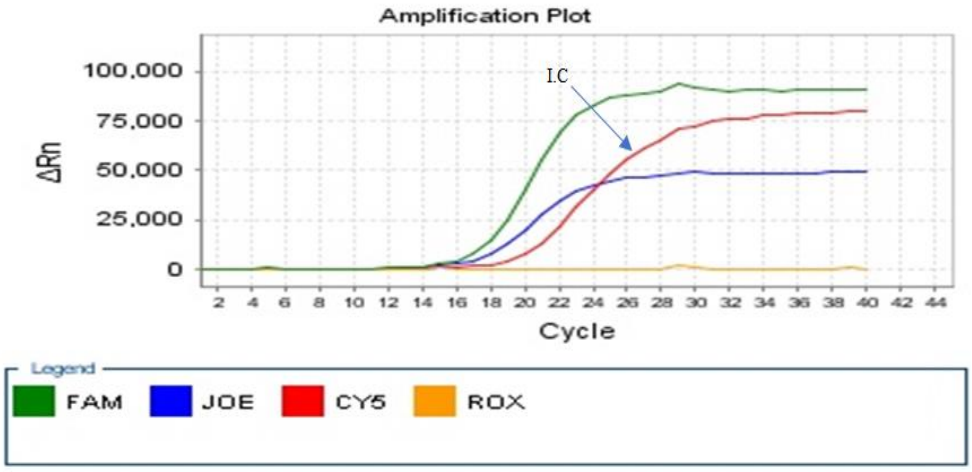

Figure (5): Genotyping of HPV, channel for FAM (Green) fluorophore (HPV 16), JOE (blue) HPV 31. Each curve characterizes as positive specimen and CY5 (Red) cannel is curve for I.C: Positive for interior control.

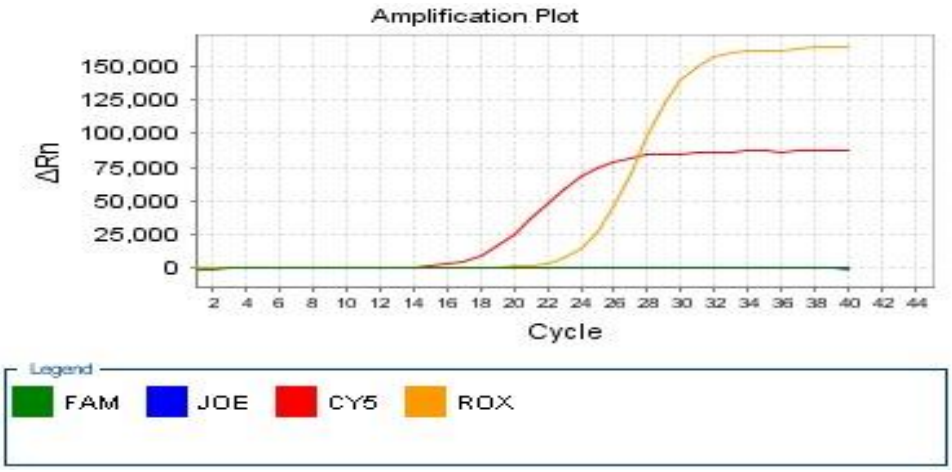

Figure (6): Genotyping of HPV, channel for Rox fluorophore (HPV 18). Orange curve characterizes a specimen positive, (CY5) Red curve for I.C: Positive for Internal control.

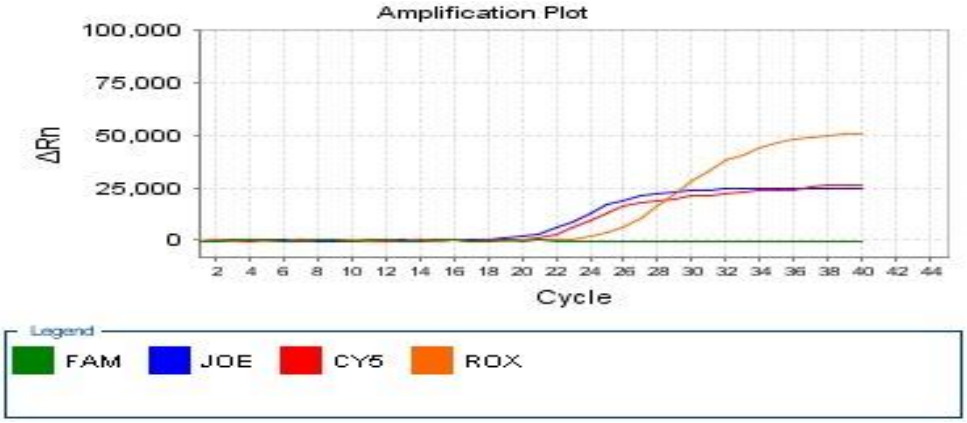

Figure (7): HR-HPV Genotyping, channel for JOE fluorophore (HPV 45), Rox fluorophore (HPV 59). Blue and Orange curve characterizes as Specimen positive, CY5 (Red) I. C curve: Positive for internal control.

Detection of RT-PCR results showed that 240 samples from women complaining from cervical problems were positive with high-risk HPV and showed positive results for 14 HPV genotype. Between HPV infection group, there has been high percentage of HR-HPV genotype 16 and genotype 18 (that is considered main causes of cervical cancer in the world), which was 12.6% for HR-HPV 16 and 9.13% for HPV18, and the maximum percentage was among persons with high grade lesions (HSIL) . Then other genotypes showed results distributed according to different rates as shown in table (2).

Table (2): The distribution of HR-HPV genotype in women with abnormal cervical smear

HPV Genotype	Number Pt.	Percentage %
Genotype 16	29	12.6 %
Genotype 18	21	9.1 %
Genotype 45	14	6 %
Genotype 31	17	7.5 %
Genotype 33	16	7 %
Genotype 35	14	6 %
Genotype 39	16	7 %
Genotype 51	15	6.5 %
Genotype 52	14	6 %
Genotype 56	16	7 %
Genotype 58	15	6.5%
Genotype 59	16	7 %
Genotype 66	14	6 %
Genotype 68	13	5.8 %
Total	230	100%

DISSCUSION

HR-HPV is one of most sexually transmitted viral disease among human in reproductive age (21). In this study, it investigated association between HPV infections and Cytological findings.There were at least fourteen distinct high-risk HPV varieties, and oncogenic human papillomavirus (HPV) infections were linked to over 95% of cases of cervical cancer (22).

RT-PCR detection results showed that 240 samples from women complaining from cervical problems were positive with high-risk HPV, according to data obtained from the Molecular Biology unit in (CPHL) /Public health/Baghdad. In HPV positive group, it has been shown that high percentage were of 16 and 18 genotypes that was considered main causes of cervical cancer in the world, this result was agreed with other studies that 36% of the population had HPV 16, 18, and that the highest percentage was found in people with high grade lesions (HSIL) (22). Moreover, all 55 cases of High grade (HSIL) also tested positive for HRHPV attendance with genotype18 noticed in 12 cases, whereas type16 was detected in 23 cases in HPV infection patients. The periodical of Arbyn`s study *et al*., associated the accurateness of HPV testing against that of repeated cytology detection of fundamental

cervical intraepithelial neoplasia of grade two or worse (LSIL) or grade three or worse (HSIL) in women with squamous intraepithelial lesions. The writers suggested that HPV testing may be suggested to triage women with ASCUS because it has developed correctness (significantly higher sensitivity and similar specificity) than repeated cytology. They likewise pointed, and then when triaging women with LSIL, an HPV testing gives higher sensitivity significant, but specificity was significantly lower, compared to repeated cytology (23). Furthermore, pre-cancerous circumstances in this study included 230 cases that alternated from atypical squamous cells of undetermined significance (ASCUS) reaching to high-grade squamous intraepithelial lesions (HSIL).

Current study results showed a highly significant association among HR-HPV infections and cytological results and that supports the claim that carcinogenic kinds of HPV are related with development of lesions to aggressive cervical tumor (24). Results have shown that high percentage of these infections for HR-HPV were instigated by whichever HPV genotypes 16 or 18 which agreed with local study that proved around (62%) of HPV infections were initiated by whichever HPV genotype 16 or 18 of the virus (18). Another study proved about 80% of cases ranging from cervical intraepithelial neoplasia of the second grade to cervical carcinoma in Malawi was positive for HR-HPV types 16 and 18 (25). According to these findings 140 patients showed negative results for HPV genotypes test with abnormal changes in Cytopathological examination but these changes were less than those with positive HPV genotypes test. Furthermore, the negative HPV cases showed high rates of ASCUS classification, while in positive HPV cases; the highest percentage of abnormal cytological changes was of LSIL type.

The relatively low sensitivity of cytological tests might be due to personal error in examination or in sample collection or other causes. These results were in agreement with additional study that aimed to estimation impact of follow-up of HPV testing after initial ASCUS diagnosis in 287 patients which demonstrated that HPV infections were communal in teenagers and suggested that HPV test positive alone it was impossible to predict which case will change into invasive carcinoma (26). Moreover, it has also been claimed that there was unclear whether the HPV DNA test decreases the occurrence of cervical cancer associated to cervical cytology and as such, the potential risks associated with false positives rise, this necessitates a thorough evaluation of the advantages and potential drawbacks of making a diagnosis based only on HPV DNA screening is required (27).

CONCLUSION

Results of the study provide evidence of the role of HPV infection in cervical carcinogenesis. Further studies are needed to test the effectiveness of adding HR-HPV screening to Pap test to increase the sensitivity of primary screening for cervical cancer. This study has shown that molecular investigation for HR-HPV might be essential for diagnosis of patients with proven epithelial abnormality in their Pap smears.

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العلاقة بين الاصابة بفيروس الورم الحليمي البشري والمرض الخلوي غير الطبيعي لعنق الرحم لدى نساء في بغداد

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الخلاصة:

خلفية عن الموضوع: يعتبر فيروس الورم الحليمي البشري (HPV) احد الامراض المنقولة جنسيا في العالم ويعتبر احد العوامل المسببة لسرطان عنق الرحم. استخدام علم الخلايا في عنق الرحم على نطاق واسع كأداة أولية في فحص سرطان عنق الرحم في جميع انحاء العالم. **الهدف من الدراسة**: كان الغرض من هذه الدراسة تحليل العلاقة بين النتائج الخلوية من مسحات عنق الرحم (.Papanicolaou (pap وحالات الاصابة بفيروس الورم الحليمي البشري في عنق الرحم كما تم تحديدها من خلال اختبار تفاعل البوليميراز المتسلسل. (PCR) بين يونيو 2021 وديسمبر 2022 .**المواد طرق العمل:** اجريت دراسة بأثر رجعي على مسحات عنق الرحم ل 370 امرأة من بغداد (اللاتي يحضرن الى مختبر الصحة العامة المركزي/ وزارة الصحة العراقية في بغداد) تم صبغها بأجراء مسحة عنق الرحم وتصنيفها بواسطة نظام تصنيف Bethesda وتم الكشف عن فيروس الورم الحليمي البشري عالي الخطورة (HR-HPV) لتحليل حالة الفيروس لعينات عنق الرحم التي تم جمعها .**النتائج**: تم اجراء اختبار الكشف عن فيروس الورم الحليمي (HR-HPV) ل 370 امرأة، اظهرت النتائج (230 من امرأة اعطت نتائج موجبة للفيروس و 140 امرأة كانت سلبية للفيروس . اظهرت نتائجنا وجود فروق ذات دلالة احصائية عالية عند ($P \leq 0.01$) للتنميط الجيني لفيروس الورم الحليمي HR- HPVومسحة عنق الرحم غير الطبيعية ذات التغير الخلوي العالي بنسبة 23.9 % ، في حين كانت بنسبة 41.3% مع مسحة عنق الرحم منخفضة التغيير الخلوي والتي تمثل اعلى معدل. بالاضافة الى 34.7% لمسحة عنق الرحم بخلايا حرشفية غير نموذجية. (ASCUS) **الاستنتاج:** اظهرت هذه الدراسة ان الفحص الجزيئي قد يكون ضروريا لتشخيص المرضى الذين يعانون من خلل في الانسجة الظهارية مثبتة في مسحات عنق الرحم.

الكلمات المفتاحية: فيروس الورم الحليمي البشري، مسحة عنق الرحم ، نتائج الفحص الخلوي غير الطبيعية.