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Assessment of the Validity and Reproducibility of the Pap Smear in Mexico: Necessity of a Paradigm Shift

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Background and Aims. An assessment was performed of the quality of Pap readings in 19 cytology laboratories (CLs) in Mexico from the Cervical Cancer Screening Program.

Methods. Nine CLs were affiliated with the Health Ministry (SSA), and ten were affiliated with the Mexican Social Security Institute (IMSS). Two sets of 200 cervical cytology specimens were prepared, one set for each institution. Fourteen percent of the specimens were positive and six were inappropriate for diagnosis (3%). All cervical cytology specimens were processed in the cytopathology laboratory at the General Hospital of Mexico, and histopathology was available for each positive case.

Results. Thirty percent of the SSA reading centers had a sensitivity of at least 80%; however, not one of the ten IMSS laboratories evaluated reached this figure. Some reading centers had a sensitivity $<65\%$, meaning that nearly half of the specimens with a cytology consistent with cervical neoplasm were not identified.

Discussion. Given these results, it is a priority to effect a paradigm shift combining various screening tests to improve adherence to standards and enhanced cost-effectiveness of the early detection of cervicouterine cancer (CC) in Mexico.

Key Words: Cervical cytology, Cervicouterine cancer, Pap smear.

Introduction

The technical quality of cervical cytology interpretation of Papanicolaou (Pap) tests is essential for the proper functioning of early detection programs (EDPs) for cervicouterine cancer (CC) (1).

Cytological interpretation in screening programs determines which women require medical attention, and misinterpretation leads to radical changes in the management of affected patients. During the past 50 years, the incidence and mortality of CC in developed countries have decreased by as much as 75% (2–4), partly due to well-organized screening programs covering most at-risk women, supplemented by proper diagnosis, treatment of precancerous lesions, and a good quality control at all stages. The situation is different in developing countries where screening programs have not been implemented or have been inadequate; consequently, the incidence and mortality of CC remain a major problem (5,6). In Mexico, the EDP for CC has been functioning for three decades. At the program's inception in 1979, the adjusted mortality rate was 11.64/100,000 women. This relatively low value was influenced by significant underreporting, which was typical at that time. Subsequently, a gradual rise was observed, reaching the highest rate in 1989 (16.17/100,000 women). Since then, a gradual and sustained downward trend occurred, reaching a rate of 7.3/100,000 women with 4,079 deaths per year in 2011, establishing a correlation between this decline and the advent of Pap screening (7–9). In recent years, CC diagnostics have been openly questioned because of the growing concern from health authorities about the shortcomings of the test (10–12) including low reproducibility (1,13) and high rates of false negatives (14) due to the low sensitivity of the test. At the national level, previous

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assessments of the sample collection quality revealed that >60% did not meet the required standards (15). Some laboratories had false negative report rates >50%, with a sensitivity of 66.3% and a wide interinstitutional variation in the test reproducibility, which reported kappa values of 0.20−0.47 (16). With the identification of HPV as the necessary cause of CC (17), the implementations of molecular tests in EDPs and of the human papillomavirus vaccine (HPV) in 2009 (for its final inclusion in the universal vaccination program of Mexico in 2012) were aimed at the female population aged 12−16 years living in high-risk municipalities (18). The first dose of the vaccine was administered in October of the same year (during the third National Health Week) to girls in the fifth grade and to girls 11 years of age who were not enrolled in school, with an extended vaccination scheme of three doses at 0, 6, and 60 months (19), thereby beginning a paradigm shift in public health strategies in Mexico. However, much remains to be done.

Materials and Methods

An assessment was performed of the technical quality of Pap smear readings in cytology laboratories (CLs) of the country during the period from October 2008−March 2009 (19).

Pap Validity and Reproducibility

The unit of observation was the CL. The staff of each CL was responsible for interpreting one of the two sets of 200 gynecological exfoliative cytology specimens at different clinical stages including the following: negative for cancer (70 and 76%), atypical squamous cells of undetermined significance (ASCUS) (2 and 0.5%), low-grade squamous intraepithelial lesions (LSIL) (13.5 and 9.5%), and high-grade squamous intraepithelial lesions (HSIL) (14.5 and 14%) for the SSA and IMSS sets, respectively. The diagnosis was performed through simulation of the daily reading routine during regular working hours without exceeding the workload rules (50 slides a day) (20).

Specimens were randomly distributed among the staff of each CL, and each new reading was independent of the reader and the previous reading, thus ensuring that the diagnostic error was also random.

The study participants were nine CLs affiliated with the SSA located in the northern, central, and southern regions of the country: Campeche State Laboratory (SL) (n = 5), Guerrero (SL) (n = 4), Hidalgo (SL) (n = 17), Jalisco (SL) SSA (n = 6), Morelos Cancer Center (n = 6), Nuevo Leon (SL) (n = 9), Puebla (SL) SSA (n = 20), Tabasco (SL) SSA (n = 18), and Yucatan (SL) SSA (n = 6). In addition, ten CLs were affiliated with the IMSS located the northern, central, and southern regions of the country: (Family Medicine Unit No. 1 Campeche (n = 4), Zone General Hospital #1 and ZGH #3A (n = 9) Federal District, ZGH #53 State of Mexico (n = 7), Hidalgo ZGH #2 (n = 3), ZGH #89 Jalisco (n = 10), Regional General Hospital #1 Morelos (n = 4), ZGH #17 Nuevo Leon (n = 4), ZGH #46 Tabasco (n = 3), and Yucatán Regional Medical Center (n = 3)). Each participating institution interpreted the same group of cytology specimens to measure the reproducibility among centers.

Reference Unit

Our gold standard consisted of two sets of 200 specimens that were interpreted by a team of three expert cytopathologists. All cytopathologists were supervised by a cytopathologist with national and international certification and over 40 years of experience as well as being the director of the Department of Laboratory Pathology at the National Autonomous University of Mexico operating at the General Hospital of Mexico. This team of experts led to the diagnosis of each specimen.

Exfoliative cytology specimens were randomly selected from a pool of 3,800 slides from the cytopathology laboratory of the General Hospital of Mexico. Access was granted to the results of the histopathological specimens positive for HSIL, invasive carcinoma, squamous cell carcinoma, and adenocarcinoma. Furthermore, the quality of the specimens was considered appropriate for diagnosis.

Data Collection Instrument

The ‘‘Cervical Cytology Request and Report Form of the Prevention and Control Program for Cervicouterine Cancer of the Health Department’’ was used, the content of which is based on the 2001 Bethesda classification (21).

Outcome Variable

The reference diagnosis by the team of expert cytopathologists at the General Hospital of Mexico was used for evaluation. The degree of agreement between cytology readings was analyzed using weighted kappa for ordinal polytomous variables. This factor estimates the degree of agreement not due to chance from the proportion of observed agreement and the proportion of expected agreement.

One hundred forty-one 4 x 4 diagnostic tables were generated (see the analysis methodology). For analysis purposes, the agreement index was further classified into a) poor agreement (K ≤0.46), b) intermediate agreement (K 0.47−0.74), and excellent agreement (K ≥0.75).

Statistical Analysis

To determine the kappa index, the reactive, reparative, and inflammatory changes as well as inadequate specimens were grouped into the category of ‘‘negative’’, given the clear criteria (22) for this analysis. The ASCUS were not required to be grouped with any other diagnosis. The diagnoses of LSIL with cells indicative of the presence of