

## Incidence Trends of Cervical Cancer in Puerto Rico, 1987-2004

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**Objective:** Cervical cancer was the leading malignancy among women in Puerto Rico when the Central Cancer Registry was first established by law in 1950. The screening program for cervical cancer in PR was initiated in 1961 when cytological laboratories were established in regional hospitals throughout the island, reaching its peak in 1973. In 2004, invasive cervical cancer ranked fifth among the top cancers in women in PR, representing 4% of all newly diagnosed cancers and 2% of all cancer-related deaths among women. The purpose of this study was to evaluate the incidence trends of cervical cancer by histology type in PR.

**Methods:** Cervical cancer cases (n = 3,516) diagnosed from 1987-2004 were obtained from the Puerto Rico Central Cancer Registry. Age-adjusted and age-specific incidence rates by histological type were calculated. Annual percent changes were estimated to evaluate the incidence trends from 1987 to 2004.

**Results:** From 1987 to 2004, the incidence of cervical cancer showed a downward trend (APC = -2.1%). Seventy-six percent (76.3%) of invasive cervical cancer cases were squamous cell carcinoma (SCC), 15.4% were adenocarcinoma (ADC), and 8.3% had other histologies. When histology was considered, a decreasing trend was observed for the incidence rates of SCC (APC = -3.2%, p < 0.05), with the greatest decrease being seen in women aged 60-74 (APC = -6.6%, p < 0.05). While the overall incidence rate of ADC remained stable (APC = 0.8%, p > 0.05), it increased in women aged 30-44 (APC = 3.8%, p < 0.05).

**Conclusion:** Overall, the incidence rates for cervical cancer (SCC in particular), have decreased in PR. However, ADC does not present a similar decreasing trend. This trend, which is similar with other populations, could be explained, in part, by a decreasing prevalence of risk factors. Nevertheless, analysis by specific age group shows variations in the risk, which need careful consideration since they could imply changes in factors associated with each of the histological types. [*P R Health Sci J* 2010;4:364-371]

*Key words:* Cervical cancer, Incidence trends, Adenocarcinoma, Squamous cell carcinoma

Cervical cancer is the second most common type of cancer among women in the world, affecting more than 500,000 women worldwide each year (1-2). In developing countries, it occupies the first or second position, while in developed countries it is the seventh most common malignancy (1-2). Every year, 83% of the world's new cervical cancer cases and 85% of all cervical cancer deaths occur in developing countries (2). In 2004, invasive cervical cancer ranked fifth among the top cancers in women in Puerto Rico (PR), representing 4% of all newly diagnosed cancers and causing 2% of all cancer-related deaths among women.

From 1950 to 1993, primary care in PR was provided at the municipal level by government health centers. The

municipalities were grouped into seven health regions for the provision of health care at the secondary level. Tertiary care was provided by specialized hospitals located in the metropolitan area of the island. In 1950, the screening program for cervical

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cancer in PR began with the island's first detection clinic (at the School of Medicine of the University of Puerto Rico). In 1957, the Department of Health of Puerto Rico began the support of screening, and by 1961, the program had established cytology laboratories and trained personnel in all of the regional hospitals throughout the island (3). Population-based data from the Puerto Rico Central Cancer Registry (PRCCR) provided evidence that incidence rates of invasive cervical cancer had been descending since 1950 (4). The decreasing trend has continued into the present, with the exception of a significant increase in incidence that occurred between the 1960s to the 1970s when the widespread implementation of the screening program had its highest effect (5). The cytological rates increased from 15.45 per 1,000 in 1962 to 176.67 per 1,000 in 1973, but afterwards the rate of cytological testing linearly decreased ( $p < 0.001$ ) to 110.92 per 1,000 in 1987. A peak rate (176.67 per 1,000) of cytological tests was observed during the period of 1972-1973 (5). The average incidence rate of invasive cervical cancer (age-adjusted to the PR 1970 population) decreased 59.4% from 24.7 per 100,000 women in 1963-1967 to 10.0 per 100,000 women in 1983-1987 (5). Although descending rates had also been observed in Europe (6) and the United States (US) (7), the risk of cervical cancer for PR as compared to US subgroups populations was similar to Non-Hispanic Blacks, lower than Hispanics, and higher than Non-Hispanic Whites for the period of 1998-2003 (8).

The effectiveness of screening programs has been documented in numerous studies (9-12). According to the International Agency for Research in Cancer (IARC), high quality conventional cytological screening programs can reduce the incidence of cervical cancer by at least 80% (13). Nevertheless, lifestyle and risk modifications can also explain the changing trend, in particular in populations with limited access to screening interventions (5, 14-15). As it was stated before, cervical cancer cases are diagnosed with almost twice the frequency in women living in less developed countries when compared to women living in more developed countries (2), an argument in favor of this being a disease associated with poverty. Low socioeconomic level and education attainment imposes a heavier burden on women's health. A significant correlation ( $p = 0.0103$ ) was observed between increasing socioeconomic level and decreasing cervical cancer rates from 1963 to 1987 in PR (5, 14).

Human Papilloma Virus (HPV) infection (most notably HPV subtypes 16, 18, 31, 33, and 45) is a major risk factor for cervical cancer (16-18). Squamous cell carcinoma (SCC) has been associated with HPV-16, which is the most prevalent type (observed in 50%-60% of cases), while HPV-18 is observed in 10%-20% of cases (18-20). In contrast, HPV-18 plays a major role in adenocarcinoma (ADC), accounting for 40%-60% of cases, while HPV-16 has been observed in 30%-55% of cases (18-20). Different HPV types are associated with SCC and ADC of the cervix, but many cofactors are equally important

for both histological types, such as lifetime number of sexual partners, age at first intercourse, oral contraceptive use, and parity (20-29). Nevertheless, smoking (current smokers) has been found to be a strong risk factor for SCC, but not for ADC of the cervix (20-21, 25, 28). Also, infection with *Chlamydia trachomatis* was associated with SCC, but not with ADC (20, 30-33). Bosch et al. (19), collected cervical cancer specimens from patients around the globe; evaluation by Polymerase Chain Reaction (PCR) revealed the presence of HPV DNA in more than 90% of these specimens. This suggests that HPV could be an important causal factor but that it needs triggering from other risks associated with cervical cancer (17). Other risk factors related to behavior are multiple sexual partners, early onset of sexual activity, lack of sexual protection, and having a history of sexually transmitted diseases. Long term use of oral contraceptives (27, 34), low socioeconomic status (35-36), having a history of tobacco use (24, 28, 37), and poor dietary patterns are also risk factors (38). Changes in the patterns of occurrence in any of these risk factors can affect the incidence of cervical cancer.

Despite the dramatic decrease in incidence and mortality rates, there are, to our knowledge, no published reports on the incidence of cervical cancer by histological type in PR. The aim of this study was to evaluate (by age group and histological type—squamous cell carcinoma, adenocarcinoma, and both) cervical cancer incidence trends in PR residents during the period covering 1987 to 2004.

## Methods

Almost ninety-eight percent (97.8%) of all invasive cervical cancer cases diagnosed in PR from 1987 to 2004 and registered by the PRCCR were included in this analysis (39). Of those invasive cervical cancer cases, 97% had microscopic confirmation of disease. About 1% of cervical cancer cases had only a positive laboratory test/serum marker, direct visualization, positive radiology, or clinical diagnosis. In situ carcinomas and cases diagnosed by death certificate only (2.2% of all cases) were not included. Tumors were categorized by histological type, according to the International Classification of Diseases for Oncology (ICD-O-3) (40), as follows: squamous cell carcinoma (codes 8050-8084, 8120), adenocarcinoma (including adenosquamous carcinoma, codes 8015, 8140-8149, 8260-8490, 8560, and 8570-8575), and all histological types analyzed together (all ICD-O-3 codes for cervical cancer).

Age-adjusted and age-specific incidence rates were calculated by histological type. Incidence rates (per 100,000 women) were estimated using SEER\*Stat software, v.6.5.5 (41), and adjusted to the 2000 PR Population data provided by the Census 2000 (US Census Bureau) (42). Differences in age distribution were assessed using chi-square ( $\chi^2$ ) statistics. Annual percent changes (APC) by histological type and age group (15-29, 30-

44, 45-59, 60-74, and 75+) were estimated using the Joinpoint Regression Program, v.3.2 (43), to evaluate the incidence trends from 1987 to 2004. The parameters used in Joinpoint to estimate APCs were 1) log transformation of the rates, 2) two-jointpoint model, 3) standard errors of rate, 4) uncorrelated error model, 5) Hudson's method, and 6) permutation model selection methods.

## Results

### Study Population

A total of 3,516 invasive cervical cancer cases (diagnosed from 1987 until 2004) were included in the analysis. Three-fourths of the cases (76.3%) were SCC, 15.4% were ADC, and 8.3% had other histologies. The median age at diagnosis was 51 years, which was similar ( $\chi^2$  1.78,  $p = 0.182$ ) for SCC (52 years) and for ADC (50 years). Table 1 displays the distribution of cervical cancer cases by age group and histology. Overall, 173 (4.9%) of cases were below 30 years of age at diagnosis. Women aged 30 to 59 years contributed 60% of the total cases. There were no significant differences in the distribution of age at diagnosis by histology in the cervical cancer cases analyzed ( $\chi^2$  7.37,  $p = 0.118$ ).

**Table 1.** Distribution of invasive cervical cancer cases by age group in Puerto Rico, 1987-2004†

Age (years)	SCC n (%)	ADC n (%)	Total n (%)
15-29	121 (4.5)	17 (3.1)	173 (4.9)
30-44	800 (29.8)	183 (33.9)	1082 (30.8)
45-59	806 (30.0)	169 (31.3)	1028 (29.2)
60-74	628 (23.4)	118 (21.9)	814 (23.2)
75+	329 (12.3)	53 (9.8)	419 (11.9)
Total	2,684	540	3,516

†SCC = squamous cell carcinoma; ADC = adenocarcinoma

Cervical cancer is a rare diagnosed in younger women in PR. Only 4.9% of cases were diagnosed in women aged under 30 years, most of these (3.4%) were diagnosed in women between the ages of 25 and 29 (Table 1). Figure 1 shows an upward trend in SCC diagnoses starting at age 20, plateauing at 45 to 55 years, and, after a dip, increasing smoothly thereafter. The age-specific incidence rates for ADC begin to rise slightly at age 25 and then remain relatively stable from 45 years onward.

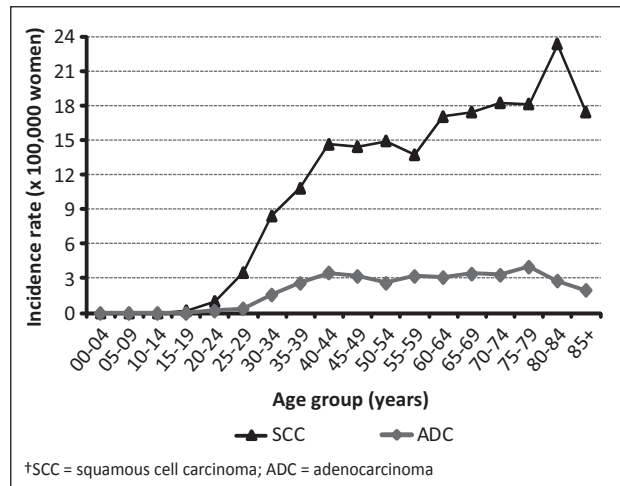
### Trends by Histologic Type and Age Group

#### All Histological Types

Age-adjusted incidence rate for cervical carcinoma showed a downward trend (from 14.9 per 100,000 in 1987 to 10.6 per 100,000 women in 2004), with an APC of -2.1% (95% CI: -3.0%, -1.3%,  $p < 0.05$ ) (Figure 2). When trends were stratified

by age group, significant decreases in incidence were observed for the groups encompassing ages 45-59 (APC = -2.2%), 60-74 (APC = -5.3%), and 75+ (APC = -5.2%) years of age (Figures 3 and 4). However, women aged 30-44 years had a statistically significant increase of 1.4% ( $p < 0.05$ ) annually, while women aged 15-29 had a similar increase of 1.4% ( $p > 0.05$ ) but it was not statistically significant (Figure 4).

**Figure 1.** Average age-specific incidence rates of cervical cancer in Puerto Rico, 1987-2004†



†SCC = squamous cell carcinoma; ADC = adenocarcinoma

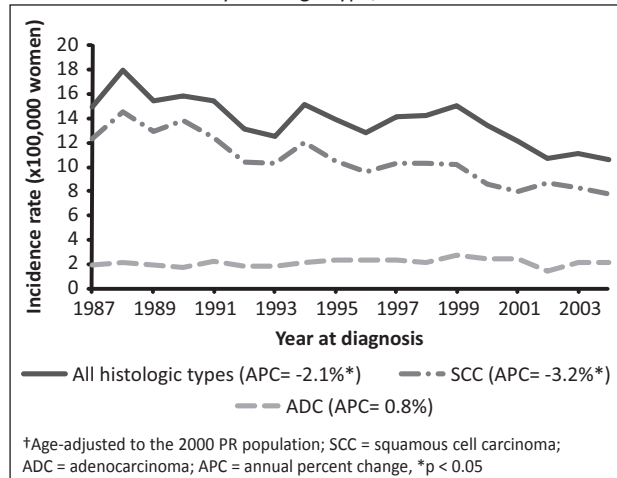
#### Squamous cell carcinoma (SCC)

The age-adjusted rates of SCC decreased from 12.3 to 7.8 per 100,000 women from 1987 to 2004 (Figure 2), with a decrease of 3.2% (95% IC: -3.9%, -2.5%,  $p < 0.05$ ) annually. Since 76% of all invasive cervical cancer cases are SCC, the trends by age for SCC are similar to the trends for all histological types combined. However, for SCC the increased rate in women aged 30-44 years (APC = 0.4%) was not statistically significant, while women aged 15-29 years showed a non-significant reduction of 2.4% ( $p > 0.05$ ) annually, contrary to the trend presented for all histological types analyzed together (Figure 4).

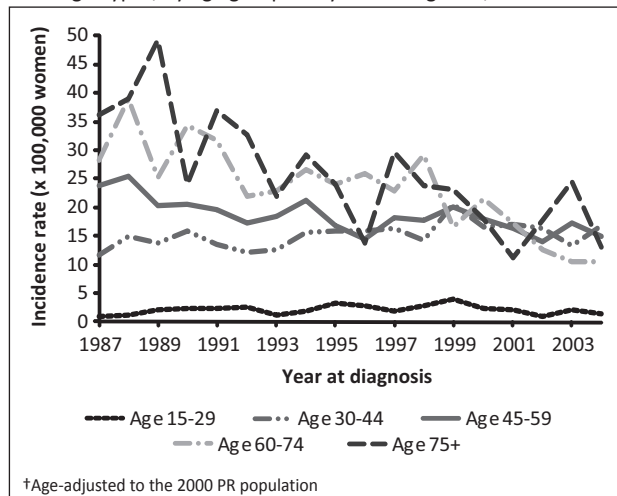
#### Adenocarcinoma (ADC)

An average of 30 cases of ADC is diagnosed annually in PR, thus the incidence rates were relatively low (ranging from 1.4 to 2.7 per 100,000 women/year) during the study period (Figure 2). ADC was less frequently diagnosed among women in PR; an increase of 0.8% (95% CI: -0.7%, 2.3%,  $p > 0.05$ ) annually was observed. Trends of ADC by age group showed a statistically significant increase of 3.8% (95% CI: 0.9%, 6.8%,  $p < 0.05$ ) annually for women aged 30-44 years, while for women aged 45-59 (APC = -0.4%) and 60-74 (APC = -2.5) years, a slight decrease in incidence was observed (Figure 4). For the youngest (15-29 years) and oldest age groups (75+ years), there were no ADC cases reported for various years; therefore, Joinpoint software could not estimate the APC.

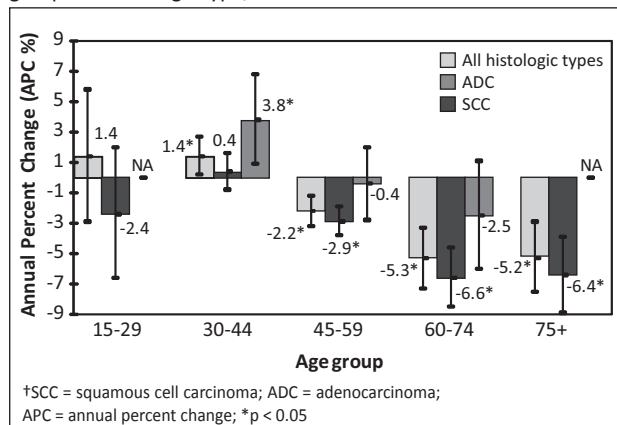
**Figure 2.** Incidence rates and annual percent change of cervical cancer in Puerto Rico by histologic type, 1987-2004†



**Figure 3.** Incidence rates of cervical cancer in Puerto Rico for all histologic types, by age group and year of diagnosis, 1987-2004†



**Figure 4.** Estimated annual percent change in cervical carcinoma incidence rates in Puerto Rico with 95% confidence intervals, by age group and histologic type, 1987-2004†



## Discussion

Over the past several decades, invasive cervical cancer incidence rates in PR have been steadily declining from 35.1 per 100,000 in 1950-54 to 8.8 per 100,000 women in 1985-89 (age adjusted to the 1970 population of PR) (4). Using cancer cases (1987-2004) from the PRCCR, our analysis showed a continuation of this trend for invasive cervical cancer and, in particular, for SCC. The decrease in overall incidence of cervical cancer principally reflects the decrease in the incidence of SCC occurring mainly in women aged 45 years or older. Nevertheless, the trend for ADC has remained stable for the same period. Similar to other populations, overall incidence trends for younger women (15-29 years) increased (10, 44-48). In this study a significant increase in ADC was seen in women aged 30-44 years of age.

Over the last decades, reproductive, lifestyle, and environmental risk factors, such as the decline in parity (49, 50), increased access to health care (51), the greater participation of women in the labor force, increased socioeconomic status and educational levels (14, 52, 53), and a decrease in tobacco use (51), have changed in PR. However, these changes could partially explain the reduction in the overall incidence rates of cervical cancer in PR. According to Grandes (5), multiple regression analysis reflected that the reduction in the rates of invasive cervical cancer in PR during 1963 to 1987 was due significantly (p = 0.0103) to the increase of the socioeconomic level and not by the screening program.

Some of the strongest identified risk factors for cervical cancer acting as cofactors to HPV are the long term use of oral contraception (22-24, 54, 55), high parity (24, 56, 57), and cigarette smoking (24, 28, 37). Recent epidemiological studies (22, 55) that evaluated the role of oral contraceptives in cervical cancer strongly suggest that women who used oral contraceptives had an increased risk of cervical cancer (up to twofold), but only those women who were both long-term users (≥5 years) and who had persistent HPV infections of the cervix. The limited available data suggest that the relative risk of cervical cancer may decrease after the use of oral contraceptives ceases (22). However, only limited data are available regarding of oral contraceptive use in married Puerto Rican women aged 15-49 years; 21.5%, 14.7%, and 1.8% of married women of 15-24, 25-34 and 35-49 years of age, respectively, used oral contraceptives (58). The fact that scarce data exist on patterns of oral contraceptive use and HPV in a Puerto Rican population, limits us in hypothesizing about the impact of these factors on cervical cancer incidence trends.

A significant association between the number of full-term pregnancies and an increased risk of invasive cervical cancer, especially SCC cancer, has been reported (57). Multiple pregnancies may have a cumulative traumatic or immunosuppressive effect on the cervix, thereby facilitating

the acquisition of HPV infection (59). Nonetheless, PR has experienced a reduction of fertility rates (49, 60), and the average number of children born of women of reproductive age (15-49 years) has decreased from 6.4 children in 1932 to 2.1 children in 1998 (49, 50). This suggests that a decline in parity could partly explain a reduction in cervical cancer but may in part contribute for the increased incidence trend of endometrial (61) and breast cancer (62, 63) observed in PR. The prevalence of hysterectomies in PR is high (13.1% for women 35 to 49 years and 32.5% for women  $\geq$  50 years old), and this procedure provides the women who have it protection against developing cervical cancer (G. Ramos, et al, Estudio Continuo de Salud, unpublished data, 2002).

The carcinogenic effect of smoking tobacco and its role in cervical cancer was largely consistent with several studies that adjusted for HPV or restricted analyses to HPV-positive women (21, 28). According to BRFSS, the prevalence of tobacco use in PR has been in decline among women during the last decades (9.9% in 1996, 8.4% in 2004) (51), a risk factor associated mainly with SCC (20, 21, 25, 28). Lifestyle factors such as obesity and poor nutritional habits (especially the reduced consumption of fruits and vegetables) need also be considered, given that these factors have undergone drastic changes in PR (51).

Some Sexually Transmitted Diseases (STDs) such as *Chlamydia trachomatis* (30, 31, 33), Human Immunodeficiency Virus (HIV) (64), Herpes Simplex Virus-2 (HSV-2) (65), and HPV infection, a major infectious etiological agent and risk factor for cervical cancer, are mainly acquired through sexual contact, which also increases the risk for cervical cancer. A possible mechanism whereby sexually transmitted infections could act is by inducing a local inflammatory response that could facilitate the establishment of a productive HPV infection (38). Transmission rates of *Chlamydia* infection in PR increased 88%, from 16.6 in 1993 to 92.7 per 100,000 persons in 2004, with the risk for women being more than 5-fold greater compared to that for men (66). These increases contrast the decreasing trend of SCC, where the effect of *Chlamydia trachomatis* appears to be more relevant for SCC than for ADC (31, 33). Moreover, PR is one of the top ten US states and territories with the highest cumulative number of HIV/AIDS cases (67). Given that cervical cancer is an important AIDS-defining malignancy (68), a significantly higher risk of cervical cancer has been observed in women with AIDS in PR, and that has not changed over time (69). This high risk of cervical cancer among women with AIDS in PR may contribute for the increasing trend observed among women aged 15-44 years, in whom HIV/AIDS is more prevalent. Even though the high risk of STDs such as *Chlamydia* infections and HIV, the high-risk sexual practice in early ages in younger cohorts (70-72), and the cofactors associated with HPV may contribute to the observed increased risk of cervical cancer among women aged 15-44 years in PR, there is no conclusive evidence to support that theory.

Widespread population-based screening programs for cervical cancer have been available in PR since 1961 (3). One possible explanation for the decreasing temporal trends in SCC incidence rates and the contrary increase in those rates for ADC observed during the study period is that screening practices—especially the conventional Papanicolaou (Pap) test—are less effective at detecting ADC than they are at detecting SCC (73). The location of ADC can make detection by a Pap smear difficult because lesions develop in multiple locations in the cervix or in a high part of the endocervix and often go undetected (73). The absence of an overall trend in ADC incidence suggests that the screening program may have less impact for ADC (44). New and improved screening methods specifically directed at cytological changes in the endocervical glands are needed in order to more effectively detect pre-invasive and early invasive ADC (48, 73, 74). Nevertheless, it is important to note that in PR the overall decreasing trend of the risk of cervical cancer (which has so far been mainly SCC) was observed about 10 years before the introduction of Pap screening at the population level (4).

Our study shows an increased risk of cervical cancer among women of 15-29 and 30-44 years of age, particularly for ADC in women aged 30-44 years. Several authors have suggested possible explanations for the increasing trend of ADC in young women such, as the increase in the prevalence of persistent HPV infection and its cofactors (45-47, 75). The prevalence of HPV in PR has not been documented at the population level. However, such factors as high-risk sexual practices at an early age, having multiple sex partners, and lifetime number of partners—which factors are associated with HPV infection—have increased in younger cohorts (70-72). Also, the low prevalence of screening in younger women results in missing pre-invasive lesions, thereby limiting effectiveness in reducing the incidence rates in the younger age groups (48, 74). According to the Behavioral Risk Factor Surveillance System (BRFSS), women aged 18-24 years were less frequently screened than women aged 35 years or older (51). For the survey conducted from 1996 to 2004, in average, less than 42% of women 18-24 years of age in PR had a screening Pap test within the past three years as compared to over 70% for women aged 25 years or older. Also, Ortiz et al. (76) estimated the prevalence of women who, in 2006, reported having had a PAP test in the preceding 3 years as being 71.9% (95% CI: 69.4%-74.4%), below the recommended 90% established by *Healthy People 2010*.

One of the strengths of our study is the data provided by PRCCR, a population based-registry with high quality standard data. In 2003, a CDC audit concluded that 95.3% of all cancer cases diagnosed and treated in hospitals facilities in PR were accurately reported to the PRCCR; a result comparable to the US median (95%) (77). However, a limitation of our study is the lack of adjustment by hysterectomy rates, which deficiency may have resulted in an underestimation of disease

occurrence (78). Also, the scarcity of invasive cervical cancer cases (particularly ADC) in women below 30 years resulted in less reliable rates. Given the small numbers observed annually for younger women, the precision of our rates is understandably low, which might lead to considerable variation in the rates. Therefore, the estimated APC incidence we report in this study reflects the relative change in what are, in absolute terms, small numbers (46). Caution is recommended in the interpretation of the clinical significance of these observed trends.

Although overall cervical cancer incidence has decreased over time, mainly due to the relatively greater reduction of SCC, ADC has not presented a similar decreasing trend. Also, our study identified an increased risk of invasive cervical cancer among women 15-44 years of age, in particular for ADC in women aged 30-44 years. The overall reduction of cervical cancer in PR may be attributable, in part, to an organized widespread screening program as well as lifestyle and environmental changes that have occurred over the last decades. However, the increased risk for ADC, particularly in younger women, suggests an argumentation of high-risk sexual practices, lower rates of appropriate screening and early detection of pre-invasive lesions, and the presence of high-risk HPV infection and its cofactors. The changing patterns of histology-specific cervical cancer incidence emphasize the importance of cancer surveillance by histopathology. The inclusion of HPV DNA tests in screening programs for high-risk women in PR would increase the detection rates of the precursors of cervical cancer for both SCC and ADC, as both histological types are associated with HPV. Future research should be undertaken over longer periods of time and should evaluate the potential risk cofactors associated with HPV, the introduction of the HPV vaccine, and the cost effectiveness of the HPV DNA testing in reducing cervical cancer incidence.

## Resumen

**Objetivo:** El cáncer de cuello uterino era la principal malignidad entre las mujeres en Puerto Rico (PR) en el año 1950, cuando el Registro Central de Cáncer de Puerto Rico (RCCPR) fue establecido por ley. En 1961, el Departamento de Salud de PR estableció el programa de cernimiento para cáncer de cuello uterino cuando implantó laboratorios citológicos alrededor de la isla, alcanzando su mayor efectividad en el 1973. En el 2004, el cáncer de cuello uterino ocupó la quinta posición entre los cánceres en mujeres, representando el 4% de todos los cánceres nuevos diagnosticados y el 2% de todas las muertes por cáncer entre mujeres en PR. El propósito del estudio fue evaluar las tendencias de incidencia de cáncer de cuello uterino por tipo histológico en PR. **Métodos:** Los casos de cáncer de cuello uterino (n = 3,516) diagnosticados desde el 1987 al 2004 fueron obtenidos del RCCPR. Tasas de incidencias ajustadas por edad y específicas por tipo histológico fueron calculadas. El cambio porcentual anual (CPA) fue estimado para evaluar

las tendencias de incidencia desde el 1987 al 2004. **Resultados:** Desde el 1987 al 2004, la incidencia de cáncer de cuello uterino mostró una reducción de 2.1% ( $p < 0.05$ ) anualmente. El 76.3% de los casos invasivos de cáncer de cuello uterino fueron de células escamosas, 15.4% fueron adenocarcinoma y 8.3% tenían otras histologías. Cuando se consideró tipo de histología, una reducción en la tendencia fue observada para las tasas de incidencia de carcinoma de células escamosas (CPA = -3.2%,  $p < 0.05$ ), con la mayor reducción en el grupo de mujeres de 60-74 años (CPA = -6.6%,  $p < 0.05$ ). Mientras que las tasas de incidencia total de adenocarcinoma permaneció estable (CPA = 0.8%,  $p > 0.05$ ), aumentó en mujeres de 30-44 años (CPA = 3.8%,  $p < 0.05$ ). **Conclusión:** En general, las tasas de incidencia de cáncer de cuello uterino (en particular carcinoma de células escamosas) han descendido en PR. Sin embargo, el adenocarcinoma no presenta una tendencia descendente similar. Esta tendencia cual ha sido similar a otras poblaciones, podría ser explicada en parte por la reducción en la prevalencia de factores de riesgos. Sin embargo, el análisis por grupo de edad específico muestra una variación en el riesgo, que necesita ser considerada puesto que podría implicar cambios en los factores asociados a cada uno de los tipos histológicos.

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