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Association of the Severity of Cervical Cancer Precursor Lesions by Age Group in Women of Reproductive Age

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ABSTRACT

Introduction: Worldwide, cervical cancer is the second most frequent type of cancer in women according to GLOBOCAN 2022, at the national level it is established as the second cause of death from malignancies in women in the reproductive stage according to data from INEGI 2021.

Objective: To analyze the association between cervical cancer precursor lesions by age group in patients of reproductive age in a primary care unit in the period September 2022 to December 2023.

Material and methods: The present work is an observational, analytical, descriptive, cross-sectional study. The data was concentrated on a basis to be processed in Excel version 2301. The study population were women of reproductive age who had altered cervical cytology from September 2022 to December 2023 from a first-level medical unit. The sample for this study is represented by 135 epidemiological studies of women with positive cervical cytology for low- and high-grade squamous intraepithelial lesion, which was obtained by sample calculation for a finite population by random sampling.

Results: Low-grade squamous intraepithelial lesion prevails in greater proportion, representing 85.92%. The range of 1-3 previous cytologies prevailed in 54%, with the presence of high-grade intraepithelial lesions in 7.4%. Likewise, the age group of 16 to 20 years was identified as the age of highest prevalence for the beginning of active sexual life in 71.1% and in second place adolescents from 11 to 15 years representing 14.81%.

Conclusion: There is a higher frequency of SIL, mainly in the age group of women from 35 to 39 years old, who were not immunized with the HPV vaccine that was introduced in 2006 for the first time in Mexico, so they could be predisposed to SILIL or carcinoma in situ in the coming years.

Keywords: Cervical Cancer; Intraepithelial Lesions; Low-Grade Squamous Intraepithelial Lesion; High-Grade Squamous Intraepithelial Lesion; Human Papillomavirus; Cervical Cytology; Pap Smear; Precancerous Lesions

Introduction

Anatomy and Histology of the Cervix

The cervix is composed of the ectocervix, which is lined by mature squamous epithelium, which is in continuity with the vaginal wall, and the endocervical canal, which is covered by mucosecretory columnar epithelium. At the level of the external cervical os, the ectocervix converges with the endocervix, thus generating the squamous-columnar junction (SCU). The area where the columnar epithelium is located above the squamous epithelium is called the transition zone, which is an environment susceptible to Human Papillomavirus (HPV) infections due to the presence of immature metaplastic squamous cells, thus being the area of origin of cancer and precursor lesions [1,2].

What is Cervical Cancer?

The National Cancer Institute (INC) defines it as cancer that originates in the cells of the cervix, before the formation of this cancer the cells of the cervix undergo changes called dysplasias, it is the transformation of normal cells of the cervix into abnormal cells [3]. On the other hand, the Clinical Practice Guideline (2011) "Prevention and timely detection of cervical cancer at the first level of care" de-

fines it as a cellular alteration that originates in the epithelium of the cervix and that manifests itself, initially through low- and high-grade precursor intraepithelial lesions, of slow and progressive progression towards invasive cancer [4,5].

Stages of Cervical Cancer

The clinical stages of cervical cancer are divided into four according to the staging system of the International Federation of Gynecology and Obstetrics (FIGO): Stage 0 Carcinoma in situ, patients in this stage have a 100% survival rate at 5 years; Stage I Confined to the cervix, where patients have an 85-47% survival rate at 5 years; Stage II : Disease beyond the cervix but does not reach the pelvic wall or lower third of the vagina with a survival rate of 65-28% at 5 years; Stage III : Disease in the pelvic wall or lower third of the vagina with a survival rate of 35-21% at 5 years; Stage IV Invades bladder, rectum, or metastasis with a survival rate of 7-4% in 5 years [6].

Risk Factors for Cervical Cancer

The most important factor in cervical oncogenesis is the high-risk HPV genotypes (16,18, 31, 33, 35, 45 among others), with genotype 16 related to 60% of cervical cancer and genotype 18 related to 10% [1].

The American Cancer Society considers the following risk factors as predisposing factors in cervical cancer (CC):

Early Sexarche: Sexarche has been studied before the age of 18 as a risk factor for cervical cancer due to the immaturity of cervical cells in adolescent girls, causing them to become more easily infected with HPV during genital intercourse [7].

Smoking: This type of practice induces a local immunosuppressive effect, which is why several studies consider female smokers to be at double risk of intraepithelial injury, which could cause DNA fragmentation contributing to the mechanism of apoptosis [8,9].

Hereditary Family History: There are women whose inherited genetic material makes the cells in their cervix unable to eliminate HPV, likewise, the persistence of the virus coupled with a susceptible NP can make the development of CC possible [7].

In Mexico, the risk factors with the highest prevalence of high-grade intraepithelial lesions in percentage per 100,000 adult women (over 15 years of age) are:

- Smoking 7.2%
- Use of oral contraceptives 4.7%
- Parity 2.3%
- HIV co-infection 0.2% [10,11]

Pathogenesis of Cervical Cancer and its Relationship with HPV

HPV belongs to the Papillomaviridae family, it is a circular double-stranded DNA virus, which has an important etiological role in cervical cancer [10]. There are several HPV genotypes, but subtypes 16 and 18 are responsible for 70% of CC cases, while subtypes 31, 33, 45, 52, 58 account for 20% of cases [11]. According to the serotype, it is estimated that 70% of infections will have a spontaneous remission during the first 12 months and 90% in 24 months, after which it is considered a persistent infection that can evolve into a neoplasm [12]. This virus is defined as: a virus that infects exclusively the immature basal cells of the squamous epithelium or the metaplastic squamous cells of the UEC. HPV penetrates to the basal layer and there it contacts its cells, causing infection, which has a high chance of regression and a limited capacity for progression. When the virus persists for more than 18-24 years, the possibility of regression is drastically reduced, especially in perimenopausal patients [1,13]. Only through persistent infection can the virus produce atypical changes in the host cells when incorporated into its genome, the proteins that cause the internalization of the virus in the cytoplasm are those of the viral capsid; L1 causes normal cell growth to be lost, resulting in the expression of the oncoproteins E6 and E7 whose fundamental role in carcinogenesis is to inhibit the suppressor genes p53 and pRB, respectively [13,14]. In the uninfected cell, the retinoblastoma protein (pRB) binds to the familiar transcription factors E2F, thus controlling cell replication, but the oncoprotein E7 is able to bind to pRB leaving E2F free and the cell enters the S phase of replication, triggering the production of p16 in an attempt to inhibit the process, The induction of replication and the appearance of genetic aberrations sets in motion a sentinel trophic response, which can cause cell differentiation, senescence and apoptosis, mediated by p53; however, E6 is able to bind to E6-AP, forming a complex that stimulates the rapid degradation of p53; every time a cell divides, erosion of the terminal chromosomal telomeres can occur, the overexpression of the hTERT subunit of telomerase indicates an increase in cellular life expectancy and brings the cell closer to immortality, being E6 capable of interacting with c-myc terminals to stimulate this hTERT subunit [15,16].

Classification of CC Precursor Lesions

Dysplasia is categorized into 3 groups, according to the degree of involvement in the epithelial layer by atypical cells. Subsequently, for several years, cervical precancerous lesions were reported using the categories of dysplasia and carcinoma *in situ* (CIS) using the Richart classification that introduces the term Cervical Intraepithelial Neoplasia (CIN):

- **CIN 1**: There is good cell maturation with minimal nuclear abnormalities and few mitotic figures, undifferentiated cells are found in deeper epithelial layers.
- **CIN 2:** It is characterized by dysplastic cellular changes restricted mainly to the middle of the lower two-thirds of the epithelium, with more marked nuclear abnormalities than CIN 1.

- **CIN 3**: Differentiation and stratification may be completely absent or exist only in the superficial quarter of the epithelium, with abundant mitotic figures. Nuclear abnormalities appear throughout the thickness of the epithelium.
- **CIS**: Normal columnar epithelium is replaced by abnormal epithelium representing loss of polarity, larger cells and nuclei, nuclear hyperchromasia, mitotic activity, decreased expression of cytoplasmic mucin, and cell stratification or accumulation [2].

In 1991, the Bethesda system was created, which is currently the most widely used system to report cervical cytology results, this system is divided into three main categories:

- **Negative For Intraepithelial Lesion or Cancer**: Where no significant abnormality is detected, findings indicating Trichomonas vaginalis infection may be detected.
- **Epithelial cell abnormalities**: where we find 2 subdivisions:

o ***Atypical Squamous Cells (ASCs)***: Where atypical squamous cells of uncertain importance *(ASC-US)* or atypical squamous cells in which a high degree of squamous intraepithelial lesion *(ASC-H)* may be found.

o **Squamous Intraepithelial Lesions** (SLIs), where we find low-grade squamous intraepithelial lesions (LSILs) where cells look slightly abnormal (CIN 1) and integrate with koilocytic atypias; high-grade squamous intraepithelial lesions (SLIs) where cells look significantly abnormal, are unlikely to disappear without treatment, are more likely to develop into cancer (CIN 2, IAS 3, CIS).

- **Glandular cell abnormality**

o Squamous cell carcinoma.

o Atypical glandular cells.

o Adenocarcinoma.

o Other malignancies. [2,16].

Screening and Detection

The most effective way to establish treatment for CC is through three basic resources [17]:

- **Cytology**: The most widely used worldwide due to its effectiveness, it has a sensitivity of 30 to 96.4% with false positives of 20-28%. It is performed through Pap smear, which should be performed annually and if 3 consecutive negative results should be repeated every 3rd year [2,14].
- **HPV test**: This is the detection of the viral DNA or RNA of high-risk types of GBV, which should be performed with an interval of 5 years if it is negative, and if it is positive, complement with cytology [10].
- **Colposcopy**: It is a diagnostic test used to evaluate vaginal, vulvar and cervical dysplasia, it is indicated when there is an immediate risk of CIN, it is performed by the acetic acid or Lugol iodine test [2,18].

Prevention

Prevention is made up of 3 phases to follow:

Primary Prevention: Based on health promotion that can reduce the exposure of the population to risk factors, in order to reduce the incidence of the disease. Similarly, the HPV vaccine before the beginning of sexual life. There are currently 4 types on the market, two of them bivalent Cervarix® and Cecolin® against genotypes 16 and 18, the quadrivalent Gardasil®, which includes genotypes 6, 11, 16 and 18, responsible for 90% of infections, the monovalent Gardasil 9®, which also includes the high-risk genotypes 31, 33, 45, 52 and 58 [14,19].

Secondary Prevention: Performing the PAP every year and after two negative results every 3 years, from the beginning of sexual life or from the age of 25 [4,17].

Tertiary Prevention: Activities for the rehabilitation and prevention of complications derived from the disease. Cancer control depends essentially on actions in the areas of health promotion and timely diagnosis [17].

Global Overview of The CCU

This pathology represents the fourth most frequent type of neoplasm in women with an incidence of 10,348 new cases in 2022 and 4,909 deaths [20-22].

Epidemiology of CC at the National Level

In Mexico since 2006 it has been the second cause of cancer death in women, in 2022 there were 4,909 deaths in women due to CC, by age group in women of 25 years of age a crude rate of 11.3 deaths per 100 thousand women was registered, and an average age at death of 59.03 years [18]. In the south of the country, there is a higher basic mortality rate per 100,000 inhabitants, highlighting: Tlalnepantla with a rate of 21.6, Totolapan with 13.1, Cuautla 12.9, Xochitepec 11.7, while in the east San Miguel Xotla stands out with a rate of 13.5, San Jerónimo Zacualpan with 13.3 [23]. According to data from the Institute of Statistics and Geography (INEGI) in Mexico, during 2021, 1,112,249 deaths were registered, of which 8% were due to malignant tumors; where the population between 20 and 29 years of age predominated as the second cause of death in women, malignant tumor of the cervix [24,25]. The cases of HPV registered nationwide in 2022 are represented by 11.7% in males and 88.3% in females with a total of 10,349 cases, highlighting in first place the State of Mexico with 1,183 cases and in second place Chiapas with 1,238 cases, in third place Mexico City with 1, 176 cases [26]. During 2020 the incidence of CC for the Americas was 74,800 new cases/year in women

aged 20 to 58 years, deaths in this age group and region were 37,700, it is estimated that the figure could increase to 87,400 new cases by 2030 [27]. In a study carried out with patients from the Family Medicine Unit No. 36, the prevalence of cervical intraepithelial lesion was found to be 4.49%, with 3.17% for LSIL and 1.32% for HSIL, where the most affected age group was 41 to 60 years [22,27].

Material and Methods

The present work is an observational study since no variables were manipulated, analytical because two study variables were associated (age group and type of lesion, either LSIL or HSIL), cross-sectional because it was carried out in a certain period (September 2022 to December 2023), retrolective because the information was collected from a database already established at the time of the study, without collecting new data during the process. The study area was a first-level medical unit in the Oriente delegation, State of Mexico. The data source included original review articles, clinical practice guidelines and the database obtained from the epidemiology service, as well as the epidemiological studies of the patients assigned to the unit. The data were concentrated in an Excel sheet version 2301 for further analysis. The analysis of results was carried out by analyzing the qualitative variables (cervical cytology, age group, degree of squamous intraepithelial lesion) were presented in percentage and proportion, the analysis of the association of the age group with the degree of squamous intraepithelial lesion was using Pearson's Chi-square where a p value of 0.825740562 was obtained and for the analysis of quantitative variables, measures of central tendency were used as a mean, medium and mode. The sample size was made by means of a simple random sampling that guarantees that all individuals that make up the white population have an equal chance of being included, choosing the formula for sample calculation of a finite population:

$$n = \frac{n * Z\frac{2}{\alpha} * p * q}{e^2\left(N-1\right) + Z\frac{1}{\alpha} * p * q}$$

Obtaining from 210 epidemiological studies a sample represented by 135 epidemiological studies, which were distributed in 6 age groups in five-year periods to facilitate data analysis and show representativeness; as well as to identify the age group or groups with the greatest vulnerability.

Results

LSIL was identified as the most prevalent lesion, represented by 85.92% (Figure 1). Regarding the number of screenings prior to detection in patients with a low- or high-grade squamous intraepithelial lesion, the range of 1-3 previous cytologies was identified as the most prevalent in 54%, a fact that suggests a low screening rate, highlighting patients with SLIL with a prevalence of 7.4%. in second place was the range of 4-6 previous cytologies, representing 23.7% (Table 1). The beginning of active sexual life with the highest prevalence identified was the range of 16 to 20 years representing 71.1%, in second place was adolescents from 11 to 15 years of age with a prevalence of 14.81%, in which 2.22% is represented by patients with SILIL (Table 2). In the analysis by age group of squamous intraepithelial lesions, 3 groups of great interest were identified, the first women aged 35 to 39 years with a prevalence of 19.2% for LSIL, secondly the group of 30 to 34 years with a prevalence of 5.1% for LSIL, in third place the group of women aged 45 to 50 years prevails with 17% for LSIL and 3.7% for LIEAG (Table 3). To evaluate the association of the chosen variables (age and type of squamous intraepithelial lesion: LSIL and HSIL) with the information obtained from the sample, an inferential analysis was performed using Pearson's Chi-square calculation (non-parametric measure) where a value of 0.825740562 was obtained, which confirms the existence of an association between the presence of LSIL in women aged 36 to 40 years and for HSIL in women aged 36 to 40 years. 31 to 40 years old.

Table 1: Previous detections (cervical cytology study) in patients with LSIL and LSIL.

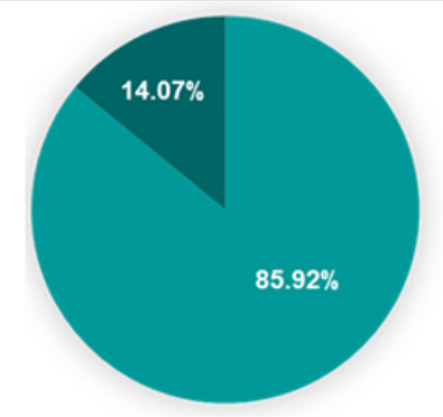
Number of previous detections									
Type of injury	1-3		4-6		7-9		>10		Total
	No.	%	No.	%	No.	%	No.	%	
LIEBG	63	46.6	28	20.7	5	3.7	20	14.8	116
LIEAG	10	7.4	4	2.9	2	1.4	3	2.2	19
Total	73	54	32	23.7	7	5.1	23	17	135

Table 2: Initiation of active sexual life in patients with LSIL and LSIL.

Type of injury	Age Range				Total
	11-15	16-20	21-25	>26	
LIEBG	17	82	15	2	116
LEAG	3	14	1	1	19
Total	20	96	16	3	135

Table 3: Relationship of precursor lesions of CC by age group.

Age group (years)	No. Patients	%	No. Patients	%	Total
	LIEBG		LIEAG		
20-24	9	6.6	1	0.7	10
25-29	17	12.5	1	0.7	18
30-34	19	14.0	7	5.1	26
35-39	26	19.2	4	2.9	30
40-44	22	16.2	1	0.7	23
45-50	23	17.0	5	3.7	28
Total	116	85.92	19	14.07	135



Note: LSIL: Low-Grade Squamous Intraepithelial Lesion. HSIL: High-Grade Squamous Intraepithelial Lesion.
Figure 1: Degree of squamous intraepithelial lesion of greater prevalence.

Discussion

Cervical cancer (cervical cancer) is a pathology of great global, national and local interest, so screening measures, such as cervical cytology, have a great impact on the prevention of cervical cancer with the identification of precancerous lesions. The development and progress of a precancerous lesion is influenced by various factors such as HPV infection, early sexarche, not using condoms or inappropriate use of condoms, as well as annual screening for the first time in each patient at the beginning of their sexual life or when they reach the age of 25. The sample studied consisted of epidemiological studies of women of childbearing age who had cervical cytology with the presence of BLISI or EGLI in the period September 2022 to December 2023, to identify the age group within the fertile population that requires special attention in the distribution of information that highlights preventive measures for HPV infection and screening for CC. The results of the present study suggest that the frequency with which patients undergo screening is very low because the range of 1-3 screenings prior to the diagnosis of a SILL or SIL prevails, this finding is consistent with what was reported by Solis and Briones in 2015 [28] where they identified a 17.65% prevalence in first-time cytologies for patients with SILL or SILBLI at an age of 41 to 60 years. which is an alarming fact because it shows a delay in the timely diagnosis of precancerous lesions and in the future of CIS. Regarding sexarchy, the data suggest that the age of onset in the highest prevalence is 16 to 20 years, a fact that contrasts with Sousa and Colmenares [29], who identified the age of highest prevalence for sexarchy between 21 and 25 years in 49.3% and in second place the range of 15 to 20 years in 34%.

while in this study, sexarchy was reported in second place from 11 to 15 years of age in 14.81%, which shows that our population expresses an earlier sexarchy, which increases the risk of suffering from CC four times more, as evidenced by other studies carried out in the Mexican population that identify sexarchy before the age of 19 as a risk factor that increases the risk of cervical cancer by four times. suffering from CC [7]. These data contribute to identifying the age group in which there is a higher incidence of early sexarchy, opening the opportunity to distribute more strongly preventive measures and appropriate sexual education through the correct use of condoms, the HPV vaccine in adolescents who have not yet started an active sexual life and screening once sexual life has begun. The results found identify the most prevalent age groups with low- and high-grade lesions, highlighting women aged 35 to 39 years for a SIL in 19.2% and women aged 30 to 34 years for SILGE in 5.1%, which allows us to identify a greater severity in younger women, which agrees with Sousa and Colmenares in 2019 [29] who identified a greater severity in the Venezuelan population. prevalence of 13% for HSIL in women aged 31 to 40 years, showing that the age of onset of high-grade lesions is increasingly prevalent in younger and younger women, a factor antecedent to developing CC in earlier stages of life and that according to INEGI in 2021 [24] malignant cervical tumor was registered as the second cause of death in women of 30 to 59 years old, which shows the risk in which the studied population is established.

Conclusion

There is a higher frequency of LSIL, mainly in the age group of women aged 35 to 39 years. Additionally, there is greater severity in women between 30 and 34 years of age when a SILIL prevails, derived from a premature sexarche that ranges from 11 to 20 years according to what has been seen in the previous literature already mentioned and the findings in this research, which means that according to the natural evolution of HPV, symptoms appear 5-10 years after contact with the virus. therefore, there is a delay in the timely detection of precancerous lesions if screening is started at 25 years of age and not from sexual contact in premature sexarchy, which contributes to evidence of serious lesions at an earlier age. Therefore, it is proposed to promote screening at the beginning of active sexual life.

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