

30 years of preventive studies of uterine cervical cancer 1982-2012

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Abstract

Purpose: To show and describe the clinical evolution of cervical cancer screening patients following the protocol established by the University of Padua. **Methods:** 12,679 patients were examined using Pap smear, colposcopy and biopsy in cases it was required. **Results:** From these large group of patients, 6,411 were diagnosed as patients at risk of developing cancer, from which 4,257 only had HPV infection, 1,150 had dysplastic lesions, 210 had cervical cancer and 794 cases were classified as simple oncogenic risk.

Keywords: preventive studies; uterine cervical cancer; human papillomavirus; gynecological care

Introduction

Since the 1990's, several epidemiological studies have established a strong evidence of relation between cervical cancer and human papillomavirus (HPV) infection. Some of the reports state, HPV has been proposed to be a necessary cause, which means that cancer does not develop unless HPV DNA is present in a persistent way [1].

Under these circumstances, cervical cancer screening has become an important part of women's health care, due to its high incidence and mortality, especially in third world countries. According to the latest statistics, the mortality rate of this cancer is three times higher in Latin America and the Caribbean than in North America and European countries. In Panama, cervical cancer is the second most common type of cancer in women and the second most common cause of death, with a morbidity rate of 25.3/100,000 habitants and a mortality rate of 7.4/100,000 habitants. Overall, is the third most common type of cancer in this country, surpassed by breast cancer and prostate cancer [2] [3].

Since its appearance in the 1940's, Pap smear has become a significant diagnostic test for notification of cervical cancer's worldwide incidence and to treat the cancer at early stages. One clear example is Canada, where the incidence rate has been decreased from 21.6 per 1000 in 1969 to 10.4 per 1000 in 1990 [4]. Despite Pap smear's impact globally, Panama still has a high incidence and mortality rate, as it was previously explained. One reason that has been proposed as a possible explanation for this

situation is under screened populations. By 2006, Panama only had 20% coverage. After a Pap smear campaign took place in the same year where 650,000 Pap tests were performed, 57% coverage was reached, and it has kept increasing since then. Nowadays, coverage is around 70%, which is still not enough to reduce the incidence of this disease (a drastic decrease is reached when the coverage is around 75%) [4]. Another possible explanation, is Pap smear's low sensitivity (50% and even 20% in some cases) which means most of the times, Pap smear is not detecting abnormalities. The sensitivity can be decreased further due to lack of expertise in sample collection for Pap smear as per previous references [5].

The current protocols suggest using Pap smear initially, and if there is any abnormal findings, patients must be submitted to more sensitive tests, such as colposcopy and biopsy as per clinical condition correlation and to treat them effectively. This combination protocol of Pap test and

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colposcopy is being followed regularly at the University of Padua which has been taken for the study of mentioned objectives.

Material and methods

In total, 12,679 women were evaluated randomly. All of them were examined either at Chemsá clinic or during the medical tours in 6 provinces of Panama. Some of them came for their annual or six months health control, and others came referred from other institutions or clinics due to any abnormal finding detected by Pap smear according to the Bethesda system (eg. 3 consecutive inflammatory Pap results, persistence of ASC-US, or ACG-NOS, low grade squamous intraepithelial lesion (LGSIL) which usually indicates CIN 1 due to HPV infection, or high grade squamous intraepithelial lesion (HGSIL) which corresponds to CIN II or III). Patient's profile corresponded to these parameters: 2 pregnancies, 2 births, 0 abortions, first menstrual period between 13 and 15 years old, first sexual intercourse between 15 and 20 years, 2 sexual partners, and almost all of them used a family planning method. Ages ranged between 18 to 90 years old.

The author of this study along with other fellow physicians took Pap smears from all patients (except in those patients whose last Pap test was taken over the last 6 months). It was then followed by colposcopy in all cases, despite the fact they only came for their health control or if they were referred by other physician. This consists in a camera which is used to observe and examine the cervix in more detail, and afterwards, three chemical substances (acetic acid 3 – 5%, Lugol solution and sodium bisulphite) are applied over the cervix. First, acetic acid was applied with a double purpose, to eliminate excessive mucous due to the denaturation of proteins, and to produce vasoconstriction, and therefore obtain a clearer image. Normal cervical tissue remains pink after acetic acid is applied, but pathological tissue is observed as a white stain. Then, Lugol solution is applied. Exocervical epithelial cells have glycogen deposits, which is why after Lugol is applied, tissue is observed purple or even black. Glandular cells on the other hand lack of glycogen which is why they do not capture this substance, and remain stainless. This latter case is what also happens with squamous metaplasia, ectropion and low or high grade intraepithelial lesions. Finally sodium bisulphite removes the Lugol solution and allows differentiating the transformation zone from any lesion. If any abnormal staining pattern was observed during the exam, a biopsy is taken immediately and treatment is administered according to each particular case.

After 26,889 colposcopies were performed along with 26,251 Pap smears and 5,868 biopsies, the results were gathered and organized in order to describe the patients initial diagnosis and their clinical evolution after the treatment, which in most cases consists cryotherapy or electrical cauterization.

Patients were classified into two large groups: healthy patients and oncogenic risk (OR) patients. The latter group refers to those patients whose results indicated the higher risk of developing cancer. Among them, there were different types of diagnoses, which were established after the cytological, colposcopy and histological results were compared and analyzed. These groups were: i) Simple HPV: These cases corresponded to patients who only had HPV infection and it was only found in the Pap smear but no lesion was found during the colposcopy. ii) Dysplasia: Patients in this group could either have had abnormal cytological findings, as well as abnormal colposcopy results. The diagnosis was later confirmed by a biopsy. Dysplasia could be either found with or without the presence of HPV. iii) Cancer: Patients in this group could either have had abnormal cytological findings, as well as abnormal colposcopy results. The diagnosis was later confirmed by a biopsy. Cancer could be either found with or without the presence of HPV. iv) Simple oncogenic risk: These patients only had observable lesions during the colposcopy, but neither the Pap smear nor the biopsy showed pathological results.

Finally, a small group of patients was chosen to verify and confirm the treatments efficiency. They were classified according to their clinical evolution in 5 groups, following certain criteria: i) Cured: Pap test: No cytological abnormality was found; Colposcopy: No lesion was observed. ii) Improved: Pap test: Either no cytological abnormality was found or the pathology degree was lower than the previous one; Colposcopy: There is a visible lesion, but its extension is smaller. iii) Persistence: Both Pap smear and colposcopy remained the same. iv) Recurrence: Patient presented either a Pap test or colposcopy abnormality after being cured. v) Progression: Both the Pap test and the colposcopy showed a higher pathology degree than the previous one.

Results

From the total of oncogenic risk patients 2,164 women were organized according to their ages (Table 1).

Most of the HPV cases were found between 25 to 35 years old. Dysplasia on the other hand was most commonly found afterwards, being the group between 45 to 49 the most affected by this condition. Among the youngest group (15 to 19), some cases of dysplasia were found and even cancer (28 and 5 cases respectively). This is not an expected finding, according to the natural behavior of the disease in which years of persistent infection are needed to develop a lesion [7].

Following the already explained criteria, from the 6,411 OR patients (which represents 50.6% of the studied population), the following results were obtained: simple HPV cases were 4,257; dysplasia was found in 1,150 cases where 1,096 were associated with HPV and 54 cases were not; 210 cases of carcinoma in situ were diagnosed, from which 145 of them were associated to HPV. Among these

Table 1 Patients according to their ages.

Ages	Simple OR	Simple HPV	Dysplasia	Cancer	Total
15-19	41	97	28	5	171
20-24	40	70	23	5	138
25-29	44	151	55	5	255
30-34	31	229	91	10	361
35-39	13	121	34	4	172
40-44	11	112	111	6	240
45-49	11	65	120	0	196
50-54	17	64	66	1	148
55-59	18	106	38	4	166
60-64	7	85	16	0	108
65-69	13	50	18	0	81
70-74	5	39	17	0	61
75-79	6	40	21	0	67
Total general	257	1229	638	40	2164

Abbreviations: OR = oncogenic risk; HPV = human papillomavirus.

patients, 44% of them were new patients, that is to say, patients who came for the first time to be examined at Chemsá clinic or during the gynecological tours (Table 2).

Table 2 Established diagnoses over the past 30 years of studies.

Type of Pathology	Quantity	Percentage
Pure HPV	4257	0.664
Dysplasia associated to HPV	1096	0.171
Dysplasia non associated to HPV	54	0.008
Cancer associated to HPV	145	0.023
Cancer non associated to HPV	65	0.01
Simple OR	794	0.124
Total	6411	1

Abbreviations: OR = oncogenic risk; HPV = human papillomavirus.

After all the diagnoses were established, it was possible to determine the sensitivity of each diagnostic technique. For instance, Pap smear by itself was able to detect 50% of the patients with any type of the previously explained conditions. Other 50% that the Pap smear negative cases was presented as low, mild or severe inflammatory results. Colposcopy detected 79% of the cases as atypical reepithelization zone (ARZ), leukoplakia or as HPV lesions. When these 2 techniques were combined with the biopsy, the sensitivity increased to a 99%.

Once the diagnoses were explained to the patients, they were all treated, either by cryotherapy, electrical cautery, or a combination of them. Other kind of treatments were topical or in certain cases, surgical treatment (hysterectomy or cervical conization). After the 1990's, the author of this study and his team did not perform any cervical conization due to various complications as consequences of this treatment, especially in pregnancies (Table 3) [8].

Table 3 Patients according the received type of treatment - 3,775 cases.

Type of treatment	Pure OR	Pure HPV	Dysplasia	Cancer	Total
Cryotherapy	229	1509	542	20	2300
Cauterization	178	305	66	0	549
Combined treatment	57	625	20	0	702
Others	11	60	73	80	224
Total	475	2499	701	100	3775

Abbreviations: OR = oncogenic risk; HPV = human papillomavirus.

After the patients were treated, they required to be checked periodically in order to confirm the treatment was indeed effective. These gynecological health controls were performed every 3 to 6 months. When the patients were completely cured, they could be checked annually.

In 2011 and 2012, 410 cases were chosen to observe their clinical evolution. As a result of the applied treatments, 369 cases were cured while the rest improved, persisted, recurred or remained the same. What must be emphasized is that none of the cases evolved to invasive cancer (Table 4).

Table 4 Clinical evolution of 400 cases.

Evolution	Number of patients	Percentage (%)
Cured	369	90
Improvement	13	3.2
Recurrence	8	1.9
Persistence	12	2.9
Progression	8	1.9
Invasive Cancer	0	0
Total	410	~100

Discussion

Panama is a small country with a high incidence of cancer, according to the statistics mentioned before. However this was not the case in this research. These results showed a low cancer incidence, and despite of the several cases of dysplasia, very few of them evolved to a more serious condition. In fact, the author of this study was able to detect and treat any found lesion achieving

a satisfactory percentage of cured patients. This could be the result of the combined use of Pap smear and colposcopy (and biopsy in cases it was required). Despite of discontinuation in America, colposcopy has proven to have a greater sensitivity compared to the Pap test. One of these evidences was found in Kuramoto's study, where they chose 2000 women from a Japanese clinic. Among them, colposcopy detected 3.3% of abnormal colposcopic findings, whereas Pap test only detected 1.1% of abnormalities [9]. In the research performed over the past 30 years, Pap smear only detected 50% of abnormalities. The undetected 50% corresponded to false negative Pap tests, in which the main diagnosis was mild, moderate or severe inflammatory Pap result, thus confirming Pap smear low sensitivity rate. Nevertheless, Kuramoto's research also pointed out that colposcopy had a high percentage of unsatisfactory results. In almost 1 out of 4 patients, the squamous columnar junction was not visualized, which could be explained by the patients ages (40 to 60 years old approximately). In this research, very few cases had an undetected squamous columnar junction.

Even though colposcopy has a lower specificity compared to Pap smear, it contributed enormously to the detection and treatment of the lesions. One of the aspects to be considered is the fact that the author of this study performs colposcopy routinely, unlike most gynecologists in our country or region, which means that he has observed normal and abnormal colposcopy findings every day to the primary care attention over the past 30 years. As Bosze established, by being constantly examining patients, the ability of the examiner to detect and diagnose both the normal and abnormal findings by performing a colposcopy increases, compared to those who only do a colposcopy for specific cases [10].

When it comes to the treatment part, it was observed that 90% of the evaluated patients who underwent treatment were cured. This is mainly due to the fact that the patients' lesions were detected in early stages. These early stages are usually the ones where Pap smear has the lower sensitivity rate [10]. Colposcopy, however, maintains its sensitivity rate constant despite the disease stage.

At the end, the evidence obtained by this author points out the increase of the gynecological examination sensitivity when both methods are combined, which latter results in a greater benefit for the patient both physically and mentally, by detecting lesions that the Pap smear alone would not have been able to detect and by reassuring the patient that they are indeed healthy and lesion free.

What was really noticeable and worrisome was the fact that very young patients were diagnosed with severe dysplasia, or even worse carcinoma in situ. Considering HPV natural history, this could possibly mean that women are beginning their sexual lives at very young ages, which supports the need for young girls to get vaccinated against

HPV and not allowing it to develop to a much worse and even deadly condition such as cervical cancer [11].

Conclusions

Patients from all ages presented some grade of cervical pathology. HPV infection was most commonly found in patients between 25 to 39 years old, whereas dysplasia, between 40 to 49 years old. Despite the young age, some cases of dysplasia and cancer were found in patients under 25 years old. According to the obtained results, Pap smear has a 50% sensibility in detecting cervical pathology. When combined to colposcopy, the gynecological exam sensibility is increased to a 79%. Finally when the biopsy is added, error percentage decreases to 1%. 90% of the patients were cured from their lesions, but most importantly, none of them evolved to invasive cancer.

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Conflict of interest

The authors declare no conflict of interest.

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