Human papillomavirus infection is principally found with cervical intra-epithelial neoplasia-III in Toluca, State of Mexico

Hugo Mendieta-Zerón [a,*], Raúl de León-Escobedo [b,1]

[a] *Faculty of Medicine, Autonomous University of the State of Mexico (UAEMex), Paseo Tollocan ESQ, Jesús Carranza, Col. La Moderna, CP. 50180, Toluca, State of Mexico, Mexico*
[b] *Department of Pathology, General Regional Hospital 220, Instituto Mexicano del Seguro Social (IMSS), Paseo Tollocan No. 660, Col. Vértice, CP. 50150, Toluca, State of Mexico, Mexico*

Summary
Introduction: To describe the prevalence of human papillomavirus infection (HPV) in cases of cervical intra-epithelial neoplasia (CIN), micro-invasive carcinoma and invasive carcinoma in Toluca, State of Mexico.
Materials and methods: Cross-sectional study analysing slides with the diagnosis of CIN I to invasive carcinoma for one year and reporting the presence of HPV; also identifying these cervical-uterine cancer stages noted during one semester in the registry of histopathological studies, at the Department of Pathology, General Regional Hospital 220, Instituto Mexicano del Seguro Social (IMSS).
Results: In one year, from a total of 5755 studies, 731 (13%) were of cervical-uterine cancer, 112 (16%) of these were positive for some stage of cervical cancer and 46.43% had HPV infection. In one semester, 2918 histopathological studies were done, 341 (11.68%) of these were cervix uterine biopsies, colposcopies and hysterectomies. 62 women (18.18%) diagnosed with CIN II—III, carcinoma in situ (CIS), micro-invasive carcinoma or invasive carcinoma and finding HPV infection in 51.92% of total cases.
Conclusions: The prevalence of HPV was higher than that reported in developed world and CIN II—III are the most common stages in Toluca, State of Mexico.
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  * Corresponding author. Present address: Felipe Villanueva sur 1209, Col. Rancho Dolores, CP. 50170, Toluca, México. Tel.: +52 722 2176605; fax: +52 722 2194122.
   E-mail address: mezh_74@yahoo.com (H. Mendieta-Zerón).
  [1] Present address: Universidad del Noreste, Tampico, Tamaulipas, Mexico; Prolongación Avenida Hidalgo 6315, Col. Nuevo Aeropuerto, CP. 89337, Tampico, Tamaulipas, México. Tel.: +52 833 2303830.

Introduction

The incidence of cervical-uterine cancer in the European Union is 13.2/100,000 and the mortality rate is 5.9/100,000 women/year [1]. In the US this is an increasing health problem whereas in Mexico it remains a leading cause of death for women with an estimated incidence and mortality of 40.5 and 17.1/100,000 respectively in the year 2000. In fact, in that year approximately 6650 women died from this cancer, the largest number in Latin America after Brazil.

In recent years, detection of precursor lesions of cervical intra-epithelial neoplasia (CIN) and human papillomavirus (HPV) infection has increased. Fortunately, these lesions can be detected in early stages, clarifying definitively a cytologic or colposcopic suspicion by histopathological study. It is important to mention that HPV infection is capable of causing changes similar to dysplasia, principally CIN I, although it can simulate changes of type CIN II or CIN III [2]. HPV infection is limited to squamous epithelium (skin and mucosa) and begins in the basal strata. Whilst the mechanisms of tumorigenesis by HPV are not well understood, it is known that viral replication is related to the epithelial cell differentiation programme, possibly through specific cellular proteins that bind to viral DNA and regulate transcription. Some oncogenic etiologic factors identified are smoking, herpes virus infection and oral contraceptive use. Based on the frequency that a genital lesions progress to carcinoma, HPV are classified as low or high grade [3].

Familial data of cervical-uterine cancer such as low socio-economic level, multiple sexual partners, early age of sexual intercourse, sexually transmitted diseases, and infection due to HPV 18 and 35 are the factors related to high-grade squamous intra-epithelial lesions (SIL) and cervical-uterine cancer, even more in developing countries where late presentation with advanced disease predominates. Furthermore, among HPV-positive women, increasing age, high viral load, high sexual activity and a low socio-economic status are associated with an increased risk of disease. Given this, cervical-uterine cancer is debatebly considered a sexually transmitted infection (STI) [4].

Previous studies have provided wide evidence that the detection and HPV typification can predict the future risk of developing a CIN, as well as the risk of low-grade lesion progression [5]. It is important to study the viral DNA because most cases around the world establish that the infection is almost completely restricted to the high-risk HPV types 14, 15, 16, 17 and 18. High prevalence of these types in certain populations could explain regional differences in cervical cancer incidence.

Based on an evaluation of the Cervical-Uterine Cancer Early Detection Program of the Department of Pathology, Faculty of Medicine, Autonomous University of the State of Mexico (UAEMex), we would expect to find a high prevalence of HPV in the different stages of cervical cancer in Toluca, State of Mexico. The aim of this study was to report the percentage of HPV infection related to the different stages of CIN detected by histopathological methods and to describe the major results of biopsies and surgical samples with diagnosis of CIN I—III, carcinoma in situ (CIS), micro-invasive carcinoma and invasive carcinoma at the Department of Pathology, General Regional Hospital 220, Instituto Mexicano del Seguro Social (IMSS), Toluca, State of Mexico. Which is the biggest second level public hospital in the Valley of Toluca, attending 198,428 people affiliated to the Mexican Social Security System and the only pathology department processing these types of slides for this population.

Materials and methods

This project obtained the institutional research board's approval from the Faculty of Medicine of the UAEMex.

Type of study: descriptive, retrospective.

We reviewed all the histopathological slides prepared in one year at the General Regional Hospital 220, IMSS, with the diagnosis of CIN I—III, micro-invasive carcinoma and invasive carcinoma, identifying those with the presence of HPV.

Secondly, we retrieved the results recorded during one semester in the registration book of histopathological studies, collecting the following data: (1) gyneco-obstetric information and (2) type of study [surgical tissue (S) or biopsy (B)]. All the samples were evaluated for the diagnosis of CIN I—III, CIS, micro-invasive carcinoma and invasive carcinoma. In addition, existence of infections, invasion, metaplasia, keratinisation, the differentiation grade and presence of other lesions was noted.

Statistical analysis was performed using the InStat 3 program using Fisher's exat test for contingency tables.

Results

During this one year, the median age of patients was 43 years old. From a total of 5755 studies, 731 (13%) were of cervical-uterine cancer, and

Table 1 Histopathological studies done in one semester.

	Cervix uterine biopsies, colposcopies and hysterectomies	Colposcopies and hysterectomies	Biopsies
Total	341	282	59
CIN I	0	0	0
CIN II	11	6	5
CIN III	16	9	7
CIS	21	10	11
Micro-invasive carcinoma	7	1	6
Invasive carcinoma	6	1	5
Adenocarcinoma	1	1	0

CIN: cervical intra-epithelial neoplasia, CIS: carcinoma in situ.

112 (16%) of these were positive for some stage of cervical cancer (CIN I: 3; CIN II: 20; CIN III: 67; micro-invasive carcinoma: 10 and invasive carcinoma: 12). Besides, 52 (46.43%) had HPV infection, CIN I: 1 (33.33%); CIN II: 8 (40%); CIN III: 35 (52.24%); micro-invasive carcinoma: 3 (30%) and invasive carcinoma: 5 (41.67%). There were no significant statistical association between any of the above groups and HPV.

During one semester the peak of cases was in women ranging between 13 and 70. The gyneco-obstetric data was in average: gestation (G): 7.07, vaginal deliveries (VD): 2.75, abortions (A): 0.77 and caesarean deliveries (CD): 0.19; distributed per diagnosis were CIN II: G = 6.22, VD = 4.77, A = 1, CD = 0.44; CIN III: G = 3.92, VD = 3.33, A = 0.25, CD = 0.16; CIS: G = 5.53, VD = 5.13, A = 0.93, CD = 0.26; micro-invasive carcinoma: G = 6.66, VD = 5.66, A = 1, CD = 0; invasive carcinoma (we could find information of only one patient): G = 12, VD = 12, A = 0, CD = 0.

From 2918 histopathological studies done, 59 (17.30%) were biopsies and 282 (82.69%) were sur-gical tissues, (the distribution per stage is showed in Table 1).

86.5% of the samples were of good quality and 13.5% were suboptimal, noting endocervix in 86.53% of cases, exocervix in 96.15% and transition zone in 86.53%, finding HPV infection in 51.92% of total cases and vascular and glandular invasion in 17.3% each. There was squamous metaplasia in 51.92% and keratinisation in 23.07%. The grade of differentiation was well defined in 55.76% and poor in 42.3%. Other lesions observed were inflammation in 50%, ulceration in 46.15%, haemorrhage in 26.93% and necrosis in 9.61%. We found chronic cystic cervicitis in 23.07%, being based on the diagnosis CIN II: 8.33%, CIN III: 25%, CIS: 58.33%, micro-invasive carcinoma: 0% and invasive carcinoma: 8.33%.

Discussion

Cancer of the uterine cervix is the second most common cancer in women worldwide. Currently, cervical screening is based on cytology. Many recent
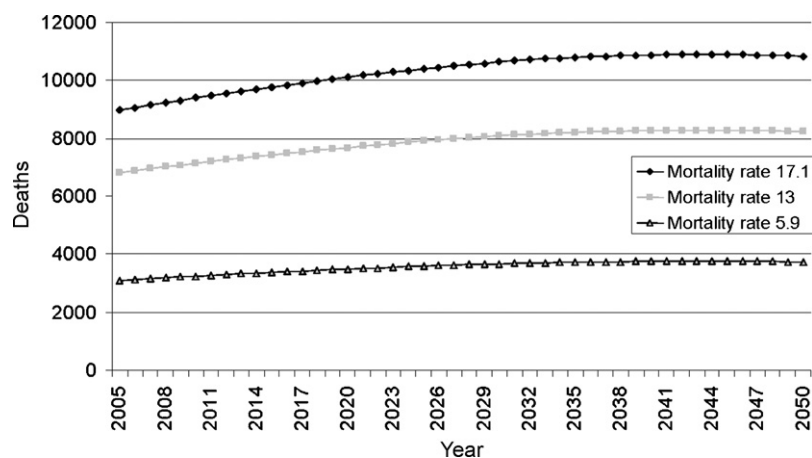

Figure 1 Trends with different mortality rates incidence projections based on: Proyecciones de la población de México 2005—2050. Consejo Nacional de Población, 2006. Available from: http://www.conapo.gob.mx/00cifras/5.htm [accessed 04.09.08].

research have highlighted the notion that low and high-grade lesions are distinct HPV infection processes. In contrast to low-grade SIL that tend to be located distally from the cervical lesions, high-grade SIL and carcinoma tend to be more proximate [6].

Cytologic screening can detect HPV which causes virtually all invasive cervical cancer and its precursor abnormalities. As high-risk HPV infection causes cervical cancer, it has been postulated that screening might become more efficient when it is based on cytology combined with high-risk HPV testing [7].

Reduced Papanicolaou (Pap) smear frequency is the primary factor attributable to development of invasive cervical cancer. Approximately 55—60% of cervical cancer cases arise in women who have never been screened or who are not adherent with screening guidelines. In this regard, countries that have implemented the Pap smear as part of opportunistic or organised cervical cancer screening programme that include quality assurance, large population coverage, and adequate follow-up, have experienced a reduction in the incidence and mortality for the disease. Unfortunately in Mexico, although a national screening programme has existed since 1974, there has not been a significant reduction in the mortality rate [8].

An important finding in our one-year screening was the high percentage of cases with CIN and HPV infection. This reinforces the assertion that HPV is the most common STI and the most widely diagnosed as well. Also, we found that the percentage of HPV increases from CIN I to CIN III. Notwithstanding the percentage per stage and that total percentage is extremely high, in agreement with the reports in the scientific literature related to developing countries, we believe that the percentage of detection could be increased by improving the technological tools, principally focussed on DNA detection of HPV [9]. We also suggest efforts to determine the principal HPV serotypes in each community to evaluate the potential benefit of HPV vaccine [10].

Despite the strong association between HPV and cervical cancer, being a risk factor for relapse, it is clear that the presence of other factors are required for it to turn conversion into malignant. In our city, where the people attending consultation at the IMSS are predominantly of low or very low income groups, there are several concomitant infections that could play an important role in the evolution of this neoplasm.

During the one semester review, the median age of 43 was higher than that reported in other studies, but third and fourth decades of life are still the predominant ranges for the appearance of this disease. Meta-analysis of the literature has revealed that disparities in cervical cancer screening rates become more pronounced with advancing age [11]. Decreased screening and treatment of precancerous lesions likely contribute to the higher incidence of cervical cancer among older minority populations, and can also explain the observed later stages of diagnosis. Adherence to follow-up after an abnormal Pap smear is also low among minority groups.

The general gyneco-obstetric antecedents show the principal risk factor for developing this malignancy in the studied population is multiparity, that in most cases was associated to an early first sexual intercourse which is also a significant risk factor for cervical cancer. The role of abortions and cervical-uterine cancer is not well defined.

The high quality in 86.5% of cases gives confidence to the results. The tissues extracted by surgical procedures were higher than those of biopsies because the General Regional Hospital is a second level health institution. The percentage of total pathological studies with at least one grade of cervical-uterine cancer (18.18%) was very high taking into account that in developed countries this is a rare disease, unlike in developing countries where this disease is relatively common, as has been published by Lizano et al. [12] who found in 101 women with pathological cytologies, there were 54 cases (53.5%) of low-grade SIL and 47 cases (46.5%) of high-grade SIL out of a total of 277 women studied.

The high prevalence and incidence of CIN, micro-invasive carcinoma and invasive carcinoma in Mexico indicates that there is a wide sector of the population escaping early detection. If mortality rates does not change in Mexico, 10,839 deaths are predicted in the year 2050. In contrary to 3739 cases of in Europe (Fig. 1).

Since most cases are CIN III and CIS, there is an option for treatment with good prognosis of these malignancy. Although some CIN I—III lesions would heal spontaneously, management is based on surgical excision of part of the uterine cervix because such lesions can potentially progress into carcinomas. Most often this treatment leads to the cure of intra-epithelial lesions but the incidence of recurrence is 4.88/10,000 woman-months (HIV-negative) [13].

It is critical to take into account the vascular and glandular invasion (percentage near 20%) to decide the pertinent therapeutical decision. To evaluate the prognosis, besides invasion, it is important to consider the findings of metaplasia, keratinization, differentiation grade and other lesions.

Within the limitations of observational, retrospective non-randomized study, our results are in agreement with those obtained from published randomized trials which state the high prevalence of HPV and cervical cancer [14]. Although the General Regional Hospital 220, IMSS, is a second level referal center and a reference center that could bias the real prevalence of HPV infection and cervical-uterine cancer, it is important to say that the rural areas have lower coverage of early cancer detection. It thus seems necessary for public health policy makers and researchers to thoroughly understand the process failures in contemporary screening environments in order to plan the implementation of future prevention modalities [15].

We conclude that HPV infection and cervical-uterine cancer have a very high prevalence in the State of Mexico, as reported in other developing countries [16]. Screening for cervical cancer based on testing for HPV increases the sensitivity of detection of high-grade CIN (II or III). Concomitant infections with HPV must be studied to identify the physiopathological involvement of each one alone or in conjunction and prognosis must be individualized taking into account all pathological data reported to evaluate the true dimension of our goals. As cervical cancer continues to cause significant morbidity and mortality worldwide, prophylactic cervical cancer vaccines seems to be a good option for its prevention.

Finally, we support the idea previously published to develop a generalized cost-effective analysis of Pap smear screening, high-risk HPV testing and the HPV vaccine, in the Mexican context. The success of detection programs for any disease resides in its implementation and for cervical cancer diagnosis this is not an exception. However, while there is still no improvement in the population's quality of life and education, advances in health programs will still be poor.

Conflict of interest

Acknowledgments

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