Effect of *Neisseria gonorrhea* Infection on Gene Expression of *p53* and *cIAP2* Genes in Cervical Cancer

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ABSTRACT

Background: *Neisseria gonorrhoeae* (*N. gonorrhea*) is one of the most common bacterial infections causing health problems in the epithelial lining of the cervix. Previous studies did not adequately address its role in cervical cancer (CEC), therefore, the current study aimed to determine the impact of *N. gonorrhea* infection on gene expression of *p53* and *cIAP2* in CEC. **Materials and Methods**: samples were collected from 20 women suffering from cervical cancer with *N. gonorrhea* infection (CC-NG), and 20 women who had cervical cancer without *N. gonorrhea* infection (CC) and 40 healthy women as the control group. *N. gonorrhea* diagnosis was done by Modified Thayer-Martin (MTM) agar and gram stain. Gene expression of *p53* and *cIAP2* was carried out using real-time PCR. **Results**: *P53* and *cIAP2* genes had high molecular expression (folding change) in CC-NG (17.172 and 31.135 respectively) and CC (16.02 and 15.45 respectively) compared to healthy control (1.00) (P>0.05). Moreover, when the expression of both genetic indicators was compared to each other an increase in gene transcription in the cases of CC-NG compared to CC was observed. The antibiotic resistance pattern for the tested *Neisseria gonorrhoeae strains was as follows:* to ceftriaxone (100%), penicillin (96%), amoxicillin (90%), tetracycline (89%) and ciprofloxacin (77%) but low to cefixime (4%), spectinomycin (5%) and azithromycin (9 2%). **Conclusion**: *N. gonorrhea* infection can be determine as risk factor for CEC development.

Keywords: ***Neisseria gonorrhea*, Gene Expression, *p53*, *cIAP2*, Cervical Cancer**

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1-INTRODUCTION

Around the world, CEC is the fourth most common cancer that leads to death. About 80% of cervical malignant growth cases happen in developing countries (1). Over the course of the last many years, the presentation of growth screening programs in some developed countries added to decreased frequency and mortality because of CEC (2). Collection of hereditary, mutation, and epigenetic adjustments after some time might be vital for a definitive cancer progression. P53 is a tumor suppressor gene and transformations of *P53* gene quality are among the most well-known hereditary modifications in numerous human malignancies (3). Over half of human cancers contain a transformation or cancellation of the *P53* mutation, going from 5 to 80% depending upon the sort, stage, and etiology of growth. Many examinations have explored a hereditary connection between these varieties and tumor defenselessness (4). Human papillomavirus (HPV)-initiated cervical malignant growth driven by the evident infection of oncoproteins E6 and E7. The E6 protein of HPV types 16 and 18 connects with E3 ubiquitin-protein ligase, bringing about the proteolysis of p53 protein (5). Most of the studies are directed towards explaining the pathological mechanism of HPV on the gene expression of *p53* (6).

Neisseria gonorrhea is a Gram-negative diplococcus responsible for the sexually transmitted disease. Infection of the female genital plot by this microbe is confined to the cervix, in both endocervical and ectocervical epithelial cells (7). Epithelial cells are the primary inducers and coordinators of the early natural insusceptible reaction during mucosal infection (8,9). Epithelial cells support the tissue-resistant microenvironment by delivering cytokines and chemokines (10). Suggests that the prevalence of cervical cancer in some subregions may be partly attributable to increased cervical inflammation resulting from a higher susceptibility to infection of the cervix by sexually transmitted infections (11).

A previous study reported that *N. gonorrhoeae* induces human endocervical epithelial cells to–constitutively expand the inhibitor of apoptosis-2(cIAP2)(12). cIAP1 and cIAP2 were initially recognized as restricting accomplices for the TNF-related factors 1 and 2 (TRAF1 and TRAF2), and a few investigations have recommended that cIAP1, cIAP2, and TRAF2 practically related (13). Regardless, the exact cell elements of cIAP1 and cIAP2 have stayed mysterious. Late-stage examinations showed that chromosomal regions carrying cIAP1 and cIAP2 expression are expressed in a few human cancers and that overexpression of these expressions was clearly associated with xenograft motility in mice (14). Unfortunately, we did not find studies on the *cIAP2* gene's relationship with CEC and the effect of bacteria on its effectiveness. Hence, understanding how these proteins function in tolerogenicity and contribute to malignant growth kinetics is a great need (15).

Finally, it must be mentioned that *N. gonorrhea* has not been sufficiently studied as a cause of cervical cancer, and its role as an epigenetic or mutant factor in stimulating or inhibiting some genes responsible for the occurrence of cancer is very limited. Therefore, this current study aims to determine the effect of *N. gonorrhea* infection on the gene expression of *p53* and *cIAP2* in CEC.

2- MATERIAL AND METHODS

Study design and sample collection: The current study is a case-control study that included sample collection from 20 women suffering from cervical cancer who had *N. gonorrhea* infection and 20 women who had cervical cancer but did not suffer from NG infection. Inclusion criteria of case choices included: age from 40-70 years, not having other types of cancer, not having HPV infection, and not having chronic diseases. Samples were collected from governmental hospitals and outpatient clinics in Diwaniyah Governorate/Iraq during the period from January 2022 to March 2023. The current study also included 40 healthy women who did not suffer from any type of cancer or infections in the genital-urinary tract as a control group. The samples included blood and swabs from the cervix, and consent was taken from all participants before sampling.

Bacterial isolates: *N. gonorrhea* diagnosed by roll swab directly on MTM medium in a large "Z" pattern to provide adequate transfer of organisms. Before that direct gram stain from swab was performed.

Antibiotics sensitivity test: Quantitative agar dilution method used to detect the MICs of antibiotics (Amoxicillin (30µg/ml), Azithromycin (15 µg/ml), Tetracycline (25 µg/ml), Spectinomycin (10 µg/ml), Cefixime (25 µg/ml), Ceftriaxone (30 µg/ml), Ciprofloxacin (20 µg/ml), Penicillin (25 µg/ml)) by inoculation of *N. gonorrhea* inoculum onto the surface of an agar plate following the incorporation of varying desired concentrations of the antimicrobial agent into molten agar medium, typically using serial two-fold dilutions (21).

Molecular study: Total RNA of all samples was extracted using the AccuZol kit according to the manufacturer's instructions. Total RNA was reversely transcribed to complementary DNA (cDNA) using (cDNA kit, СИНТОЛ Company / Russia). The test was worked by a reaction volume of 25 µl according to the manufacturer's instructions. The expression levels of *p53* and *cIAP2* genes were estimated by Quantitative Real-Time PCR (RT-qPCR). To confirm the expression of the target gene, RT-PCR EVA green assay was used. The mRNA levels of the endogenous control gene (β-Actin) were amplified and used to normalize the mRNA levels of the *p53* and *cIAP2* genes. Primers that are used for RT-qPCR are listed in table (1).

Table (1): Primer's sequence of *p53* and *cIAP2* that used for RT-qPCR

Gene	Sequence	Ref.
P53	Forward primer: 5' TGCGTGTGGAGTATTTGGATG 3'	(37)
	Reverse primer: 5' TGGTACAGTCAGAGCCAACCTC 3'	
cIAP2	Forward primer: 5' GCTTTTGCTGTGATGGTGGACTC 3'	(38)
	Reverse primer: 5' CTTGACGGATGAACTCCTGTCC	

Ethics Approval

The study protocol was approved by the Medical Ethics Committee of Al-Diwaniyah Hospital's ethical review committee (No. 151-2022 dated 2/1/2022). All members gave composed informed assent after checking on the review depiction.

Statistics

Statistical analysis was carried out using Statistical Packages for Social Sciences version 20 with Microsoft Excel 2010. Statistically, a probability value less than 0.05 was considered significant.

3-RESULTS

The statistical analysis of the current study did not detect significant differences in the age mean of the studied groups (*P*= 0.077). The ages of cervical cancer patients infected with *N. gonorrhea* (CC-NG) ranged between 44-67 years, with an average age of 58 years. Likewise, the ages of patients with cervical cancer and non-NG infected patients (CC) ranged from 41-70 years, with an average age of 60 years, while the ages of healthy women in the control group ranged between 40-70 years, with an average age of 52 years, as shown in Table (2).

Table (2): Comparison of the age's mean of cases and control groups

Age properties /years	**CC-NG cases**	**CC cases**	**Control**	**P value**
Age range	44 - 47	41 - 70	40 - 70	
Mean	58	60	52	0.077
Standard deviation	5.11	4.81	7.02	
Standard error	1.14	1.07	1.57	
Number	20	20	40	

In this study, it was difficult to find an appropriate number of cervical cancer patients infected with *N. gonorrhea*, and for more than a year. However, The phenotypic results were as follows: Small opaque, grayish-white to colorless, raised, glistening, and smooth colonies on MTM are seen and after staining were gram-negative, coffee-bean-like bacterial pairs in side leukocytes as shown in figure (1).

Data in Figure (2) represent the prevalence of antibiotic resistance among tested strains was high to penicillin (96%), amoxicillin (90%), tetracycline (89%) and ciprofloxacin (77%) but low to cefixime (4%), spectinomycin (5%) and azithromycin (92%). Interestingly, all isolates were susceptible to ceftriaxone.

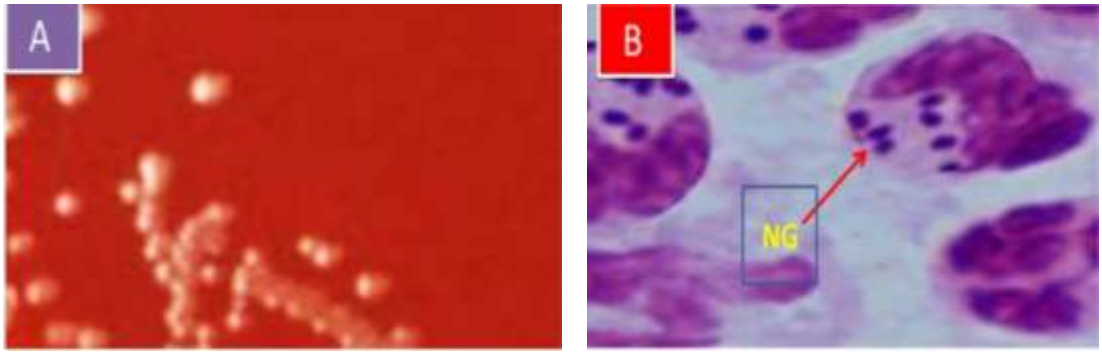

Figure (1) lab test of *Neisseria gonorrhea*. A; bacterial growth on MTM, B; results of gram stain show *N. gonorrhea* inside leukocytes.

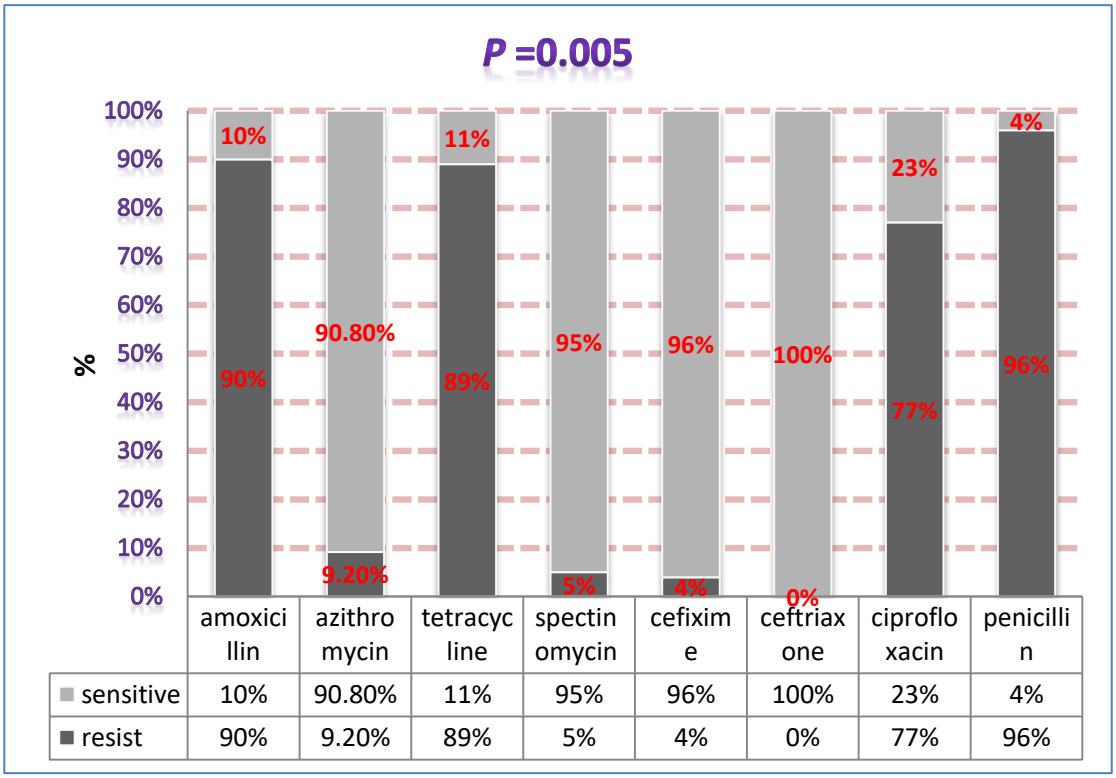

Figure (2) Antibiotics sensitivity test of N. gonorrhea by Quantitative agar dilution method

Analysis of relative gene expression was undertaken using Real- Time Quantitative PCR and the folding Method ($2^{-\Delta\Delta ct}$) of Livak *et al*., (2001) (36). Results showed that *P53* and *cIAP2* had high gene expression (folding change) in CC-NG (17.172 and 31.135 respectively) and CC (16.02 and 15.45 respectively) patients compared to healthy control (1.00) ($P<0.05$) **(table 3)**. Moreover, when comparing the expression of both genetic indicators, the present study showed an increase in gene transcription in the cases of CC-NG (17.172 and 31.135 for *P53* and *cIAP2* respectively) compared to CC (16.02 and 15.45 for *P53* and *cIAP2* respectively).

Linear Pearson correlation showed that the correlation between gene expression of *P53* and *cIAP2* in CC patients was moderately positive (r= 0.2287, P= 0.0001), meaning that the factors did not depend on working with each other (figure 3), while the positive correlation was good (r= 0.4932, P= 0.0001) between them in NG-CC (see figure 4).

Table (3): mRNA expression of *P53* and *cIAP2* in studied subjects.

Genes	Mean of folding ($2^{-\Delta\Delta CT}$)			X^2	P value
	CC-NG	CC	Control		
P53	17.172	16.020	1.00	5.37	0.037*
cIAP2	31.135	15.45	1.00	7.44	0.022*
P value	0.027	0.591	1.00		

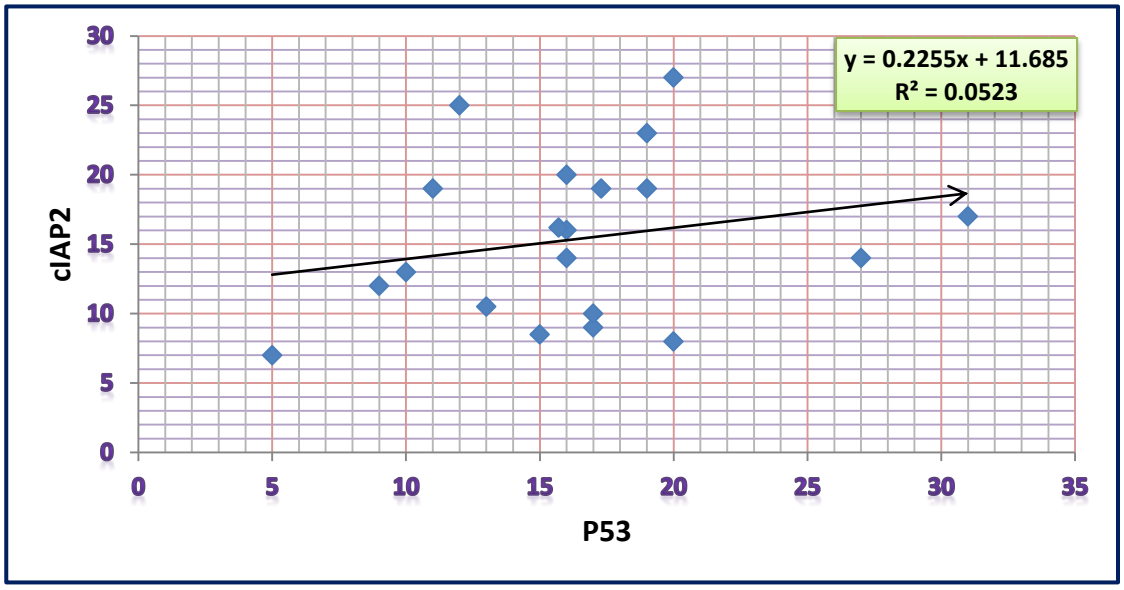

Figure (3) Pearson's correlation coefficient of gene expression (folding change ($2^{-\Delta\Delta CT}$)) of P53 and cIAP2 in CC cases (r= 0.2287, P= 0.0001)

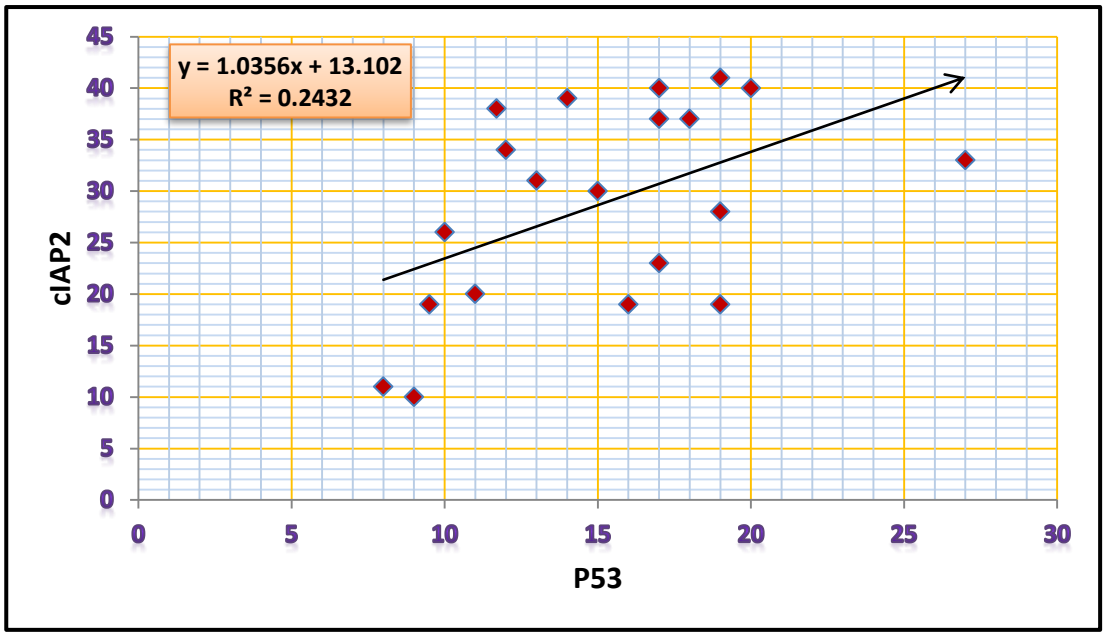

Figure (4) Pearson's correlation coefficient of gene expression (folding change ($2^{-\Delta\Delta CT}$)) between P53 and cIAP2 in CC-NG cases (r= 0.4932, P= 0.0001)

4-DISSCUSION

Current results showed that the prevalence of *N. gonorrhea* was low (only 20 cases) in women with cervical cancer although the length of the study period was for more than a year. Perhaps the reason for this is due to the treatment of bacteria before diagnosing the tumor, as the symptoms of infection with *N. gonorrhea* are similar to the initial symptoms of cervical cancer, which makes the first choice for treating these cases is antibiotics. As the appearance of vaginal discharge indicates a microbial infection that is always treated with antibiotics, and it must be noted that most obstetrics and gynecology outpatient clinics in Iraq prescribe antibiotics directly when there is vaginal discharge even before or without a laboratory diagnosis for pathogens. Moreover, the use of different types of antibiotics may have contributed to ending the *N. gonorrhea* infection before the appearance of cervical cancer symptoms (24).

The results of the antibiotic sensitivity test showed that the *N. gonorrhea* isolates were multi-resistant because this study did not have an isolate that was resistant to one or two antibiotics, but it was the least resistant to five antibiotics that appeared in only two isolates. However, ceftriaxone was the most effective in killing bacteria. These results are consistent with previous studies (16,17,18) that found high resistance to antibiotics by *N. gonorrhea*, and perhaps this is one of the reasons why some isolates are present so far in cervical cancer patients in AL-Diwaniyah City. According to healthcare specialists, the treatment of *N. gonorrhea* requires effort and follow-up, and it is considered one of the most difficult types of bacteria that can be encountered (40).

The current study is in line with studies that found high resistance to penicillin in *N. gonorrhea* isolates. The presence of plasmid-mediated β-lactamases in gonococci causes a significant increase in the level of resistance to penicillin compared with that related to chromosomal mutations (19,20,39). Unemo and Shafer (2014) mentioned that *N. gonorrhea* is evolving into a superbug with resistance to previously and currently recommended antimicrobials for the treatment of gonorrhea, which is a major health concern. Unfortunately, the susceptibility of gonococcal isolates to ceftriaxone has been decreasing globally, and resistance to azithromycin is already prevalent in many settings. Accordingly, these synergistic antimicrobial effects might not be effective long-term solutions and,

additionally, are not affordable in many resource-low settings (22,23). Furthermore, more expensive antimicrobials, such as ceftriaxone, are frequently not available even for monotherapy in low-resource settings (23)

The present results showed that the expression of genes *P53* and *cIAP2* increased in cervical cancer patients compared to control and that *N. gonorrhea* has an effective role in the increasing expression of these genes. The exact mechanism of increasing gene expression for these markers in CEC is unknown, and the role of *N. gonorrhea* in this disease has not been studied. So the impact of *N. gonorrhea* on *P53* and *cIAP2* pathway was not detected before our study.

After reviewing the research and studies that dealt with the immune response of *P53* and *cIAP2* in patients with CEC cases infected *with N.gonorrhea*, It was found that infection stimulates the immune system through the secretion of many cytokines that activate some receptors on the surface of epithelial cells, causing abnormal multiplication of these cells, leading to cancer (24,25). The current study believes that the virulence factors that *N. gonorrhea* possesses are the main factor in exacerbating this process. It was found that the development of cervical cancer when infected with NG was associated with increased gene expression for *P53* and *cIAP2* through three pathological pathways linked to each other, the first through TGF-β, Nuclear Factor kappaB (NF-kB) and Yes-associated protein (YAP) (26,27).

The increase in *P53* expression fold can be explained by the fact that mutated P53 will be overexpressed as shown by Sdia *et al*., although the wild type P53 will be downregulated. (41)

Human tumors most frequently contain specific genetic mutations, the most common of which are in the p53 tumor suppressor gene. They happen just once in a blue moon, in any case, in growths in which p53 might be inactivated by collaboration with cell or *N. gonorrhea* proteins. NF-kB and YAP, two transcription factors associated with tumor growth, interact with mutant p53 protein (26,34).

cIAP2 is part of the IAP family. IAPs affect cell relocation through various downstream atoms. cAP2 has been associated with the pathology of human malignant growths because of their overexpression and capability as blockers of cell death in different tumors (28). The NF-κB family is composed of transcription factors that play a crucial role in the regulation of immune responses and inflammation. XIAPs and cIAPs promote NF-B, which in turn inhibits cell migration. As of late NF-κB has as of late produced an impressive role in controlling commencement, movement and protection from treatment (29). Instead, accumulating evidence suggests that cIAP1 and 2 are involved in various signal transduction pathways, including NF-κB activation in response to TNFα during malignant growth in humans. Changes in or loss of cIAPs have been distinguished as molecular groups that add to the constitutive actuation of NF-κB in hematopoietic malignancies (30).

Enlistment of cervical malignant growth by cIAP2 might be expected agitation of TNF-a by *N. gonorrhea* that incites collection of cIAP2 which intervenes K-63 polyubiquitination of receptor interfacing protein 1(RIP1). RIP1 in this manner enacts the IKK complex, bringing about the actuation of authoritative NF-κB buildings (31,32).

Porin ion channel protein (PorB), colony opacity-associated (Opa) proteins, and reduction modifiable protein (Rmp) are the three primary outer membrane proteins that *N. gonorrhea* produces. Two key microbes are related to sub-atomic examples (PAMPs), lipooligosaccharides (LOS), and the sort IV pili (18,33). With the exception of Rmp, most of these virulence factors are capable of phase and/or antigenic variation. What's more, the plentiful external layer protein, PorB, where all gonococcal strains express one of the PorB isotypes - PorBIA or PorBIB. Opa protein might be dynamic invulnerable reactions such as TNF and TGF-b that work on certain receptors that actuate over quality articulation of P53 and cIAP2 (34,35).

5-CONCLUSION

n. gonorrhea isolated from cervical cancer cases was multi-resistant to antibiotics, and it was found that ceftriaxone is the most lethal antibiotic for this bacteria. the current study also found increased gene expression for *p53* and *ciap2* in cervical cancer compared to the control group. the present study has noticed that *n. gonorrhea* acts as an inducer or risk factor to increase the chance of cancer occurring because of its effect on *p53* and *ciap2* genes or perhaps on other genes, however, future studies are recommended to study the effects of *n. gonorrhea* infections in cervical cancer patients on the mutant forms and the wild type of *p*53.

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تأثير اصابة النَّيسَرِيَّةُ البُنِّيَّة على التعبير الجيني لجينات *p53* و *cIAP2* في سرطان عنق الرحم

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الخلاصة

خلفية عن البحث: النيسرية البنية (*N. gonorrhea*) هي واحدة من الاصابات البكتيرية الأكثر شيوعا والتي تسبب مشاكل صحية في البطانة الظهارية لعنق الرحم، لم تتناول الدراسات بشكل كافٍ دورها في سرطان عنق الرحم، وبالتالي، تهدف الدراسة الحالية إلى تحديد تأثير عدوى النيسرية البنية على التعبير الجيني لـ *p53* و*cIAP2* لدى السيدات المصابات بسرطان عنق الرحم.**المواد وطرق العمل**: تم جمع عينات من 20 امرأة تعاني من سرطان عنق الرحم مصابات بالنيسرية البنية (CC-NG)، و 20 امرأة مصابة بسرطان عنق الرحم غير مصابات بالنيسرية البنية (CC) و 40 امرأة سليمة كمجموعة سيطرة. تم تشخيص بكتريا النيسرية البنية بواسطة أجار ثاير مارتن المعدل (MTM) وصبغة جرام. من جانب آخر، تم تحديد التعبير الجيني لـ *p53* و *cIAP2* باستخدام تفاعل البوليمريز المتسلسل بالزمن الحقيقي real time-PCR. **النتائج:** كان لجينات *P53* و*cIAP2* تعبير جزيئي عالي في CC-NG (17.172 و31.135 على التوالي) وCC (16.02 و15.45 على التوالي) مقارنة مع مجموعة السيطرة (1.00) (P>0.05). علاوة على ذلك، عند مقارنة التعبير لدى كلا المؤشرين الجينيين، نلاحظ زيادة في نسخ الجينات في حالات CC-NG مقارنة بـ CC. واظهرت نتائج دراسة مقاومة المضادات الحيوية لعزلات النيسيرية مقاومة عالية للمضادات الحيوية للسيفترياكسون (100٪)، والبنسلين (96٪)، والأموكسيسيلين (90٪)، والتتراسيكلين (89٪)، والسيبروفلوكساسين (77٪)، ولكنها منخفضة للسيفيكسيم (4٪)، والسبكتينومايسين (5٪). وأزيثروميسين (9 2٪). **الاستنتاجات:** الاصابة بالنيسرية البنية يمكن أن تحدد كعامل خطورة لتطور أو حدوث سرطان عنق الرحم .

الكلمات المفتاحية: النيسرية البنية ، التعبير الجيني، *p53, cIAP2* ، سرطان عنق الرحم.