Decreasing Cervical Cancer Mortality in Mexico: Effect of Papanicolaou Coverage, Birthrate, and the Importance of Diagnostic Validity of Cytology

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Abstract

Background: The reduction in cervical cancer mortality in developed countries has been attributed to well-organized, population-based prevention and control programs that incorporate screening with the Papanicolaou (Pap) smear. In Mexico, there has been a decrease in cervical cancer mortality, but it is unclear what factors have prompted this reduction.

Methods: Using data from national indicators, we determined the correlation between cervical cancer mortality rates and Pap coverage, birthrate, and gross national product, using a linear regression model. We determined relative risk of dying of cervical cancer according to place of residence (rural/urban, region) using a Poisson model. We also estimated Pap smear coverage using national survey data and evaluated the validity and reproducibility of Pap smear diagnosis.

Results: An increase in Pap coverage ($\beta = -0.069$) and a decrease in birthrate ($\beta = 0.054$) correlate with decreasing cervical cancer mortality in Mexico. Self-reported Pap smear rates in the last 12 months vary from 27.4% to 48.1%. Women who live in the central (relative risk, 1.04) and especially the southern (relative risk, 1.47) parts of Mexico have a greater relative risk of dying of cervical cancer than those who live in the north. There is a high incidence of false negatives in cervical cytology laboratories in Mexico; the percentage of false negatives varies from 3.33% to 53.13%.

Conclusions: The decrease in cervical cancer mortality observed in Mexico is proportional to increasing Pap coverage and decreasing birthrate. Accreditation of cervical cytology laboratories is needed to improve diagnostic precision. (Cancer Epidemiol Biomarkers Prev 2008;17(10):2808–17)

Introduction

Developed countries have implemented universal cervical cancer detection programs based on Papanicolaou (Pap) testing, and these programs have been the primary reason for a reduction in cervical cancer incidence and mortality over the last 50 years (1-3). However, virtually no reports exist about developing countries that quantify a reduction in cervical cancer mortality due to Pap screening (and treatment of cancers that are detected with this diagnostic tool).

In Mexico in the early 1980s, the national prevention and control program for cervical cancer faced daunting challenges. National trends included an increase in mortality due to cervical cancer in all age groups (4); <15% of the eligible female population had ever had a Pap smear; and coverage was particularly low in extremely underdeveloped and poor areas (5). There was also an absence of epidemiologic monitoring and of quality control measures for collection and diagnosis of cervical cytology samples (6-8). At the beginning of the 1990s, an evaluation of the quality of cervical cytology specimens in Mexico reported that >60% lacked endocervical cells, mucus, and/or metaplasia cells. In addition, some cervical cytology screening centers reported >50% false-negative results (9).

In this context, 30 years after the initiation of a national program geared toward detection, treatment, and prevention of cervical cancer in Mexico, we evaluated the progress made in terms of reductions in mortality, level of Pap coverage, and quality of Pap diagnosis. The evaluation focused on the effect of birthrate and Pap coverage on cervical cancer mortality during the 1979-2004 period, self-reported Pap smear use in the last year based on national survey data, and also included a study on the quality (reproducibility and validity) of cervical cytology diagnosis through a sampling of 24 cervical cytology laboratories in the northern, central, and southern parts of Mexico.

Materials and Methods

Different methodologic strategies were used to evaluate the effect of the national cervical cancer screening program in Mexico: a linear regression model, a Poisson model, analysis of national survey data, and a study on cytologic diagnostic validity and reproducibility.
Analysis of Mortality Due to Cervical Cancer in Mexico, 1979-2006: Linear Regression and Poisson Models

Linear Regression Model. Cervical cancer mortality rates in Mexico during 1979-2006 were analyzed using official information obtained from the National Institute of Statistics, Geography, and Data Processing (INEGI) database. This system registers cervical cancer tumors using a coding system that classifies both the primary origin and specific location of tumors according to the 9th and 10th Editions of the International Classification of Diseases (ICD-9 and ICD-10). Tumors originating and located in the cervix are classified with code 180 (ICD-9, used until 1997) or code C53 (ICD-10). The denominator was the age-standardized world population during the study period (10).

To explain the trends in cervical cancer mortality rates in Mexico for 1979-2006 and correlate them with birth rate and Pap smear coverage at the national level, a linear regression model was developed based on the null hypothesis that $\beta$ is zero. The $\beta$ coefficient is the change in $Y$ (the dependent variable; in this case, the standardized rate of cervical cancer mortality) for each unit that an independent variable increases or decreases (the independent variables in this model are birth rate, Pap smear coverage, and gross national product). To control for the effect of age structure and the demographic transition observed in Mexico, the rates of cervical cancer mortality were standardized based on the age structure of the world population. In addition, to take into account any relationship with socioeconomic factors, we included the gross national product in this model. We applied a logarithmic function to the cervical cancer mortality variable to make linear the relationship with the independent variables (birthrate, Pap smear coverage, and gross national product).

Poisson Model. To estimate the relative risk of dying of cervical cancer in each of Mexico’s states, a multiplicative Poisson model was constructed and adjusted for age and place of residence (urban/rural), using as reference values the Mexico City mortality rates, which represent the lowest standardized mortality rate at the national level. The probabilistic Poisson model was used to evaluate cervical cancer mortality risk as an unusual event on a continuous scale; this type of model makes it possible to observe regional differences in the relative risk of dying of cervical cancer. The Poisson regression model was constructed using the annual number of cervical cancer deaths (for each state in Mexico) as the dependent variable and the state of residence and urban/rural residence as the independent variables. The rural and urban residence variables were constructed based on theoretical definitions, so statistical variance in the analysis of the database information is possible. For this reason, and for the purposes of this study, the rural population is defined as municipalities with a population <15,000 inhabitants, and urban population is defined as municipalities with $\geq$15,000 inhabitants. The cervical cancer mortality risk was assessed as a function of urban/rural residence for the female population, as shown in the following equation:

$$\log(E(y)) = \beta_0 + \beta_{state} + \beta_{urban/rural}$$

Self-Reported Pap Smear Use in Mexico Based on National Survey Data. The decrease in cervical cancer mortality observed in developed countries has generally been attributed to prevention through early detection with the Pap test administered by an organized detection program, in conjunction with appropriate treatment of detected lesions (1-3). In recent years, the Mexican government has made a huge effort to expand the coverage and effectiveness of the cervical cancer prevention and control program. However, the extent to which these goals have been reached has yet to be determined. Therefore, self-reported Pap testing in the last 12 mo was used as an indicator of coverage per age group, based on the national survey data. The potential annual coverage of the cervical cancer early detection program in Mexico is 4 million Pap smears for a population of $\sim$26 million women $>25$ years of age in the year 2004.

National Health Survey 2000. Data from the National Health Survey in 2000 (ENSNA2000; ref. 11) were analyzed. This survey was developed by the Mexican Ministry of Health with the National Institute of Public Health, using a probabilistic, multistage, stratified, cluster sample design. For the present study, data for women $\geq$20 years of age were analyzed. The study sample is representative at both state and national levels. Information on Pap smear use was collected from 20,813 sexually active women.

National Reproductive Health Survey 2003. The National Reproductive Health Survey for 2003 (ENSA2003; ref. 12) was developed through a collaboration by the National Center for Gender Equity and Reproductive Health, the Regional Center of Multidisciplinary Research of the National Autonomous University of Mexico (CRIM), and the National Institute of Public Health. A multistage, stratified sampling strategy was used, and data collection was carried out in two phases. One phase involved a probabilistic survey that included urban and rural areas at the national level, and the second phase involved a state-level survey in eight states from throughout the country: Chiapas, Guerrero, Oaxaca, Guanajuato, Puebla, San Luis Potosi, Sonora, and Tamaulipas. For this analysis, data for sexually active women ages 15 to 49 y were used. The information taken from this survey was the percentage of women who have had sexual relations and who reported a Pap smear in the last 3 years, ever in their lives, or who have never had a Pap smear in their lives.

Pap Coverage Among Economically Disadvantaged Mexican Women: Opportunities Program Surveys 2002-2003. To determine Pap coverage among economically disadvantaged (poor) women, we used data from surveys of beneficiaries of the Mexican poverty reduction program, called the Opportunities Program (this conditional transfer program is akin to the U.S. Welfare Program). The first survey (13) was conducted among program beneficiaries who lived in urban areas in 2002, and the second survey (14), conducted in 2003, included equal participation from urban and rural residents who were Opportunities Program beneficiaries. In the first survey (urban, 2002), reproductive health data were analyzed for 14,058 sexually active women of ages 15 to 49 y. The information taken from this survey was the percentage of women living in urban areas who were...
beneficiaries of the poverty reduction program and have had sexual relations, and who reported a Pap smear in the last year or who have never had a Pap smear in their lives. In the second survey conducted (rural and urban, 2003), data were collected from a sample of 14,424 sexually active women between the ages of 15 and 49 y.

These surveys are representative of the target population of the Opportunities Program; i.e., women living below the poverty line who receive economic support and other benefits (e.g., health education, nutritional supplements) through this governmental poverty reduction program. Using these survey data, we analyzed the level of Pap smear coverage in this specific population; coverage was defined simply as a self-reported Pap smear in the last 12 mo. The information taken from the second (2003) survey was the percentage of women living in rural or urban areas who were beneficiaries of the poverty reduction program, who have had sexual relations, and who reported a Pap smear in the last year.

National Health and Nutrition Survey 2006. Data from the National Health and Nutrition Survey in 2006 (ENSANUT2006; ref. 15) were analyzed. As with the version carried out in 2000, this survey was developed by the Mexican Ministry of Health, through the National Institute of Public Health, using a probabilistic, multi-stage, stratified, cluster sample design. For this analysis, data for women ≥20 years of age were included. The study sample is representative at both state and national levels. The information taken from this survey was the percentage of women who have had sexual relations and who reported a Pap smear in the last year.

Evaluation of Diagnostic Validity and Reproducibility at 24 Cervical Cytology Laboratories in Mexico. Finally, an evaluation of 24 cervical cytology laboratories in Mexico was carried out during June-September in 2005. Two hundred twenty cervical cytology specimens were obtained from the cytopathology laboratory of the General Hospital of Mexico in Mexico City. According to the diagnostic reference, who was a pathologist with more than 30 years of experience and accredited by the Mexican Academy of Cytology, 20 (9%) of the specimens were insufficient for a diagnosis, due to a lack of indicators from the cervical transformation zone (endocervical cells, mucus, and metaplasia cells). The prevalence of cervical intraepithelial neoplasia II or more severe lesions in the study sample was 14.5%, and each diagnosis was corroborated with histopathologic studies. Twenty-four laboratories were identified from throughout the central, northern, and southern parts of Mexico, to each of which the same group of 220 cervical cytology specimens were distributed so that the centers could be compared with a reference standard. The diagnostic results were generated as each laboratory traditionally conducts their routine analysis independent of the number of cytotechnicians. The diagnostic nomenclature used was cervical intraepithelial neoplasia in accordance with Mexican official norms for the prevention and control of cancer before the year 2005. The cervical cytology laboratories that participated were located in the following states (with more than one in the first state): Veracruz, Mexico City, Mexico State, Guerrero, Hidalgo, Queretaro, Tlaxcala, Morelos, Puebla, Oaxaca, Michoacan, Nayarit, San Luis Potosi, Guanajuato, Aguascalientes, Yucatan, Campeche, Zacatecas, Hermosillo, and Baja California.

Results Evaluation of Cervical Cancer Mortality Trends in Mexico, 1979-2006. During the study period, there were officially 102,544 cervical cancer deaths reported in Mexico. Starting in the early 1980s, an increase in the number of cervical cancer-related deaths is observed in Mexico; the rate continues to increase, reaching the highest frequency in the 1990s, after which a slight decrease and then a plateau are observed (Fig. 1). In absolute numbers, the largest number of deaths reported was 4,620 in the year 2000. During the study period, the average annual growth rate in number of cases was 0.76%.
The cervical cancer mortality rate in Mexico rapidly increased at the start of the eighties and reached its highest rate in 1989, with 10.22 deaths per 100,000 women. The mortality rate began to diminish at the beginning of the 1990s until 2004 when it reached 8.01, which is still not below the 1979 rate of 7.28. Nevertheless, for the 1989-2004 period, mortality rate decreased by 2.94, which equals about 3 fewer deaths per 100,000 women (Fig. 1). In Mexico, a significant decrease in birthrate is observed starting in the 1980s, and there has been a gradual increase in Pap smear coverage, with an especially sharp increase in 1998 (Table 1).

The linear regression model was used to determine which factors were associated with the observed decrease in cervical cancer mortality rates; according to this model, the two factors that determine the recent decrease in cervical cancer mortality in Mexico are an increase in Pap coverage (β = −0.069) and lower birthrate (β = 0.054; Fig. 2). Thus, for each unit of increase in Pap smear coverage, cervical cancer mortality decreases by 0.069; for each unit of decrease in birthrate, the cervical cancer mortality rate decreases by 0.054. Specifically, this means that as the birthrate decreases in Mexico, cervical cancer mortality also decreases, and as the Pap smear coverage increases, cervical cancer mortality decreases as well. As shown in Fig. 2, annual Pap smear coverage and gross national product have an inverse association with cervical cancer mortality rates. According to the goodness-of-fit test, the linear regression model had a good fit. This model explains 91% of the variance in the cervical cancer mortality rates (R² = 0.91).

Poisson regression was used to determine the relative risk of dying due to cervical cancer given rural or urban residence, the region of residence, or state of residence. This model shows that in the year 2000, a Mexican woman who lived in a rural area had a 3-fold greater cervical cancer mortality risk compared with a woman who lived in an urban area (Table 2). Likewise, in 2000, women living in states in the southern part of Mexico had a higher cervical cancer mortality risk compared with women living in states in the northern or central parts of the country. Women living in the central and southern regions have higher risks of dying due to cervical cancer as compared with those living in the north (the northern region was used for comparison). Thus, women living in the central region have a relative risk of dying due to cervical cancer of 1.04, and those who live in the south have a relative risk of 1.47, both as compared with the women who live in the north (Fig. 3). However, in 2004, the difference in the relative risk of mortality among women living in a rural area (as compared with women living in urban zones) was no longer statistically significant. In addition, by 2004 only some states showed a statistically significant difference.

### Table 1. Cervical cancer mortality rates standardized by age and world population, birthrate, and annual coverage of cervical cytology (Pap smear), 1979-2006, Mexico

<table>
<thead>
<tr>
<th>Year</th>
<th>Cervical cancer mortality rate</th>
<th>Age-standardized rate</th>
<th>Birthrate</th>
<th>Pap coverage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1979</td>
<td>33,031,932</td>
<td>2.405</td>
<td>7.28</td>
<td>11.64</td>
</tr>
<tr>
<td>1980</td>
<td>33,929,737</td>
<td>2.543</td>
<td>7.49</td>
<td>12.07</td>
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<tr>
<td>1981</td>
<td>34,829,988</td>
<td>2.626</td>
<td>7.54</td>
<td>12.12</td>
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<tr>
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<td>35,729,292</td>
<td>2.960</td>
<td>8.28</td>
<td>13.32</td>
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<td>36,625,667</td>
<td>3.057</td>
<td>8.35</td>
<td>13.43</td>
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<td>37,518,540</td>
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<td>8.81</td>
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<td>9.30</td>
<td>14.93</td>
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<td>40,196,199</td>
<td>3.900</td>
<td>9.70</td>
<td>15.47</td>
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<td>41,081,201</td>
<td>4.096</td>
<td>9.97</td>
<td>15.90</td>
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<td>1989</td>
<td>41,961,341</td>
<td>4.290</td>
<td>10.22</td>
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<td>1990</td>
<td>42,827,794</td>
<td>4.280</td>
<td>9.99</td>
<td>15.62</td>
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<td>1991</td>
<td>43,682,422</td>
<td>4.194</td>
<td>9.60</td>
<td>14.96</td>
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<td>1992</td>
<td>44,529,824</td>
<td>4.346</td>
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<tr>
<td>1995</td>
<td>46,967,754</td>
<td>4.392</td>
<td>9.35</td>
<td>13.97</td>
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<tr>
<td>1996</td>
<td>47,725,446</td>
<td>4.526</td>
<td>9.48</td>
<td>13.96</td>
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<td>1998</td>
<td>49,151,719</td>
<td>4.545</td>
<td>9.25</td>
<td>13.26</td>
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<tr>
<td>1999</td>
<td>49,834,760</td>
<td>4.590</td>
<td>9.21</td>
<td>12.98</td>
</tr>
<tr>
<td>2000</td>
<td>50,499,519</td>
<td>4.620</td>
<td>9.15</td>
<td>12.75</td>
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<tr>
<td>2001</td>
<td>51,143,166</td>
<td>4.512</td>
<td>8.82</td>
<td>12.16</td>
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<tr>
<td>2002</td>
<td>51,765,793</td>
<td>4.330</td>
<td>8.36</td>
<td>11.40</td>
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<td>2003</td>
<td>52,368,972</td>
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<td>8.26</td>
<td>11.15</td>
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<td>2004</td>
<td>52,954,018</td>
<td>4.241</td>
<td>8.01</td>
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<td>2005</td>
<td>53,522,389</td>
<td>4.273</td>
<td>7.98</td>
<td>10.46</td>
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<td>2006</td>
<td>54,077,059</td>
<td>4.134</td>
<td>7.64</td>
<td>9.88</td>
</tr>
</tbody>
</table>

*Cervical cancer mortality rates standardized by age and world population; rate per 100,000 women. Source: ref. 10.

*Bithrate per 100,000 women. Source: Mexican National Population Council (CONAPO) population projections for Mexico, 1970-2030.

*Pap coverage: percentage of women ages ≥25 y who received a Pap smear (as reported by the Ministry of Health). Source: Women’s Cancer Prevention and Control Program, Ministry of Health, Mexico.

*Cancer Epidemiology, Biomarkers & Prevention

in terms of the effect of the region (north, central, or south) on cervical cancer mortality. This suggests that the relative risk of cervical cancer mortality in Mexico no longer differs by urban or rural residence, and only sometimes differs by state of residence. Similarly, by the year 2006, conclusive differences are no longer observed in the risk of dying of cervical cancer related to rural residence, as compared with living in an urban area. However, in 2006 there continued to be a greater risk of dying of cervical cancer among women residing in the southern part of the country.

**Evaluation of Pap Smear Coverage in Mexico, Measured through National Surveys.** In Mexico, according to the National Health Survey in 2000 (ENSA 2000), 31.0% of women reported receiving a Pap test during the last year. According to the National Reproductive Health Survey (ENSAR), in 2003 this percentage increased to 37.8% (Fig. 1). As for the periodicity with which Mexican women receive Pap tests, the ENSAR indicates that in 2003, 37.8% of women reported receiving this test in the last 12 months, 28.8% in the last 1 to 3 years, 5.8% more than 3 years ago, and 27.6% had never been tested (Fig. 4).

According to these data, 66.6% of women reported a Pap smear during the last 3 years. The cervical cancer prevention program in Mexico recommends a Pap smear once every 3 years (after two subsequent negative yearly smears), and about two thirds of Mexican women report compliance with this recommendation. Although this indicates an important improvement in Pap coverage in Mexico in recent years, the fact that almost a third (27.6%) reported never having received a Pap smear in their lifetimes is a motive for concern. In addition, according to the National Health Survey (ENSA) in 2000, a third (32.7%) of the women who reported a Pap test did not know their test results.

According to the 2002 Urban Opportunities Survey, 30.1% of women (with a low socioeconomic level) reported a Pap smear during the last year. Likewise, 58.5% of these women reported at least one Pap test in their lifetimes. Therefore, a high percentage (41.5%) of Mexican women who are beneficiaries of the governmental poverty reduction program had never had a Pap test in their lives as of the year 2002.

We also analyzed the coverage registered in the 2003 Opportunities Survey for rural and urban populations. This survey only collected information on self-reported Pap tests during the previous 12 months. By 2003, 39% of women from urban areas who were Opportunities Program beneficiaries reported a Pap smear in the last 12 months; thus, reported Pap smear use increased by almost 9% in comparison with 2002 (30.1%). Also noteworthy is that 48.1% of women from rural areas (who were beneficiaries of the poverty reduction program) reported a Pap smear in the last 12 months (as compared with 39% of beneficiaries from urban areas). This seems to indicate that the Opportunities Program, which promotes health service use (and specifically Pap smears) among beneficiaries, is contributing to greater use of early detection services among women that reside in rural areas.

**Diagnostic Validity and Reproducibility in Cervical Cytology Laboratories in Mexico.** The evaluation of the quality of cervical cytology diagnosis in Mexico (independent of the quality of the specimen because the same samples were analyzed by all laboratories) reveals that ~67% of cervical cytology laboratories evaluated had >25% false-negative results (Fig. 5). Four cervical cytology laboratories had over 45% false-negative results. This includes 121 cervical cytology specimen assessments of invasive cervical cancer that were not identified and 31 diagnoses of adenocarcinoma that were false negatives.

**Discussion**

Cervical Cancer Mortality, Pap Smear Coverage, and Birthrate. In Mexico, 30 years after establishing the national cervical cancer prevention and control program,
there has been a modest but significant decrease in mortality due to this cancer. The main determinants of this decrease are an increase in early detection through the Pap smear and lower birthrate. Our analysis shows that Pap smear coverage alone does not explain the observed decrease in cervical cancer mortality and that other factors should be explored. The two important factors explored here are birthrate (through the linear regression analysis) and the possibility that quality of care aspects (such as low quality of cytologic diagnosis) may be limiting the effect of gains in Pap smear coverage on cervical cancer mortality rates.

At the same time, we show that in the last 5 years in Mexico, self-reported Pap smear use has increased: 66% of Mexican women between the ages of 25 and 65 years report a Pap test in the last 3 years. Nevertheless, a large number of Mexican women (27.6% according to one national survey) still report never having had a Pap test in their lifetimes. In addition, an extremely high level of false-negative results still exists, indicating the poor quality of cervical cytology analysis.

The situation in Mexico, with a decrease in cervical cancer mortality and an increase in Pap smear coverage, is somewhat similar to that of other Latin American countries such as Chile, where a reorganization of the cervical cancer prevention and control program achieved greater Pap smear coverage and probably contributed to a decrease in cervical cancer mortality. Whereas in Mexico the mortality rate decreased from 10.22 per 100,000 women in 1989 to 8.01 in 2004, in Chile the mortality rate per 100,000 women decreased from 12.8 in 1980 to 6.8 in 2001 (16). A similar secular decrease in incidence rates of invasive cervical cancer can be observed in many geographic areas in Latin America, particularly documented in the cancer registries of Puerto Rico, Costa Rica, and Cali, Colombia (17).

During the 1979-2004 time period in Mexico, three trends can be observed: cervical cancer mortality and the birthrate decreased, whereas Pap smear coverage increased. The decrease in birthrate is closely correlated with cervical cancer mortality rates. One possible explanation of why the decrease of the birthrate is correlated with and proportional to the decrease in cervical cancer mortality is that high parity is considered a cofactor in development of cervical neoplasia, particularly for women infected with human papilloma virus (HPV; ref. 18). Multiparity has been found to be a cervical cancer risk factor (19), and this is also true for Mexican women (20, 21). Causal models of multiparity and cervical cancer have been proposed as a biological mechanism for this correlation, including the effect of cervical trauma and hormonal effects (22-25).

Cervical Cancer Screening Coverage. A high level of screening (Pap) coverage is the key element that has been responsible for the decreasing cervical cancer incidence and mortality rates in countries with organized detection programs (26). High levels of coverage of eligible women with Pap screening have been achieved principally in developed countries. For example, two different studies in the United States focusing on nationally representative samples found that annual Pap smears were reported by 56% and 59% of women, whereas 93% and 99% of women reported at least one Pap smear in their lifetimes (27, 28). In the United Kingdom, by 1994, 85% of eligible women had had a Pap smear in the last 5 years, and the decreasing incidence of invasive cervical cancer and mortality rates in women under the age of 55 years, which occurred in the 1990s, can be attributed to greater Pap smear coverage (29). In Finland, 72% to 95% of women (depending on the age group, with higher rates at older ages) receive invitations to Pap screening every 5 years, and >70% of those invited have a Pap smear. The observed 80% decrease in age-adjusted incidence of and mortality from cervical cancer in Finland can be attributed to a well-organized screening program, which regularly extends invitations to almost all eligible women (30).

In contrast with the high level of Pap smear coverage achieved in developed countries, in Mexico, as reported by the Ministry of Health, Pap coverage is ~25% (Table 1), whereas self-reported Pap rates in the last 12 months vary from 27.4% to 48.1%. The rates reported by the Ministry of Health have probably not increased because health system capacity has not increased (for which greater funding for infrastructure, supplies, and

<table>
<thead>
<tr>
<th>State</th>
<th>Area (urban/rural)</th>
<th>2000</th>
<th>2006</th>
<th>RRI (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Area (urban/rural)</td>
<td>3.07 (2.64-3.56)</td>
<td>0.95 (0.84-1.07)</td>
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<td></td>
</tr>
<tr>
<td>Northern region</td>
<td>1.07 (0.79-1.44)</td>
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<tr>
<td>Baja California</td>
<td>0.59 (0.18-0.89)</td>
<td>0.77 (0.60-0.98)</td>
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<td>Baja California Sur</td>
<td>6.79 (2.13-21.66)</td>
<td>1.18 (0.76-1.84)</td>
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<tr>
<td>Coahuila</td>
<td>4.07 (1.84-8.98)</td>
<td>1.04 (0.82-1.30)</td>
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</tr>
<tr>
<td>Chihuahua</td>
<td>4.5 (2.16-9.39)</td>
<td>0.97 (0.79-1.20)</td>
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<tr>
<td>Durango</td>
<td>7.62 (3.6-16.14)</td>
<td>0.84 (0.62-1.14)</td>
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<tr>
<td>Nuevo Leon</td>
<td>2.75 (1.27-5.97)</td>
<td>0.84 (0.66-1.03)</td>
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<td>San Luis Potosi</td>
<td>8.92 (4.42-17.98)</td>
<td>1.18 (0.88-1.59)</td>
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<td>0.83 (0.65-1.06)</td>
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<td>Sonora</td>
<td>4.17 (1.9-9.12)</td>
<td>1.24 (1.00-1.54)</td>
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<td>Tamaulipas</td>
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<td>1.27 (1.04-1.54)</td>
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<td>Zacatecas</td>
<td>7.9 (3.75-16.67)</td>
<td>0.96 (0.71-1.30)</td>
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<td>Central region</td>
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<td>1.27 (0.99-1.62)</td>
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<td>Aguascalientes</td>
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<td>0.80 (0.55-1.16)</td>
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<td>Colima</td>
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<td>1.83 (1.31-2.57)</td>
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<td>Mexico City</td>
<td>1.00 (—)</td>
<td>1.00 (—)</td>
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<tr>
<td>Guanajuato</td>
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<td>0.72 (0.46-1.12)</td>
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<td>Hidalgo</td>
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<td>1.00 (0.84-1.18)</td>
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<td>Mexico State</td>
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<td>0.91 (0.79-1.05)</td>
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<td>Michoacan</td>
<td>8.21 (4.2-16.05)</td>
<td>1.11 (0.92-1.34)</td>
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<td>Morelos</td>
<td>8.88 (4.2-18.45)</td>
<td>1.64 (1.31-2.05)</td>
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<td>Nayarit</td>
<td>10.59 (4.84-23.17)</td>
<td>1.47 (1.10-1.97)</td>
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<td>Puebla</td>
<td>8.81 (4.56-17)</td>
<td>1.23 (1.04-1.45)</td>
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<td>Queretaro</td>
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<td>0.86 (0.66-1.19)</td>
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<td>1.47</td>
<td>3.12 (1.01-9.78)</td>
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NOTE: Sources: Vital Statistics, Mortality Registry, INEGI/Ministry of Health, 2000 and 2006; Mexican National Population Council (CONAPO) population projections for Mexico 1970-2030. Abbreviations: RRI, relative risk index; 95% CI, 95% confidence interval.
Another likely contributing factor is the recently implemented policy of recommending a Pap test every 3 years (not every year) for women who have had two consecutive negative tests previously. Self-reported rates of Pap testing in the last year in Mexico are higher than those reported by the health system, and other studies have also shown that self-reported screening for cancer tends to be somewhat higher; in addition, time since the last screening test is more prone to be incorrect when self-reported, and so this may have contributed to the survey data that showed higher self-reported rates of Pap testing in the last year (31-35). In addition, not all the surveys were nationally representative; therefore, the higher rates reported by certain groups of women may correspond to truly higher rates in those subpopulations.

Coverage rates (self-reported or not) may be lower in Mexico as compared with European countries and the United States also because cervical cancer screening programs are more costly and less effective in developing countries than the equivalent programs implemented in developed countries (36). Both laboratory processing and the transportation of samples can be more expensive in developing countries because there are lower levels of resource efficiency than in developed nations (37). In spite of a lack of resources and possible higher costs, this analysis indicates that the government agencies in charge of cervical cancer screening and treatment in Mexico

Figure 3. Comparison of relative risk of cervical cancer (CC) mortality by region, adjusted by rural/urban residence, Mexico, 2006.

Figure 4. Pap rates in the last 12 mo, self-reported by women in a number of national surveys, Mexico, 2000-2006.
have made important strides in increasing the level of Pap coverage and seem to have had at least some success in promoting higher levels of Pap use, specifically among women who are poor and who live in rural areas.

Effective strategies used to increase the coverage of cervical cancer screening, detection, and treatment programs in developed nations include extending invitations (personalized or not) by mail or phone to women periodically, reminders for health care providers about which patients are due for screening, health education pamphlets or letters with information about cervical cancer and the Pap smear, the implementation of guidelines for health care personnel, and computerized systems that track the screening process (38-41). Personalized invitations using population registries are used in many countries with organized detection programs, with some achieving attendance rates of >70% (42).

One study indicates that the use of HPV testing in combination with the Pap smear could be a cost-effective alternative for cervical cancer screening in Mexico. This study compared the sensitivity of an HPV test (for high-risk subtypes) based on a self-collected vaginal sample with that of an HPV test of a physician-collected cervical sample and a Pap smear (43). The sensitivity for HPV and Pap samples taken by a health professional was 98%. The negative predictive value of the combination of the HPV and the Pap tests was virtually 100%. These results indicate that a more effective screening strategy could include an HPV test on a sample obtained by a health professional in combination with a Pap smear. The self-collected vaginal samples for HPV testing might be an alternative for women who refuse to have a Pelvic exam.

In countries such as Mexico, the use of these alternative screening strategies (HPV testing in combination with Pap testing, and HPV testing on self-collected samples) should focus on regions with low levels of Pap test coverage, a lack of health care infrastructure, and rural and economically disadvantaged communities.

Diagnostic Validity and Reproducibility in Cervical Cytology Laboratories. The evaluation of the diagnostic validity and reproducibility of cervical cytology laboratories in Mexico shows that there is a serious problem in terms of quality control. This study indicates that the low rates of high-grade cervical lesions detected are not due to screening of women at low risk for cervical neoplasia (and exclusion of women at high risk; ref. 44). Instead, it would seem that it can be explained by the poor quality that exists in the smear collection process and especially in cytologic diagnosis, which has also been evidenced by other studies in Mexico (9).

In fact, in the sample of Mexican cytologic laboratories evaluated here, false negatives were observed not only in adenocarcinoma but also in cervical high-grade squamous intraepithelial lesions in specimens that were of sufficient quality for diagnosis (in this case, sample collection was not the issue). In this respect, adequate diagnostic quality in cervical cytology is directly related to adequate training of cytopathologists, uniformity of diagnostic criteria, use of an efficient nomenclature, and implementation of quality control mechanisms both in terms of specimen collection and diagnostic precision (45).

Worldwide practice of cervical cytopathology has been influenced by six major events in recent years: (a) the
regulation of quality in cytopathology laboratories in the United States (46); (b) the Bethesda system of diagnostic nomenclature (47); (c) the possibility of automated diagnosis with PAPNET (48), Cytyc and NeoPath, among others (49); (d) automated specimen preparation (50); (e) the discovery that the HPV is a necessary although insufficient cause of cervical cancer (51); and (f) the introduction of prophylactic vaccines against HPV (52, 53).

The problems related to quality of cytologic diagnosis in developing countries such as Mexico include training and certification processes for cytotechnicians as well as the lack of certified technicians. In Mexico, most cytologic diagnoses are done by cytotechnicians with a limited amount of professional training, sometimes only 6 months in duration. In addition, cytotechnicians often have a heavy workload, with >40 specimens to diagnose in a workday. In routine practice, a slide (with a Pap smear) can include only a few abnormal cells, and this is something that can easily be missed by a tired technician at the end of an exhausting workday (54). The incapacity to recognize abnormal cells can constitute another source of error in nonaccredited personnel. Where accreditation programs have been instituted in an effort to minimize this type of error (55, 56), an improvement in diagnostic practice has been observed (57, 58). Our study indicates that in Mexico, implementation of accreditation standards for cytotechnicians is urgently needed. Both the introduction of external quality control mechanisms in cervical cytology laboratories and improved training of cytotechnicians are also necessary (59). In Mexico, a consensus must be established among healthcare decision-makers, administrators, and providers in terms of the need for quality control mechanisms, standardization of diagnosis, periodic certification, and continuing education for personnel working in cervical cytology laboratories (60).

**Recommendations**

The data presented here suggest that cervical cancer prevention and control programs in countries such as Mexico could be reorganized in the following ways:

(a) Expand the coverage of the detection program while maintaining uniform quality for all parts of the country and renewing the focus on disadvantaged rural and urban regions.

(b) Create quality control mechanisms for all the processes involved in the cervical cancer prevention and control program.

(c) Establish periodic accreditation of cytopathology laboratories and individual cytotechnicians by an appropriate professional association and promote the standardization of cervical cytopathology curricula.

(d) Integrate diverse screening strategies, such as combined Pap smear and HPV testing, all of which should be regulated.

(e) Regulate colposcopy to avoid overtreatment, given both the high economic cost implied and that it creates unnecessary anxiety among women at risk.

(f) Implement health education and promotion strategies aimed at increasing women’s knowledge about cervical cancer detection and treatment.

(g) Develop research on cost-effectiveness and organizational issues in the introduction of rapid manual reevaluation as an internal quality control mechanism for Pap smear analysis.

(h) If clinical laboratories that analyze HPV tests are established, they should be accredited and regulated.

(i) Develop mathematical cost-effectiveness models to evaluate the introduction of new primary and secondary cervical cancer prevention strategies in countries with limited resources for prevention and control.

**Disclosure of Potential Conflicts of Interest**

No potential conflicts of interest were disclosed.

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**References**


Decreasing Cervical Cancer Mortality in Mexico: Effect of Papanicolaou Coverage, Birthrate, and the Importance of Diagnostic Validity of Cytology


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