Assessment of Cervical Cancer Incidence, Histopathology, and Screening Practices Among Hispanic Women in Latin America and Michigan

by

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To

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Table of Contents

List of Tables

List of Figures

List of Abbreviations

ADC	Adenocarcinoma
APBCR	Arequipa Population-based Cancer Registry
ASR	Age-standardized rate
BRFSS	Behavioral Risk Factor Surveillance Survey
CI	Confidence interval
CI5	Cancer Incidence in Five Continents
CI5-IX	Cancer Incidence in Five Continents, Volume IX
DCO	Death certificate only
HPV	Human papillomavirus
IARC	International Agency for Research on Cancer
ICD-O-3	International Classification of Diseases for Oncology, 3rd Edition
LAC	Latin America and the Caribbean
LMCR	Lima Metropolitan Cancer Registry
MBCCCP	Michigan Breast and Cervical Cancer Control Program
MV	Microscopically verified
NBCCEDP	National Breast and Cervical Cancer Early Detection Program
NH	Non-Hispanic
OR	Odds ratio
SCBRFS	Special Cancer Behavioral Risk Factor Survey
SCC	Squamous cell carcinoma
SE	Standard error
TCR	Trujillo Cancer Registry
UA	Unknown age
UB	Unknown basis of diagnosis
US	United States
VIA	Visual inspection with acetic acid
YLL	Years of life lost

Abstract

Cervical cancer is the third most common cancer among women worldwide, with 85% of its global burden occurring in less-developed countries. Although incidence rates of cervical cancer have declined in recent years, high rates persist in Latin America and the Caribbean (LAC) and among Hispanics in the United States (US). With global population growth and aging, the number of cervical cancer cases is expected to increase 46% by 2030. Effective prevention and control efforts will be needed; however, they should be based on accurate estimations of cervical cancer incidence and histopathology, and should consider local screening behaviors.

In LAC, data from 14 population-based cancer registries were used to examine variation in cervical cancer incidence and histopathologic types. In Peru, data obtained from three population-based cancer registries were used to evaluate within-country differences in cervical cancer incidence and histopathologic types. In Michigan, the Special Cancer Behavioral Risk Factor Survey was used to assess cervical cancer screening (Pap test) practices and identify predictors of screening.

Results demonstrated substantial variation in age-standardized cervical cancer incidence rates (ASR) across LAC (ASR: 14.58-43.95 per 100,000). Histopathologic types also varied widely, and patterns of age-specific incidence curves fluctuated considerably across the LAC region. In Peru, heterogeneity was found among registries in the incidence of overall, age-, and histopathology-specific cervical cancer. Results from one registry, Trujillo (1984-2002), showed significant trends toward decreasing

overall cervical cancer incidence, but suggested increasing trends in adenocarcinoma incidence among young women (15-29 years). In Michigan, screening behaviors of Hispanics and non-Hispanic whites were similar; however, Hispanics still reported being recently screened (83.0%) at levels below Healthy People 2020 targets (93.0%). Younger age, higher education, having health care coverage, and cervical cancer knowledge were identified as significant predictors of cervical screening among Hispanics in Michigan.

Cervical cancer prevention and control efforts should focus on understanding local cervical cancer incidence and distribution of histopathologic types, together with prevalence and predictors of cervical cancer screening behaviors. With this insight, public health policies could be implemented favoring more effective methods of primary and secondary prevention.

Chapter 1

Introduction

Overview

Chronic diseases are the leading cause of global mortality, and are projected to increase over the next two decades (1, 2). Cancer is a significant contributor to global mortality, causing 7.6 million deaths in 2008 (3), and is expected to increase in importance as global cancer mortality rises 74% to cause 13.1 million deaths by 2030 (4). While cancer is traditionally recognized as a disease affecting high-income countries, the majority of new cancer cases (56%) and deaths (63%) occur in low- to middle-income countries (3, 5). This especially holds true for cervical cancer. Among women worldwide, cervical cancer is the third most common cancer and fourth most common cause of cancer death, accounting for 529,800 new cases and 275,100 deaths each year (6). In fact, more than 85% of the global burden and 88% of the global mortality due to cervical cancer occur in developing countries, where it ranks as the second most common cancer among women (3).

Despite declining cervical cancer incidence and mortality rates worldwide (7), the absolute number of cervical cancer cases is expected to rise 46% by 2030 (4). In developing countries cervical cancer cases are projected to increase 62%, compared to only 8% in more-developed countries by 2030 (4). Demographic changes, including population growth and aging, will make the largest contribution to the rising cervical

cancer burden (8, 9). With 20% global population growth, from 6.9 billion in 2010 to 8.3 billion in 2030 (10), the cervical cancer cases are expected to increase, even when age-specific cervical cancer rates are stable or declining (4, 8). In addition, middle- and old-aged populations (40-74 years) will increase 45%, from 2.1 in 2010 to 3.0 billion in 2030, comprising one-third of the world's population (10). Considering that cervical cancer risk is highest in middle- and older-aged women (Figure 1.1) (4), combined with the expected increase in life expectancy, the number of cervical cancer cases will rise substantially as populations become older, even if population size remains constant (8, 9).

Vaccination against the human papillomavirus (HPV), the causal risk factor for cervical cancer, is predicted to prevent the development of most cervical cancers and may prove to be the most effective method to reduce the future burden of cervical cancer (8). However, successful implementation of HPV vaccination programs may be challenging, especially in low-resource settings, where vaccine costs are high and vaccine delivery is difficult. Therefore, at this time, it is difficult to predict the impact of the vaccine on the future burden of cervical cancer in developing countries.

Public Health Significance

Among less-developed regions, Latin America and the Caribbean (LAC) bear a disproportionate burden of cervical cancer. Presently, some of the highest cervical cancer incidence and mortality rates are found in LAC, alongside Africa and Southeast Asia (Figures 1.2 and 1.3) (3, 4). In terms of weighted years of life lost (YLL), cervical cancer is the leading cause of YLL among women between the ages of 25 and 64 in LAC, contributing more YLL than any other cancer, tuberculosis, maternal conditions, or AIDS

(11). Given the current age-specific incidence rates and changes in population demographics (growth and aging), the number of newly-diagnosed cervical cancer cases is projected to rise 63% in LAC by the year 2030, with a 122% increase in burden among older women and 50% increase among younger women (4). In Peru, where cervical cancer is the leading cause of cancer among women, the burden is expected to increase 73% by 2030 (4).

Even in a developed country such as the United States (US), where appreciable declines in cervical cancer incidence and mortality rates have been documented (7, 12), marked disparities exist among certain populations. Cervical cancer burden is unequally distributed across racial and ethnic groups in the US (13, 14). Hispanic women, in particular, suffer the greatest burden of cervical cancer, with incidence rates up to twice those of non-Hispanic white women (13-15). Considering Hispanic populations are projected to grow from 49 million in 2010 to 111 million by 2050, a 128% increase (versus 11% among non-Hispanics), the burden of cervical cancer among Hispanics in the US is expected to increase concomitantly (16).

The disproportionately high cervical cancer burden in less-developed countries and economically disadvantaged populations may be explained by differences in the availability, accessibility, and utilization of cervical cancer screening (6, 8). Disparities may also be due to variation in the underlying distribution of cervical cancer risk factors, particularly the prevalence of HPV infection (6, 8). Cervical cancer prevention and control efforts should focus on understanding the magnitude and nature of the cervical cancer burden across different regions of the world, recognizing the avoidable risk factors, and emphasizing public health priorities (8).

Despite our progress in understanding the epidemiology of cervical cancer, considerable gaps in knowledge remain. First, detailed cervical cancer incidence data collected by cancer registries in LAC are seldom published; therefore, a large proportion of the world's cancer burden goes unnoticed. Second, temporal changes in cervical cancer burden are often limited to inferences based on developed countries; however, these inferences may not accurately reflect changes in developing countries. Third, studies on racial and ethnic disparities in cervical cancer screening have varied in their conclusions depending on the population being studied, limiting our ability to make valid assessments of cervical cancer screening behaviors. The dissertation research presented here addresses these gaps by investigating regional variation in cervical cancer incidence across LAC, temporal trends in cervical cancer incidence within Peru, and racial/ethnic disparities in cervical cancer screening practices with a focus on Hispanic women in the US.

Specific Aims

The goal of this dissertation research was to advance our knowledge of cervical cancer burden and screening practices among Hispanic women in LAC and Michigan by utilizing available data from population-based cancer registries across LAC and from the Michigan Special Cancer Behavioral Risk Factor Survey.

Aim 1: To examine the variation in invasive cervical cancer incidence for population-based cancer registries in the Latin American and Caribbean region using published and unpublished data from the International Agency for Research on Cancer for the 5-year time period 1998-2002.

4

Aim 2: To evaluate cervical cancer patterns in Peru by examining geographical variation in the two most common histopathologic types of invasive cervical cancer, squamous cell carcinoma and adenocarcinoma, and analyzing differences over time using data from the Lima, Trujillo, and Arequipa population-based cancer registries.

Aim 3: To assess cervical cancer screening behaviors among Hispanic women aged 40 years and older residing in Michigan by evaluating differences in the prevalence of self-reported Papanicolaou (Pap) test screening by race and ethnicity, and identifying significant predictors of screening, using data from the Michigan Special Cancer Behavioral Risk Factor Survey.

Background

Etiology and risk factors

Infection with HPV is the strongest causal risk factor for cervical cancer, and persistent infection with one or more high-risk carcinogenic types is necessary in the development of cervical cancer (8). HPV-16 and HPV-18 are the most common types, found in over 70% of invasive cervical cancers worldwide (17, 18). Among women with normal cervical cytology, HPV prevalence ranges from 10-12% worldwide (18, 19); however, prevalence varies significantly by region. According to recent estimates, Sub-Saharan Africa (24%), Eastern Europe (21%), and Latin America and the Caribbean (16%) showed the highest prevalence, and Western Asia (1.7%) showed the lowest prevalence (19). These estimates indicate that HPV is one of the most common sexually transmitted infections worldwide (18). Fortunately, most cervical HPV infections are

cleared or suppressed by the immune system 1-2 years following exposure and do not

progress to cervical cancer (17).

Because of the high prevalence of HPV infection and comparatively low

incidence of cervical cancer among women worldwide, certain cofactors have been

implicated in the development of cervical cancer (20). These cofactors include, but are

not limited to, tobacco smoking, long-term hormonal contraceptive use, high parity

(number of children), and coinfection with the human immunodeficiency virus (HIV)

(21). Other probable cofactors include immunosuppression, and coinfection with

Chlamydia trachomatis or herpes simplex virus-2 (HSV-2), among other nutritional and

genetic factors (20-22). Sexual behavioral patterns, such as sexual intercourse at an early

age and multiple sexual partners, and low socioeconomic status have also been described

as potential cofactors for HPV infection (23-25).

Histopathology

Squamous cell carcinoma (SCC), originating in squamous epithelial cells, is the

most common histopathologic type of cervical cancer, accounting for 85-90% of all

invasive cervical cancers worldwide (8, 26). Adenocarcinoma (ADC), originating in

glandular epithelial cells, is the next most frequent histopathologic type and accounts for

the remaining 10-15% of invasive cervical cancers, along with other rare types (8, 27).

With the introduction of population-based cervical cancer screening, incidence

and mortality rates for cervical SCC have declined (8, 26). In contrast, incidence rates for

cervical ADC have been increasing, especially among young women in developed

countries such as the US, Canada, and in Western Europe (27-31). In LAC, little is

known about local trends in cervical SCC or ADC. One study demonstrated increasing

trends in cervical ADC among young women in Brazil, an upper middle-income country in South America (32).

This trend toward increasing rates of cervical ADC is likely due, in part, to the unintended effects of cytology-based cervical cancer screening, which may not adequately detect the pre-cancerous lesions leading up to ADC (precursor lesions). Cervical ADC precursor lesions are typically located higher in the endocervical canal, making them less accessible than SCC precursor lesions during Pap test screening and ultimately allowing invasive cervical cancer to develop (28, 33, 34). Furthermore, increasing rates of cervical ADC among young women may reflect changing sexual behaviors and increased transmission of HPV types (34).

Secondary prevention using cytology-based screening

Cytology-based cervical cancer screening, or the Papanicolaou (Pap) test, detects cervical cancer and its precursor lesions through the collection and microscopic examination of cervical cells (33). Despite the success of Pap screening in reducing cervical cancer incidence and mortality in developed countries (7), doubts have been raised regarding its accuracy and cost-effectiveness, especially in low-resource countries. Several studies have found wide variability in test sensitivity and specificity, which has been attributed to the subjective nature of interpreting cytology results (33, 35). However, to improve the performance of the Pap test, liquid-based cytology was introduced in the mid-1990s and is now the most widely used cervical cancer screening method worldwide (33). Still, the success of cytology-based screening in developing countries has been limited. Given that cytology-based cervical cancer screening must be repeated frequently

by trained personnel to achieve maximum effectiveness, alternative cervical cancer control methods have been developed, especially for use in less-developed countries (35).

Alternative methods of secondary prevention

In resource-poor settings, alternative methods to cytology-based screening have been evaluated in the diagnosis of cervical cancer and its precursor lesions. Visual inspection is a cost-effective but inherently subjective method of screening involving clinical examination of the cervix using the naked eye, and is often combined with an application of diluted acetic acid or Lugol's solution (33). The most promising alternative to cytology-based screening is HPV DNA testing, where various techniques may be used to detect the presence of high-risk carcinogenic HPV types in cervical specimens (33). A randomized clinical trial of cervical cancer screening in India found HPV DNA testing to be the most effective and reproducible of all screening methods studied, including cytology, visual inspection with acetic acid (VIA), and HPV DNA testing (36). In fact, study investigators concluded that a single round of HPV DNA testing significantly reduced the incidence of advanced cervical cancer and cervical cancer mortality over an 8-year period, which was more than a single round of cytology-based screening or VIA (36).

Primary prevention using HPV vaccination

The most important innovation in cervical cancer prevention thus far has been the HPV vaccine. Studies have shown current vaccines to be effective in preventing cervical cancer caused by HPV types included in the vaccine; however, those cancers caused by HPV types not included in the vaccine will not be prevented (8). Furthermore, vaccination does not prevent the development of precursor lesions in women who had

8

been infected with high-risk HPV prior to immunization (8), highlighting the need to continue cervical cancer screening while HPV vaccinations are being introduced. With the long latency period between HPV infection and cervical cancer development (8), HPV vaccines are not expected to substantially reduce cervical cancer incidence for several decades, further emphasizing the importance of screening.

Sources of Cervical Cancer Data

<u>Population-based cancer registries</u>

Cancer registries play an important part in estimating and monitoring trends in cancer incidence, evaluating the effectiveness of prevention and control interventions, and influencing cancer control policies (37, 38). In more-developed countries, sophisticated health care infrastructure, among other resources, permits high quality cancer registration; however, in less-developed countries, where health care facilities and resources are limited, cancer registration may be of low quality (39). Nonetheless, despite the potential for limited data quality, cancer registries in less-developed countries may provide valuable information regarding the cancer burden in those countries, especially for cervical cancer.

Few opportunities exist for cancer registries in developing countries to disseminate their findings. Even the leading source of cancer registration data, Cancer Incidence in Five Continents (CI5), published by the International Agency for Research on Cancer (IARC), frequently excludes data from developing countries because they often do not meet strict quality requirements. The most recent volume of CI5 (CI5-IX) included only 11 of the 29 LAC registries that had submitted data for inclusion, covering

only 4.3% of the LAC population (37, 39); in comparison, 54 of 58 North American registries were included, covering 80% of the North American population (37, 39). All data submitted to CI5 for inclusion undergo evaluation by an editorial board, where defined quality criteria are used to assess the comparability, validity, and completeness of registry data. However, the quality indicators used by CI5 editors are based on data from all cancer sites combined, and may not necessarily reflect the quality of data from specific, individual cancer sites. Cervical cancer, for example, is relatively easy to diagnose, and may exhibit higher data quality than other cancer sites that are more difficult to diagnose.

Population-based surveys

While cancer registries are the primary source of cancer incidence data, they rarely include information on cancer risk factors and screening practices. Population-based surveys can be used to gather information regarding cancer knowledge, attitudes, and screening behaviors. The Centers for Disease Control Behavioral Risk Factor Surveillance System (BRFSS) is an annual telephone survey used to monitor changes in the health behaviors and preventive practices of US adults, and often includes modules on cancer-related behaviors (40). However, some states conduct additional surveys to gather detailed information on local cancer risk factors and behaviors; in Michigan, this survey is known as the Special Cancer Behavioral Risk Factor Survey (SCBRFS).

The Michigan SCBRFS was designed to monitor change in cancer-related behaviors and knowledge for cervical, breast, colorectal, and prostate cancers. It is an ongoing population-based, cross-sectional telephone survey, similar in methodology to the BRFSS, targeting adults aged 40 years and older (41). A baseline survey was

conducted in 2001-2002, with subsequent surveys repeated in 2004, 2006, and 2008. To facilitate analyses among certain racial and ethnic minority groups, the SCBRFS was designed to oversample these populations. Data from the SCBRFS have been used to conduct local assessments of cancer-related behaviors, develop specific cancer control strategies, and implement community-based intervention programs across Michigan (41).

Summary and Chapter Overview

As the world population undergoes considerable growth and aging over the next two decades, the global burden of cervical cancer is expected to rise. Among Hispanic women in LAC and the US, demographic changes coupled with high cervical cancer incidence and mortality rates will contribute significantly to the expected increase in cervical cancer burden. Cervical cancer prevention and control efforts will be crucial in minimizing the increase in cervical cancer incidence among Hispanic populations in LAC and the US; however, efforts must first focus on understanding the magnitude and nature of the burden. Although often underutilized, the use of population-based cancer registry data is a valuable method in providing local assessments of cervical cancer burden across LAC and Peru, and will enable region-specific recommendations for screening or other preventive measures. Further, the use of population-based survey data to examine local cervical cancer screening behaviors will provide added insight, encourage additional research, and ultimately guide recommendations on cervical cancer control among Hispanics in Michigan and the US. This dissertation research adds to the international and domestic cervical cancer literature by advancing our knowledge of cervical cancer

burden and screening practices among Hispanic women in both LAC and Michigan (in the US).

Chapter 2 provides a comprehensive analysis of the descriptive epidemiology of cervical cancer across LAC using incidence data from 14 population-based cancer registries, after first ascertaining that the quality of cervical cancer reporting was adequate. In Chapter 3, cervical cancer incidence patterns in Peru were evaluated by examining variation in the two most common histopathologic types (SCC and ADC), and analyzing temporal differences using data from three population-based cancer registries. In Chapter 4, an assessment of self-reported cervical cancer screening behaviors was conducted for Hispanic women in Michigan using data from the SCBRFS. This chapter also evaluates differences in the reported prevalence of cervical Pap test screening by race and ethnicity, and identifies significant predictors of reported screening. Lastly, a summary of the primary research findings, implications for public health policies, and future research directions are discussed in Chapter 5.

Figure 1.1. Estimated age-specific incidence rates for cervical cancer, by region (Globocan, 2008).
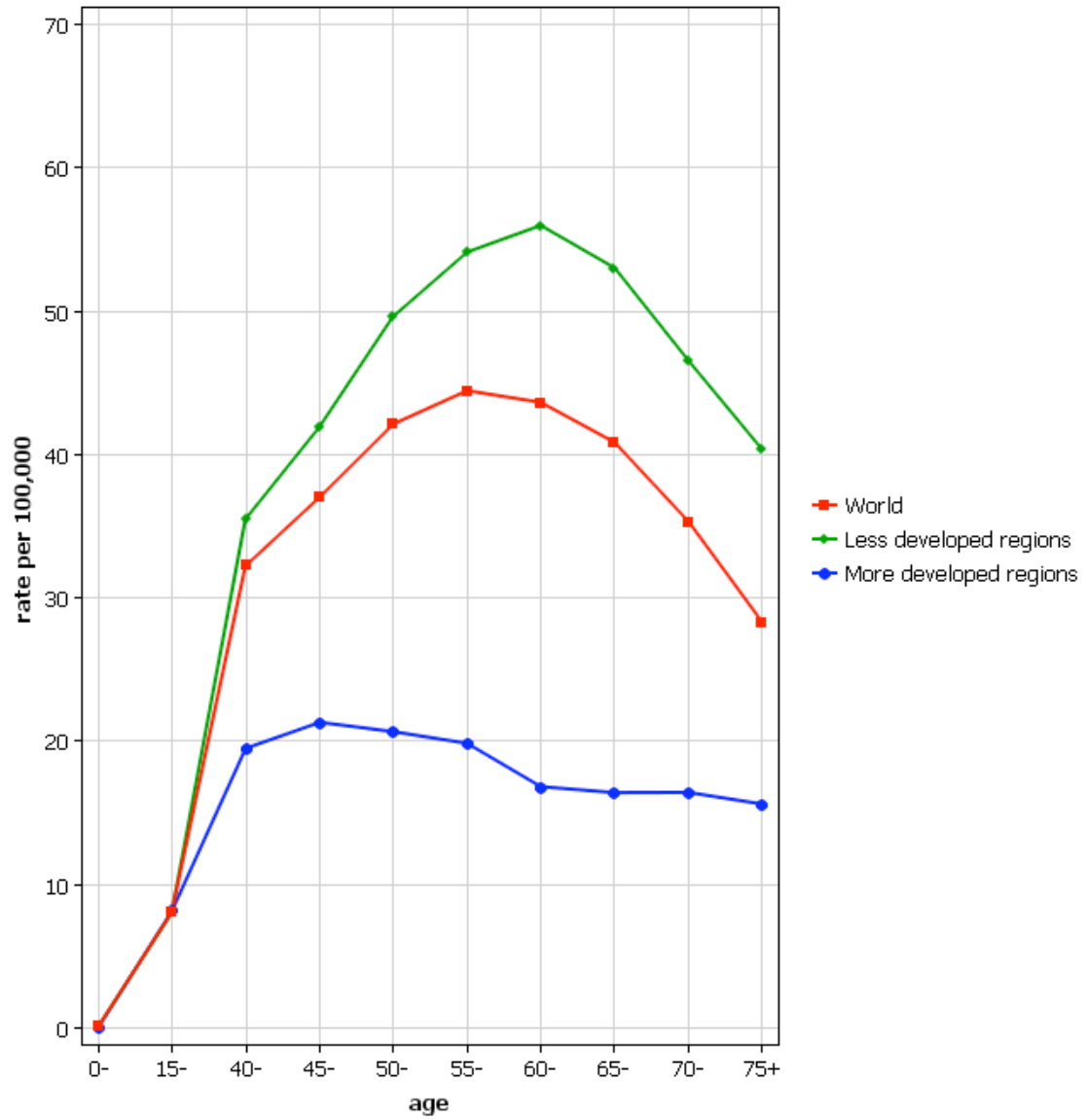
Reference (4).

Figure 1.2. Estimated age-standardized incidence rates (per 100,000) for cervical cancer (Globocan, 2008).

0   5.8   12.2   21.0   34.7   57
Age-standardised incidence rates per 100,000

GLOBOCAN 2008, International Agency for Research on Cancer
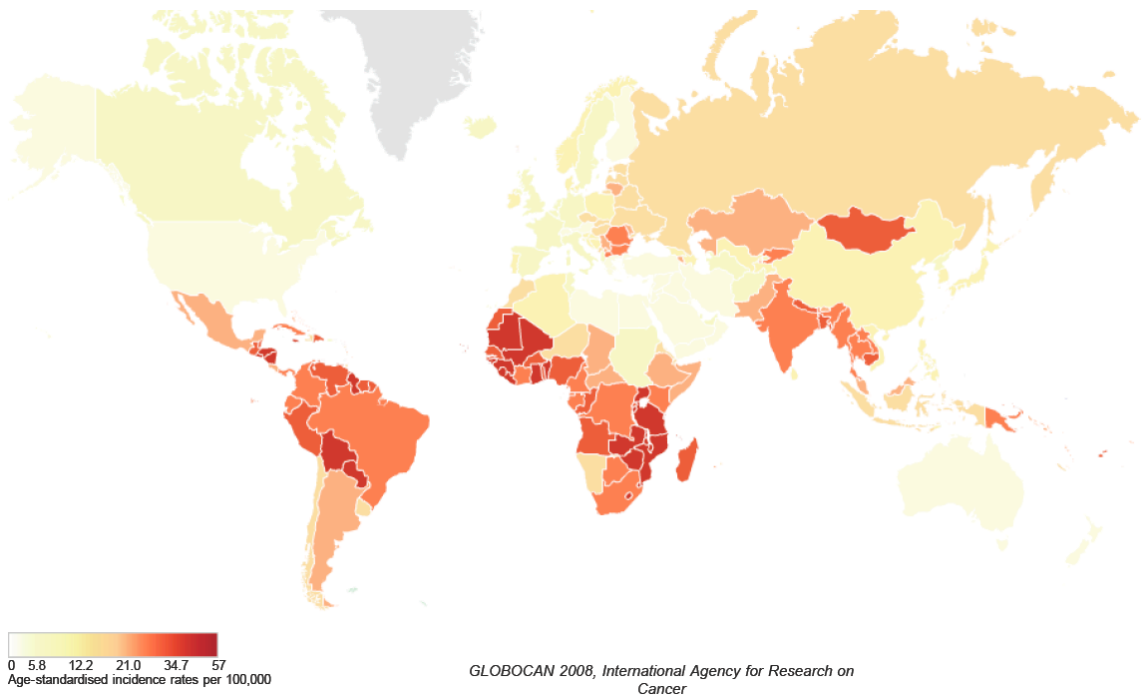
Reference (4).

Figure 1.3. Estimated age-standardized mortality rates (per 100,000) for cervical cancer (Globocan, 2008).

0   1.9   4.9   9.7   17.3   42
Age-standardised mortality rates per 100,000

GLOBOCAN 2008, International Agency for Research on Cancer
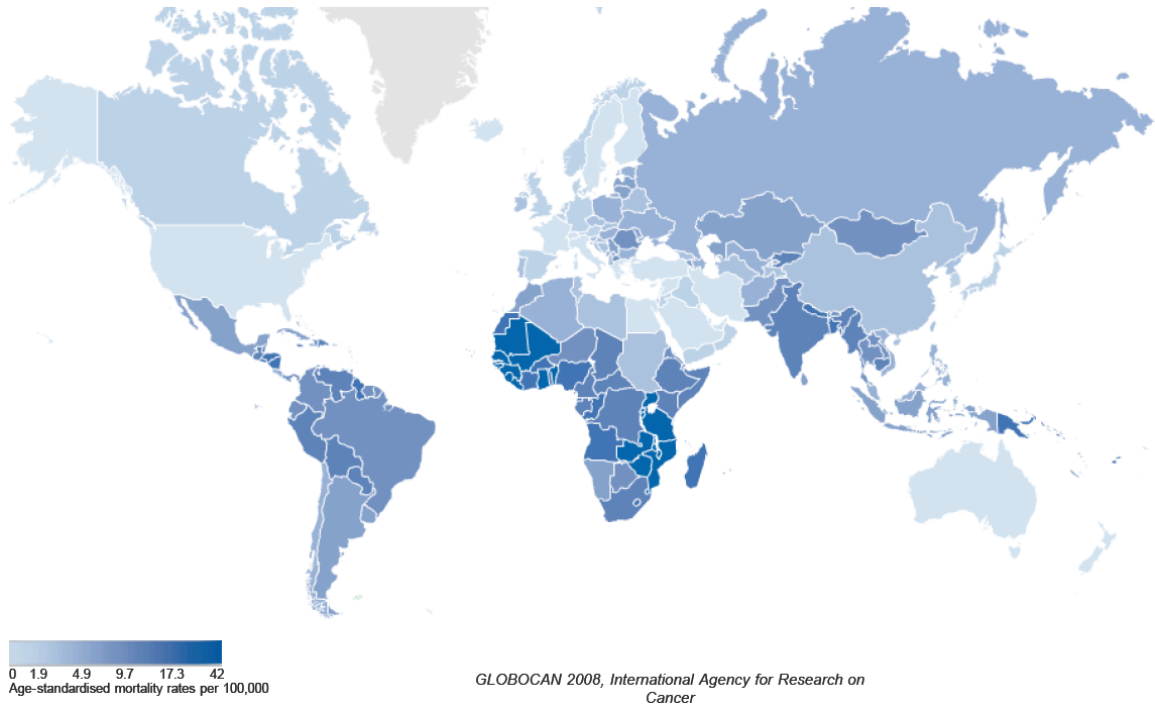
Reference (4).

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Chapter 2

Variation of Cervical Cancer Incidence in Latin America and the Caribbean

Introduction

Cervical cancer remains a significant global health problem despite the fact that it is highly preventable. It is the third most common cancer among women worldwide, with an estimated 529,800 new cases and 275,100 deaths in 2008 (1, 2). More than 85% of the global burden and 88% of the global mortality due to cervical cancer occur in developing countries, where it is the second most common cancer among women (1, 2). Although the incidence of cervical cancer is declining worldwide, high rates persist in many regions of Latin America, Africa, and South Asia (2-4).

Cancer registries play an important role in building infrastructure for essential health research, producing statistics on disease occurrence, and monitoring trends in cancer incidence by collecting, coding, and classifying cancer cases (5, 6). The International Agency for Research on Cancer (IARC) has published data from population-based cancer registries routinely since the 1970s; Cancer Incidence in Five Continents (CI5) documents the worldwide burden of cancer by making available comparable data on cancer incidence from a wide range of geographical locations over five-year time periods, most recently for 1998-2002 (5).

Prior to publication, cancer registries receive an invitation from IARC to send their data to the CI5 editors (5). Data quality is then evaluated by an editorial board, using

IARC international standards and defined quality criteria (5, 7). The indicators used by CI5 editors to assess the comparability, validity, and completeness of registry data are based on data used to estimate overall cancer rates, from all cancer sites combined, during the assessment period (5, 7). Therefore, if a registry submits data that does not meet quality criteria for all cancer sites combined, data from the entire cancer registry will be excluded, regardless of the quality of the data available for any individual cancer site. Certain cancers—such as pancreatic, liver, and esophageal cancers—may lower overall data quality when combined with other cancer sites since they are often lethal or difficult to diagnose (8-10).

Cervical cancer and its precursor lesions, on the other hand, are potentially more easily diagnosed, and therefore data quality may be higher for this cancer site. The uterine cervix is accessible for physical examination and detecting early cervical precursor lesions. Furthermore, cervical cancer and its precursor lesions have well-established diagnostic criteria and available technologies for detection and diagnosis, such as cytology-based screening (11). Although few organized cervical cancer screening programs exist in Latin America and the Caribbean (LAC), opportunistic screening programs have been implemented, thereby increasing cervical cancer awareness in this region (12, 13).

In the LAC region, 29 cancer registries from 11 countries submitted data to IARC for inclusion in CI5 Volume IX (CI5-IX); however, only 11 registries from 8 countries were actually included in that publication (5). Data from 18 registries were excluded due to insufficient data quality for all cancer sites combined. Currently, inferences on cancer burden in LAC are based on rates from the 11 registries included in CI5-IX. Given the

current level of interest in cervical cancer burden and prevention, those 11 registries may not adequately represent the cancer burden in different regions in LAC. Evaluation of information from more cancer registries may lead to better understanding of the profile and descriptive epidemiology of cervical cancer in this region.

The objective of this study was to provide a comprehensive analysis of the descriptive epidemiology of invasive cervical cancer based on data from population-based cancer registries in LAC that were both included and excluded from CI5-IX, after first ascertaining that the quality of cervical cancer reporting was adequate. International standards for quality criteria used by IARC were employed (5, 7). We evaluated whether systematic variation in invasive cervical cancer incidence rates exists among registries included and excluded from CI5-IX by examining age-standardized, histopathology-specific, and age-specific rates.

Materials and methods

Invitation letters requesting permission to evaluate invasive cervical cancer data were sent to all 29 cancer registries in LAC that had submitted data for inclusion in CI5-IX, 20 of which granted permission to use their data for this analysis. Of the 20 registries that granted data access, nine had been included in CI5-IX [Bahía Blanca (Argentina), Brasília (Brazil), Cuiabá (Brazil), Goiânia (Brazil), São Paulo (Brazil), Cali (Colombia), Costa Rica, Quito (Ecuador), and Trujillo (Peru)], and 11 registries had been excluded from CI5-IX [Curitiba (Brazil), Fortaleza (Brazil), João Pessoa (Brazil), Salvador (Brazil), Cuba, Santiago de Cuba (Cuba), Villa Clara (Cuba), Guatemala, Arequipa (Peru), Lima (Peru), and Trinidad and Tobago]. A flow chart describing the methods used

21

in deciding which registries to analyze for this study can be found in Figure 2.1. The Institutional Review Board at the University of Michigan approved the study proposal.

Statistical Methods and Analysis

Statistical analyses for this paper were completed in Microsoft Office Excel and SAS/STAT software (Version 9; SAS Institute, Cary, NC). We first conducted a quality assessment using only invasive cervical cancer data to determine whether each registry had sufficient data quality. The same quality indicators used by IARC for all cancer sites combined in CI5-IX were employed to examine the quality of cervical cancer data (5). These indicators included the proportion of cases microscopically verified (MV%), registered from a death certificate only (DCO%), and with an unknown basis of diagnosis (UB%) (5). The acceptable limits for data quality indicators were based on international standards and modified by the authors to better reflect cervical cancer data: MV% between 75 and 98%, DCO% less than 10%, and UB% less than 10%. It should be noted that while a high MV% is desirable in developed countries, a value that is near perfect in developing countries suggests an over-reliance on pathology laboratories in diagnosing cervical cancer cases, and inability to locate cases diagnosed by other means (14). The cervical cancer-specific quality assessment was performed on all registries that had been either included in or excluded from the CI5-IX publication. Subsequent analyses were performed on all registries that met the necessary quality criteria for cervical cancer data.

Age-standardized cervical cancer incidence rates were calculated for each population-based cancer registry over the five-year time period 1998-2002; the same years covered by CI5-IX. Age-standardized rates were calculated using the direct standardization method and utilized Segi's world standard population (5, 15). Age-

22

standardized incidence rates were expressed as the number of new cervical cancer cases per 100,000 women per year (5, 15). Estimated variances of these rates were based on a modified Breslow and Day's method (5, 15, 16) and their associated 95% confidence intervals (CI) were approximated based on the assumption of normally distributed rates (5, 15). Differences between age-standardized cervical cancer incidence rates were then calculated, and the statistical significance of each difference was determined using a z-score.

Age-standardized incidence rates for the two most common histopathologic types of cervical cancer, squamous cell carcinoma (SCC) and adenocarcinoma (ADC) (17), were also calculated using direct standardization and Segi's world standard population (5, 15). The histopathology-specific incidence rates were determined for each population-based cancer registry, and associated 95% CI were calculated using the normal approximation method described above.

Crude, age-specific incidence rates for cervical cancer were calculated for women between the ages of 15 and 64 years. No cervical cancer cases were reported in women younger than 15 years of age in the registries analyzed. Incidence rates for women older than 64 years were not calculated due to the sharp decline in incidence rates observed among older age groups in many registries. This fall-off of cervical cancer incidence rates at older ages may indicate under-ascertainment of cases in those age groups, and therefore the age-specific incidence rates for these age groups have been disregarded (18, 19). Age-specific incidence rates were expressed as the number of new cervical cancer cases per 100,000 women per year for a given age group.

The effect of CI5-IX inclusion status on registry-specific cervical cancer incidence rates (i.e., to compare whether or not the rates for registries included in CI5-IX differ significantly from the rates for registries excluded from CI5-IX) was examined using a generalized linear mixed model with a negative binomial distribution and log link with the offset being the catchment population. This model was designed to estimate the between-registry variation in cervical cancer incidence among the population-based cancer registries under study. Random G-side effects were included in the model to allow for random variation between registries, and R-side effects were included to account for the possible correlation of incidence rates across years within the same age group. The final model for registry-specific cervical cancer incidence rates included the following covariates: year, age group, an interaction term for year and age group, and CI5-IX inclusion status. Data from the two regional Cuban cancer registries (Santiago de Cuba and Villa Clara) were removed from this regression analysis because of the overlap in cases with the national cancer registry of Cuba. Regression models were generated using the GLIMMIX procedure in SAS/STAT software.

Results

Table 2.1 highlights the results from the cervical cancer-specific data quality assessment undergone by each of the 20 participating LAC cancer registries. All nine registries that had been included in CI5-IX met the cervical cancer-specific quality requirements. In addition, five of the 11 registries that had been excluded from CI5-IX met these quality requirements. Thus, a total of 14 population-based cancer registries met the necessary quality requirements for cervical cancer diagnosis according to this

assessment and were analyzed in this study. Of the six cancer registries that did not meet the quality requirements and were removed from this analysis, three registries exceeded the acceptable proportion of cases registered from a death certificate only [Curitiba (Brazil), Salvador (Brazil), and Trinidad and Tobago], one exceeded the acceptable proportion of cases microscopically verified [João Pessoa (Brazil)], one only provided a single year of data and was in its first year of operation [Arequipa (Peru)], and one was a hospital-based cancer registry rather than a population-based one (Guatemala). While these registries did not meet the requirements for our study, they may be suitable for the needs of other studies at a local level.

In Table 2.2, age-standardized cervical cancer incidence rates are provided for the 14 LAC population-based cancer registries under study; Figure 2.2 demonstrates the geographical variation in age-standardized incidence rates. These rates demonstrated a wide range of values (14.58-43.95 per 100,000 women per year). Trujillo (Peru), a registry that had been included in CI5-IX, reported the highest age-standardized rate of 43.95, while Villa Clara (Cuba), a registry that had been excluded from CI5-IX, reported the lowest rate of 14.58. The highest rates (33.92-43.95) were reported by registries that had been included in CI5-IX [Goiânia (Brazil), Brasília (Brazil), Cuiabá (Brazil), and Trujillo (Peru)]; however, the intermediate rates (22.41-33.13) appear to have been reported mostly by registries that had been excluded from CI5-IX [Lima (Peru), Santiago de Cuba (Cuba), and Fortaleza (Brazil)]. The lowest rates (14.58-21.06) were reported by an assortment of registries, some of which had been included in CI5-IX and some excluded from CI5-IX.

Age-standardized incidence rates for the two most prevalent histopathologic types of cervical cancer, squamous cell carcinoma (SCC) and adenocarcinoma (ADC), are also given in Table 2.2. Rates ranged from 9.09-37.27 for cervical SCC, and 1.11-3.63 for cervical ADC. Similar to results for overall cervical cancer incidence, Trujillo (Peru) reported the highest SCC incidence rate of 37.27, while the lowest SCC incidence rate was reported in Villa Clara (Cuba), 9.09. Brasília (Brazil) reported the highest ADC incidence rate of 4.95, while Villa Clara (Cuba) reported the lowest ADC incidence rate, 1.11.

Table 2.3 presents differences in age-standardized rates for overall cervical cancer, between pairs of registries. Each cell represents the paired difference in rates between the corresponding row and column registries. For example, in the first cell (upper-left) of the table, the value 6.26 represents the difference in rates between Trujillo (Peru) (43.95) and Cuiabá (Brazil) (37.69), and this difference appears statistically significant ($p<0.05$). In fact, most differences between registries were statistically significant.

In Figure 2.3, age-specific cervical cancer incidence curves are illustrated for each registry. Across the 14 registries examined, the incidence of cervical cancer generally increases with age, as expected. However, the patterns of age-specific incidence curves fluctuated considerably. Some curves rise consistently as age increases while others rise sharply and level off at older age groups; this phenomenon could be related to the under-ascertainment of cervical cancer cases in older age groups (18, 19).

The generalized linear mixed model shows that after controlling for year and age group, the mean cervical cancer incidence rates were 10.4% higher for those registries

that had been included in CI5-IX as compared to those registries that had been excluded from the CI5-IX publication; however, these results were not statistically significant (ß=0.099, p=0.541). Furthermore, the estimated variance between registries (0.050) was smaller than the variance among different age groups within each registry (0.557).

Discussion

Using cervical cancer incidence data from 14 population-based cancer registries in LAC, we examined differences in cervical cancer incidence rates among cancer registries. This is the first study to examine variation in cervical cancer incidence among this large number of LAC cancer registries for the time period 1998-2002. By observing age-standardized, histopathology-specific, and age-specific cervical cancer incidence rates, we found heterogeneity among registries, thus highlighting the importance of examining data from as many registries as possible when characterizing risk across a region.

Age-standardized incidence rates demonstrated a wide range of values (14.58-43.95), as did histopathology-specific rates (SCC: 9.09-37.27; ADC: 1.11-3.63) and age-specific rates (Table 2.2). The heterogeneity in cervical cancer incidence rates among the registries examined may be related to the data quality of each cancer registry (15); however, it may also be influenced by the presence, or absence, of organized screening programs within the geographic regions covered by these registries, as well as differences in the prevalence of cervical cancer risk factors (12). Furthermore, regional variation may exist in the efficiency of health care systems, where access to diagnostic and treatment

27

facilities for all socioeconomic levels could vary by region, which might also contribute to the heterogeneity found in this study (7).

Across the LAC region, screening practices vary widely. Costa Rica has had opportunistic cytological screening available since the 1970s, but a national screening program did not begin until 1995 (12). Brazil launched a national cytology-based cervical cancer screening program in 1998; however, this program has only been considered successful in a few regions of Brazil (12). Peru, a country with some of the highest cervical cancer incidence rates in LAC, has made cervical cancer a national priority for decades; however, despite creating a national plan in 1998 that outlined strategies for cervical cancer prevention, low screening coverage persists (20, 21). Argentina also created a national program against cervical cancer in 1998, which was never fully implemented, therefore in 2008 a project to improve the national program began (22). Colombia recently implemented a national cervical cancer prevention program in 2006, and has been successful in improving the number of cytology-based screenings nationwide (23). Future research needs to further elucidate the effect of cervical cancer screening programs, both organized and opportunistic, on cervical cancer incidence in this region.

The CI5 publications routinely report on cancer incidence in the LAC region; however, a disproportionate number of registries in developing countries have been excluded due to inadequate data quality (5). As technology advances and registration practices become more efficient, data quality has improved (5), but many cancer registries in developing countries have not had the opportunity to take advantage of such technological advances especially in comparison to more developed countries (6).

Furthermore, financial support for cancer registries in developing countries is often inconsistent. Since many registries rely heavily on government funding, changes in the local political climate easily threaten the sustainability of cancer registries in developing countries. Without funding, cancer registries may be forced to suspend registration-related activities until new sources of funding can be obtained, which may severely impact data continuity and quality. Increasing the utilization of low-cost technology, such as web-based cancer registration, and securing long-term, stable sources of funding may improve the overall data quality of cancer registries in LAC and other developing countries.

A potential limitation of this study involves the representativeness of cancer registries in LAC. Only two registries (Costa Rica and Cuba) had nationwide coverage; all others were regional cancer registries covering large, urban centers. Rural women were not represented in this study because no cancer registries existed in rural areas of LAC. As a result, the findings and conclusions of this study should only be generalized to women living in urban areas of LAC. However, despite our inability to document cervical cancer incidence in rural LAC, we speculate that incidence rates for late-stage cervical cancers would have been higher in rural areas compared to urban areas. In rural areas cervical cancer screening facilities are limited, and pre-cancerous cervical lesions are more likely to go undetected; therefore, we would expect a larger number of late-stage, invasive cervical cancers in this region, compared to urban areas. To accurately assess cervical cancer incidence among women in LAC, cancer registries should be implemented in rural areas, in addition to urban areas, of LAC.

Additional limitations should be considered. Only 20 of the 29 cancer registries that had provided data for inclusion in CI5-IX granted permission for data use. Had we analyzed a larger number of registries, we speculate that we would have been able to visualize even greater heterogeneity. Despite performing a cervical cancer-specific quality assessment to ensure that we included only high quality cervical cancer data, the data provided by cancer registries that had been excluded from CI5-IX should be interpreted with caution, as they may not represent valid or reliable estimates of cervical cancer incidence (5). Although we identified statistically significant differences in age-standardized incidence rates between pairs of registries, making multiple comparisons may result in the identification of statistically significant differences due to chance alone (15). Nonetheless, this analysis provides a broader understanding of the profile of cervical cancer in LAC than has been available previously.

A major strength of this study is its methodology. We utilized a novel approach by first assessing the cervical cancer-specific data quality of each cancer registry. By doing so, we were able to include a more diverse group of LAC registries in our analysis than the CI5-IX had included in its publication, without compromising data quality. The comparative nature of this study is also a strength. Much can be learned about cervical cancer prevention and control by comparing cervical cancer incidence rates within such a geographically diverse region. Lessons learned from this study could be applied to other low- to middle-income countries where limited data are available. Additionally, similar analyses could be performed for other cancer sites, especially if those cancers are considered preventable and of high priority for public health policy.

In conclusion, cervical cancer incidence rates in LAC vary across the region. By only including 11 cancer registries from LAC in the CI5-IX publication, and thereby excluding 18 cancer registries, the extent of this variation is not apparent. However, by using existing data, conducting a data quality assessment, and performing an in-depth evaluation of one cancer site (cervical cancer), we were able to provide a more complete picture of cervical cancer incidence across the LAC region. We therefore recommend that data from population-based cancer registries in low- and middle-income countries be utilized, once data quality has been established, to better understand cancer distribution, screening programs, and health care systems, thus enabling region-specific recommendations on cancer control and prevention interventions.

Table 2.1. Cervical cancer data quality assessment for the 20 cancer registries in Latin America and the Caribbean that granted permission for data use.

	Registration Time Period	Population, Females (N)	Cervical Cancer Cases (N)	Microscopically Verified (%)	Death Certificate Only (%)	Unknown Basis of Diagnosis (%)
				Acceptable Range		
				75% - 98%	≤ 10%	≤ 10%
Registries Analyzed						
Bahía Blanca (Argentina) [I]	1998-2002	147,977	139	95.0	2.9	2.2
Brasília(Brazil) [I]	1998-2001	1,047,388	1,154	91.2	2.2	6.3
Cuiabá (Brazil) [I]	2000-2002	362,919	302	89.1	5.6	2.6
Fortaleza (Brazil) [E]	1998-1999	1,105,401	581	91.0	4.8	0.7
Goiânia (Brazil) [I]	1999-2002	574,049	711	98.5	1.1	0.1
São Paulo (Brazil) [I]	1998-2002	5,444,354	6,028	85.6	4.1	0.0
Cali (Colombia) [I]	1998-2002	972,645	1,314	93.8	2.1	0.0
Costa Rica [I]	1998-2002	1,927,041	1,655	89.2	3.3	0.0
Cuba [E]	1998-2002	6,039,915	6,369	91.7	0.0	8.0
Santiago de Cuba (Cuba) [E]	1998-2002	523,370	790	94.8	1.6	0.0
Villa Clara (Cuba) [E]	1998-2002	423,800	393	95.2	3.3	0.0
Quito (Ecuador) [I]	1998-2002	734,477	637	93.4	3.9	0.0
Lima (Peru) [E]	1998	3,653,980	728	88.6	4.5	0.0
Trujillo (Peru) [I]	1998-2002	312,412	498	96.2	2.6	0.0
Registries Not Analyzed						
Curitiba (Brazil) [E]	1998-2000	818,170	561	79.3	13.0	6.1
João Pessoa (Brazil) [E]	1999-2002	320,987	260	100.0	0.0	0.0
Salvador (Brazil) [E]	1998-2002	1,273,529	663	85.5	11.9	1.8
Guatemala [E, 1]	1998-2002	1,301,228	1,297	97.8	0.0	0.0
Arequipa (Peru) [E, 2]	2002	197,103	258	98.3	0.0	0.0
Trinidad and Tobago [E]	1998-2002	629,315	584	83.9	15.1	0.0

Abbreviations: N, number.

[I]Included in CI5-IX.

[E]Excluded from CI5-IX.

[1]Hospital-based cancer registry.

[2]Newly established cancer registry.

Table 2.2. Age-standardized cervical cancer incidence rates and 95% confidence intervals in Latin America and the Caribbean, by histopathologic type and registry.

Registry	Cervical cancer overall		Squamous cell carcinoma (SCC)		Adenocarcinoma (ADC)	
	ASR[1]	95% CI	ASR[1]	95% CI	ASR[1]	95% CI
Trujillo (Peru) [I]	43.95	(39.97, 47.92)	37.27	(33.62, 40.93)	3.63	(2.49, 4.77)
Cuiabá (Brazil) [I]	37.69	(33.21, 42.17)	27.22	(23.39, 31.05)	3.80	(2.39, 5.21)
Brasília(Brazil) [I]	37.65	(35.36, 39.95)	24.37	(22.54, 26.21)	4.95	(4.14, 5.77)
Goiânia (Brazil) [I]	33.92	(31.33, 36.51)	24.11	(21.91, 26.31)	4.86	(3.88, 5.84)
Fortaleza (Brazil) [E]	33.13	(30.38, 35.88)	22.34	(20.08, 24.60)	2.50	(1.77, 3.23)
Cali (Colombia) [I]	27.92	(26.43, 29.41)	19.76	(18.51, 21.01)	2.98	(2.50, 3.47)
Santiago de Cuba (Cuba) [E]	26.35	(24.48, 28.23)	21.90	(20.19, 23.61)	1.50	(1.04, 1.96)
Lima (Peru) [E]	22.41	(20.75, 24.06)	13.85	(14.21, 16.98)	2.79	(2.21, 3.37)
São Paulo (Brazil) [I]	21.06	(20.54, 21.59)	13.69	(13.26, 14.12)	2.67	(2.48, 2.86)
Quito (Ecuador) [I]	20.04	(18.43, 21.66)	16.06	(14.60, 17.52)	2.00	(1.50, 2.50)
Costa Rica [I]	18.94	(18.00, 19.89)	13.66	(12.86, 14.46)	2.58	(2.23, 2.93)
Cuba [E]	17.58	(17.14, 18.02)	16.13	(13.13, 13.90)	1.16	(1.04, 1.27)
Bahía Blanca (Argentina) [I]	16.03	(13.27, 18.80)	11.41	(9.05, 13.77)	1.33	(0.55, 2.11)
Villa Clara (Cuba) [E]	14.58	(13.11, 16.05)	9.09	(7.92, 10.26)	1.11	(0.71, 1.51)

Abbreviations: ASR, age-standardized rate; CI, confidence interval; SCC, squamous cell carcinoma; ADC, adenocarcinoma.
[I]Included in CI5-IX.
[E]Excluded from CI5-IX.
[1]Rate per 100,000 women per year.

Table 2.3. Differences in age-standardized cervical cancer incidence rates between pairs of registries in Latin America and the Caribbean.

	Cuiabá (Brazil)	Brasília (Brazil)	Goiânia (Brazil)	Fortaleza (Brazil)	Cali (Colombia)	Santiago de Cuba (Cuba)	Lima (Peru)	São Paulo (Brazil)	Quito (Ecuador)	Costa Rica	Cuba	Bahía Blanca (Argentina)	Villa Clara (Cuba)
Trujillo (Peru)	6.26*	6.30**	10.03**	10.82**	16.03**	17.60**	21.54**	22.89**	23.91**	25.01**	26.37**	27.92**	29.37**
Cuiabá (Brazil)		0.04	3.77	4.56	9.77**	11.34**	15.28**	16.63**	17.65**	18.75**	20.11**	21.66**	23.11**
Brasília (Brazil)			3.73*	4.52*	9.73**	11.30**	15.24**	16.59**	17.61**	18.71**	20.07**	21.62**	23.07**
Goiânia (Brazil)				0.79	6.00**	7.57**	11.51**	12.86**	13.88**	14.98**	16.34**	17.89**	19.34**
Fortaleza (Brazil)					5.21**	6.78**	10.72**	12.07**	13.09**	14.19**	15.55**	17.10**	18.55**
Cali (Colombia)						1.57	5.51**	6.86**	7.88**	8.98**	10.34**	11.89**	13.34**
Santiago de Cuba (Cuba)							3.94**	5.29**	6.31**	7.41**	8.77**	10.32**	11.77**
Lima (Peru)								1.35	2.37*	3.47**	4.83**	6.38**	7.83**
São Paulo (Brazil)									1.02	2.12**	3.48**	5.03**	6.48**
Quito (Ecuador)										1.36**	2.46**	4.01*	5.46**
Costa Rica											1.36**	2.91	4.36**
Cuba												1.55	3.00**
Bahía Blanca (Argentina)													1.45

Example: The value 6.26 represents the absolute difference in rates between Trujillo (Peru) and Cuiabá (Brazil) registries; they differ significantly (p<0.05).
Note: Rate per 100,000 women per year.
*p<0.05.
**p<0.01.

Figure 2.1. Flow chart describing which registries from Latin America and the Caribbean had been included in or excluded from CI5-IX, and which had been analyzed or not analyzed in the current study.
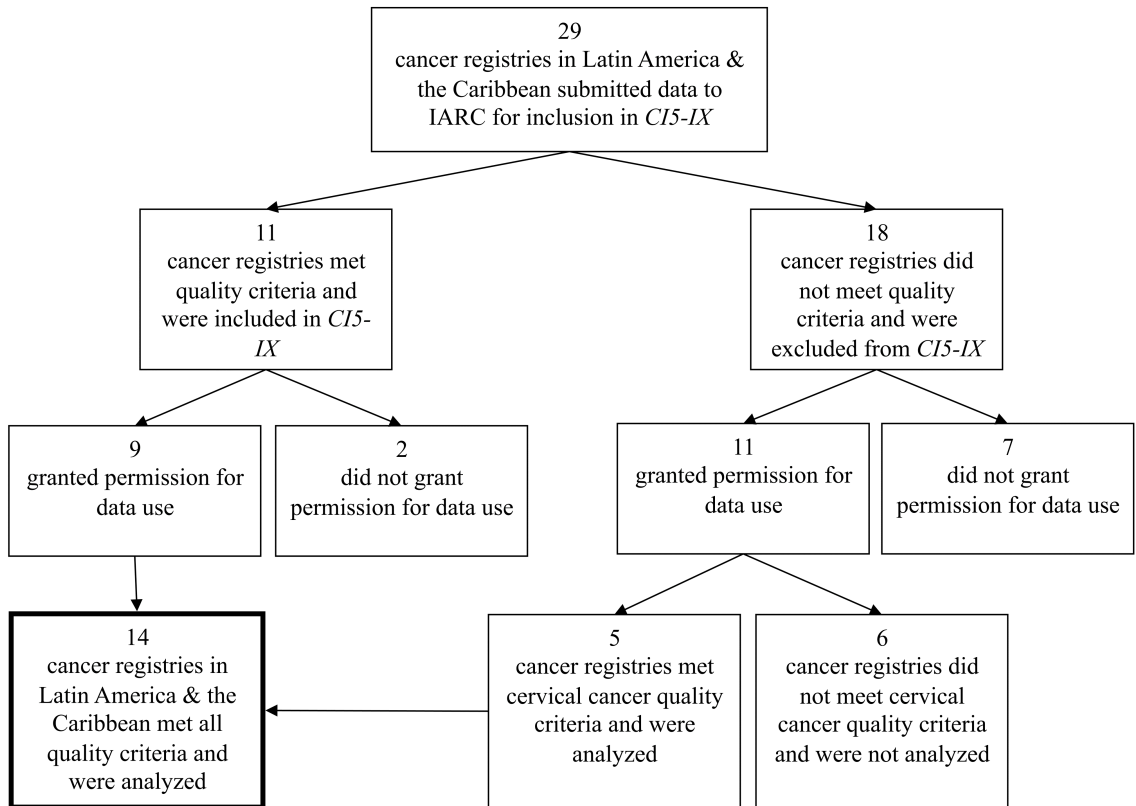
Figure 2.2. Map of Latin American and Caribbean cancer registries, with proportional age-standardized overall cervical cancer incidence rates.
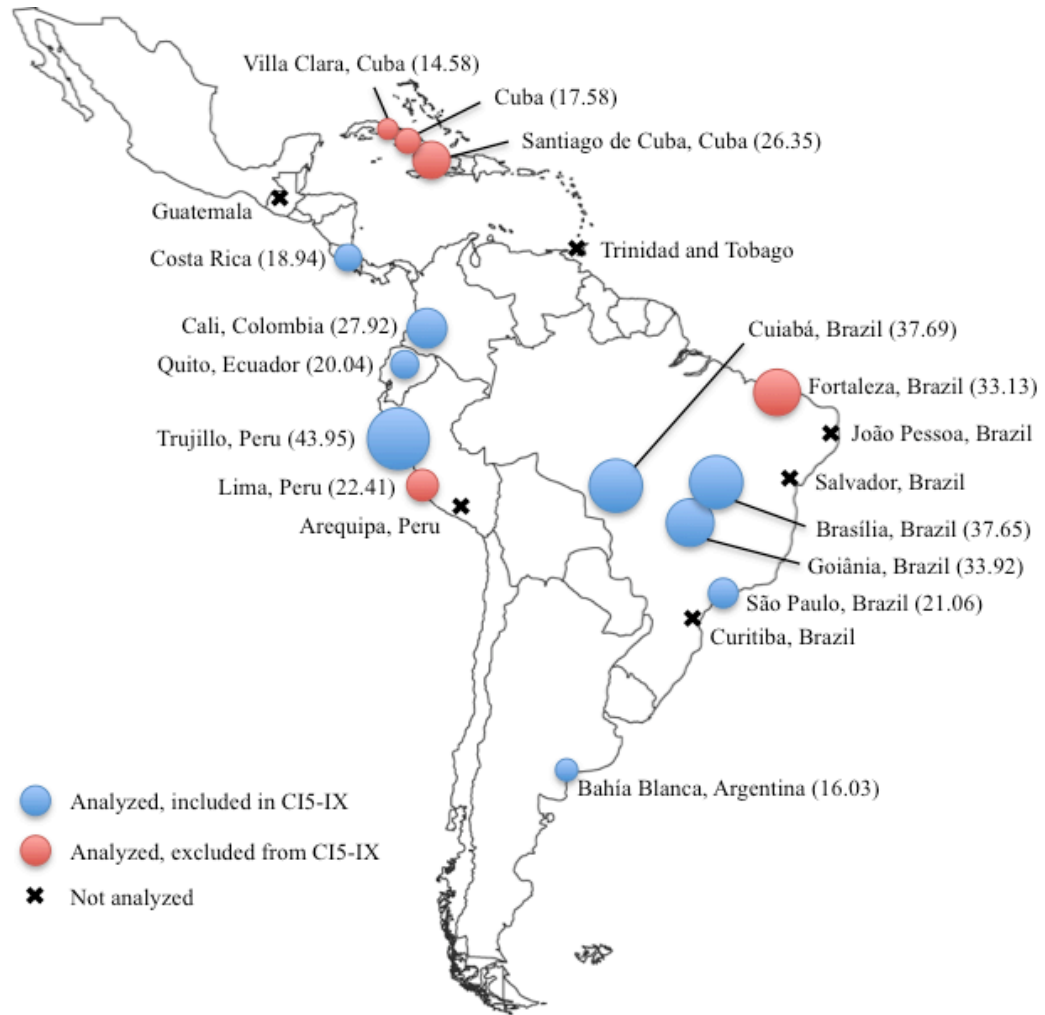
Figure 2.3. Age-specific cervical cancer incidence rates in Latin America and the Caribbean, by registry.
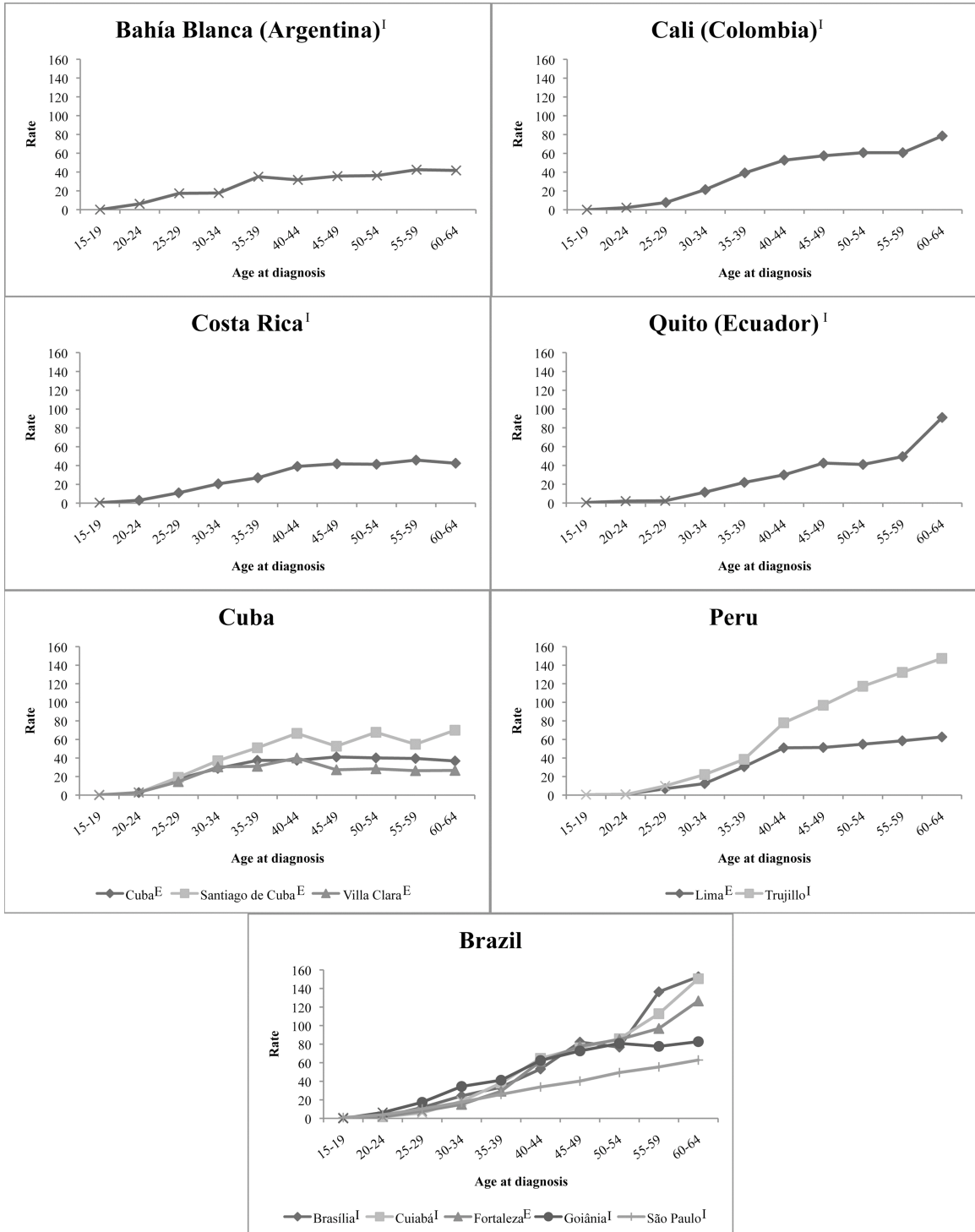
Note: Rate per 100,000 women per year.
[I]Included in CI5-IX.
[E]Excluded from CI5-IX.
✕ Rate based on fewer than 20 cases.

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Chapter 3

Regional Variation in Histopathology-Specific Incidence of Invasive Cervical Cancer Among Peruvian Women

Introduction

Cervical cancer is the third most common cancer among women worldwide (1, 2). More than 85% of the global cervical cancer burden occurs in less developed countries where cervical cancer ranks as the second most common cancer among women (1, 2). With the introduction of population-based cervical screening programs (Papanicolaou or Pap test), the incidence and mortality from cervical cancer have declined, most notably for the most prevalent histopathologic type of cervical cancer, squamous cell carcinoma (SCC) (3, 4). However, the opposite trend has been seen among rates for the second most prevalent histopathologic type, adenocarcinoma (ADC) (5). Incidence rates for cervical ADC have been increasing, especially among young women in developed countries such as the United States (US), Canada, and in Western Europe (6-8), and more recently among upper middle-income countries such as Brazil (9).

Peru, an upper middle-income country in South America, has one of the highest incidence and mortality rates of cervical cancer in the world (2, 10). To date, no national, organized cervical cancer screening program has been established in Peru. As in much of Latin America, Pap test screening in Peru has been sparsely implemented, especially in rural areas. Moreover, quality of Pap testing is sub-optimal with low quality control, insufficient coverage of women who are at risk, and poor follow-up of women with

40

abnormal results (3). For cervical cancer screening programs to be successful, infrastructure, trained personnel, and a widely acceptable screening method are needed; however, the burden of cervical cancer must first be described.

In order to appropriately assess the current cervical cancer burden in Peru and develop recommendations for a routine, population-based screening program for Peruvian women, it is important to recognize differences in the patterns of cervical ADC and SCC histopathologic types, along with changes in these patterns over time. Changes in histopathology-specific incidence rates may reflect changes in screening behaviors, changes in the distribution of causal risk factors for SCC and ADC (11, 12), changes in the distribution of HPV co-factors over time (13), or may reflect changes in the quality and sensitivity of the Pap test (14). Evaluations of the histopathologic profile of invasive cervical cancer in Peru could guide policy regarding the need to supplement Pap test cytology with newer screening methods. If the high rates of SCC remain unchanged in Peru, and/or if rates of ADC are found to be increasing, additional methods of prevention and screening, such as HPV vaccination or high-risk HPV DNA testing, could be especially beneficial in this country (15-17).

In Peru, information is lacking regarding the relative distribution of the two main histopathologic types, SCC and ADC. One study found that in Lima, the capital of Peru, 12.6% of invasive cervical cancer cases were diagnosed as ADC and 87.4% as SCC (18); however, this hospital-based case-control study was conducted over a short time period, 1996-1997, and included a small sample size (18). To recognize the potential changes in the pattern of cervical cancer burden in Peru, population-based cancer registry data can be used to examine regional variation and trends over time in cervical ADC and SCC.

The objective of this study was to evaluate cervical cancer patterns in Peru by examining the intra-country variation in the two most common histopathologic types of invasive cervical cancer, SCC and ADC, and analyzing differences over time using data from three population-based cancer registries: Lima, Trujillo, and Arequipa. We hypothesized that incidence rates of cervical SCC and ADC would vary significantly between the three registries in Peru. The highest rate of ADC and lowest rate of SCC were expected in Lima, compared to Trujillo or Arequipa, because Lima is the most economically developed city in Peru. Second, we hypothesized that the incidence of cervical SCC would show trends toward decreasing rates over time, and the incidence of cervical ADC would show trends toward increasing rates over time, as has been observed in many developed countries.

Materials and methods

In this study we analyzed cervical cancer incidence data retrieved from three population-based cancer registries covering the three largest urban centers of Peru: Lima, Trujillo, and Arequipa. The Lima Metropolitan Cancer Registry (LMCR) is both an active and passive cancer registry covering approximately 4.5 million women living in 49 districts of Lima and Callao Provinces (19). The LMCR was founded in 1968, discontinued in 1978, and revived in 1990 (19). The most recent registration period included cases diagnosed between 1990-1998. The Trujillo Cancer Registry (TCR) is an active cancer registry, covering approximately 350,000 women living in 5 districts of La Libertad Province (20). The TCR was founded in 1983, and began population-based data collection in 1984 (20). The most recent registration period included cases diagnosed

42

between 1984-2002. The Arequipa Population-based Cancer Registry (APBCR) is an active cancer registry covering approximately 410,000 women living in 15 districts of Arequipa Province (21). The APBCR was founded in 2001, but did not begin registration activities until 2002 (21). The most recent, reliable registration period included cases diagnosed between 2004-2006. Each cancer registry provided details, including histopathology, on all newly diagnosed cervical cancer cases for the registration period available. The Peruvian cancer registry directors and The Institutional Review Board at the University of Michigan approved the study proposal.

Data quality assessment

      To determine whether each registry met international data quality requirements, we conducted a data quality assessment using only data on invasive cervical cancer cases. The same quality indicators used by the International Agency for Research on Cancer (IARC) in Cancer Incidence in Five Continents Volume IX (CI5-IX) were employed to examine the quality of cervical cancer data (10). These indicators included the proportion of cases microscopically verified (MV%), registered from a death certificate only (DCO%), with an unknown basis of diagnosis (UB%), and with an unknown age (UA%) (10). The acceptable limits for data quality indicators were based on international standards and modified by the authors to better reflect cervical cancer data: MV% between 75-98%, DCO% ≤10%, UB% ≤10%, and UA% ≤20%. The cervical cancer-specific data quality assessment was performed on all three Peruvian cancer registries for the available registration time periods.

Cervical cancer cases

Cases diagnosed as invasive cervical cancer in women aged 15 years and older were included in this study; cases diagnosed as in-situ, or in women younger than 15 years of age, were excluded. Tumor morphologies were coded by each registry according to the International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3). For the purposes of this study, morphology codes were grouped into one of the following histopathologic types: 1) squamous cell carcinoma (SCC) (ICD-O-3 codes 8050-8078, 8083-8084); 2) adenocarcinoma (ADC) (ICD-O-3 codes 8140-8141, 8190-8211, 8230-8231, 8260-8263, 8310, 8380, 8382-8384, 8440-8490, 8560-8569, 8570-8574, 8576); or 3) other carcinoma (ICD-O-3 codes for all other specified and unspecified carcinomas). Classification of histopathologic type was based on IARC criteria (10), except we included adenosquamous carcinoma (ICD-O-3 codes 8560-8569) as ADC because they are biologically similar and have been grouped with ADC in prior studies (22). All non-carcinomas, including sarcomas, melanomas, and mixed tumors, as well as unspecified malignant tumors, were excluded from histopathology-specific analyses; however, they were included in analyses involving cervical cancer overall.

Population denominators

Population data were obtained in the form of national census data from the Peruvian National Institute of Statistics and Information (INEI) (23-25). Female population size for each registry coverage area was available from the latest three censuses: 1981, 1993, and 2007. For the intercensal years, we assumed linear population growth between censuses to estimate the annual female population at risk for each registry area.

We also examined the age distribution of the female population for each census year and registry area by constructing population pyramids (Figure 3.1). The underlying age structure for women aged 15 years and older was determined to be similar across registry areas for each census year; therefore, we decided not to age-standardize cervical cancer incidence rates when making comparisons across registries.

Statistical methods and analysis

The statistical analyses for this paper were completed using SAS/STAT software (Version 9; SAS Institute, Cary, NC). Incidence rates were first calculated for each registry over the appropriate registration time period. Crude incidence rates for cervical cancer overall (defined as all cervical cancer types combined) were calculated. Crude incidence rates were expressed as the number of new cervical cancer cases per 100,000 women per year (10, 26). Age-specific incidence rates were also calculated for cervical cancer overall. To do this, age was categorized into one of five, 15-year age groups: 15-29 years, 30-44 years, 45-59 years, 60-74 years, and 75+ years. Age-specific incidence rates were expressed as the number of new cervical cancer cases per 100,000 women per year for a given age group.

Histopathology-specific incidence rates were calculated for each registry over the appropriate registration time period. These crude incidence rates were specific to cervical carcinomas, and included two histopathologic types: SCC and ADC. Histopathology-specific incidence rates were expressed as the number of new cervical cancer cases for a given type per 100,000 women per year. Furthermore, age-specific incidence rates were calculated for each histopathologic type, using the age group categories mentioned above.

Age- and histopathology-specific incidence rates were expressed as the number of new cervical cancer cases for a given type per 100,000 women per year for a given age group.

Exact Poisson 95% confidence intervals (CI) were calculated for each of the incidence rates mentioned above using a published macro in SAS/STAT software (27). Typically, in cancer literature, CI are based on an approximation of the normal distribution (28-30); however, an exact method is preferred when working with age- and histopathology-specific incidence rates, where the sample sizes are likely small (27).

Cervical cancer incidence rates (crude, age-specific, and histopathology-specific) were assessed for statistically significant changes over time using linear regression. These trend analyses were conducted using the GLM procedure in SAS/STAT software. The direction of each trend was determined by the beta coefficient, and statistical significance was based on an alpha-level of 0.05. Trend analyses were conducted for the Lima and Trujillo registries only; the Arequipa registry contained too few years to conduct this type of analysis.

In addition to calculating incidence rates, we calculated the proportion of each histopathologic type using all cervical carcinomas as the denominator. Proportions were calculated for each registry, over the appropriate time period. We then assessed statistically significant differences in proportions of carcinoma types between pairs of registries using a chi-square test (alpha=0.05). The proportion of carcinoma types was also calculated for the Lima and Trujillo registries, by year, to investigate changes over time. The proportion was transformed using the arcsine square-root to achieve normality, and was modeled using linear regression (31). To further illustrate the relationship between the incidence of cervical SCC and ADC, the ratio of cervical squamous cell

46

carcinoma cases to adenocarcinoma cases (SCC:ADC) was calculated for each registry, over the appropriate time period.

Results

Table 3.1 provides the results of the cervical cancer-specific data quality assessment for each of the three Peruvian cancer registries. Quality indicators for both Lima and Trujillo were within acceptable limits, as defined above; however, the proportion of cases microscopically verified in Arequipa (99.3%) was above the acceptable limit (98.0%). While the data from Arequipa did not meet all the international data quality requirements, the paucity of available cervical cancer data in Peru led us to include this registry in our analyses.

In Table 3.2, crude and age-specific cervical cancer incidence rates for cervical cancer overall are presented, along with case counts and 95% CI, for each registry. The crude incidence rates for cervical cancer overall differed significantly across registries: Arequipa (47.2, 95%CI: 43.4,51.2), Trujillo (36.1, 95%CI: 34.5,37.8), and Lima (18.9, 95%CI: 18.4,19.3). Age-specific incidence rates for cervical cancer overall did not differ between Arequipa and Trujillo; however, rates in Lima were significantly lower than in Arequipa and Trujillo for the following age groups: 30-44 years, 45-59 years, 60-74 years, and 75+ years.

Histopathology- and age-specific cervical cancer incidence rates, along with case counts and 95% CI, are also provided in Table 3.2. The incidence rates for cervical SCC were significantly lower in Lima (14.0, 95%CI: 13.6,14.4) compared to Arequipa (29.7, 95%CI: 26.7,33.0) and Trujillo (30.0, 95%CI: 28.6,31.6). In contrast, incidence rates for

cervical ADC did not differ significantly across registries. Age-specific incidence rates for SCC showed similar results to cervical cancer overall. For women over 30 years of age, SCC-specific cervical cancer incidence rates for Lima were significantly lower than Arequipa and Trujillo. For women 15-29 years, the SCC-specific rate for Lima was significantly lower than Trujillo only. Age-specific incidence rates for ADC demonstrated that only one age group, 45-59 years, had a significantly lower incidence rate in Lima compared to Trujillo.

Figure 3.2 presents time trends in cervical cancer incidence rates (overall, SCC, and ADC) for all ages in Lima and Trujillo. Decreasing time trends were present in Lima for cervical cancer overall (ß=-0.103, p=0.250) and cervical SCC (ß=-0.029, p=0.697); however, these trends were not statistically significant. In Trujillo, significant decreasing time trends were found for cervical cancer overall (ß=-0.479, p=0.011) and cervical SCC (ß=-0.345, p=0.024). In contrast, increasing time trends were found for ADC-specific rates in both Lima (ß=0.051, p=0.349) and Trujillo (ß=0.050, p=0.239), but neither trend reached statistical significance.

In Figure 3.3, cervical cancer incidence rates are given for each registry over time, by age group and histopathology (overall, SCC, and ADC). For cervical cancer overall, significant decreasing time trends were found in one age group in Lima (45-59 years: ß=-3.280, p=0.005) and in several age groups in Trujillo [(30-44 years: ß=-1.684, p=0.005), (45-59 years: ß=-2.963, p=0.012), (60-74 years: ß=-5.038, p=0.001)], with marginally significant declines in the oldest age group in Trujillo (75+ years: ß=-7.839, p=0.067). Similarly, for cervical SCC, significant decreasing time trends were found among age groups in Lima (45-59 years: ß=-2.384, p=0.001) and Trujillo [(30-44 years: ß=-1.399,

p=0.029), (45-59 years: ß=-2.447, p=0.009), (60-74 years: ß=-4.067, p=0.004)], again

with marginally significant declines in the oldest age group in Trujillo (75+ years: ß=-

4.931, p=0.082). For cervical ADC, marginally significant increasing time trends were

found among the youngest age group in Trujillo (15-29 years: ß=0.016, p=0.101);

increasing trends in cervical ADC were also found among younger age groups in Trujillo

[(30-44 years: ß=0.061, p=0.665), (45-59 years: ß=0.232, p=0.362)], and among young

women in Lima [(15-29 years: ß=0.008, p=0.551), (30-44 years: ß=0.096, p=0.467)],

however, these trends did not reach statistical significance.

Table 3.3 presents the proportions of cervical carcinoma types for each registry.

The proportion of cervical SCC was significantly different across registries (p<0.0001);

the proportion was highest in Trujillo (89.5%) followed by Lima (82.7%) and Arequipa

(72.4%). The proportion of cervical ADC was significantly higher in Lima (12.7%)

compared to both Arequipa (7.9%) and Trujillo (7.8%), with no significant difference

existing between Trujillo and Arequipa. To investigate changes in the proportion of

cervical carcinoma types over time, proportions were modeled for Lima and Trujillo

using linear regression (data not shown). No significant time trends existed in the

proportion of carcinomas diagnosed as SCC for either registry. On the other hand, the

proportion of carcinomas diagnosed as ADC increased significantly over time in Trujillo

(ß=0.005, p=0.034). Lastly, the SCC:ADC ratio of carcinomas was found to be highest in

Trujillo (11.4:1), followed by Arequipa (9.2:1), and Lima (6.5:1).

Discussion

 This study examined differences and time trends in crude, age-specific, and histopathology-specific invasive cervical cancer incidence rates across registries using data from three population-based cancer registries in Peru. To our knowledge, this is the first study to use cancer registry data to examine heterogeneity in cervical cancer histopathology among Peruvian women. We found variation in cervical cancer incidence rates across registries, and over time in certain registries and among specific age groups. We also observed trends that indicate a rise in the burden of cervical ADC, particularly among young women in Trujillo. The evidence of substantial variation and trends in histopathology-specific cervical cancer incidence rates suggests that cancer registry data is a useful source in examining shifting patterns in the cervical cancer burden of low- to middle-income countries once data quality has been established.

 Overall cervical cancer incidence rates demonstrated significant geographical variation across regions of Peru, with the highest rate found in Arequipa, followed by Trujillo, and Lima. We predicted cervical cancer burden to be greatest in Trujillo, the smallest and least developed region studied. However, given that the Arequipa Population-based Cancer Registry had been recently established in 2002, it is possible that in addition to incident cases the registry collected prevalent cases, leading to an overestimate of cervical cancer incidence, which is a common tendency of newly established registries (32). In the histopathology-specific analyses, we saw that incidence rates for cervical SCC were highest in Trujillo, followed by Arequipa, and Lima, as expected; however, cervical ADC-specific incidence rates did not differ significantly across registries. Geographical variation in cervical cancer incidence may reflect

50

differences in the prevalence of HPV infection, and differences in patterns of sociodemographic and behavioral factors. Studies examining intra-country variation in cervical cancer incidence have found marked differences in incidence that reflect disparities in rates of poverty, education, smoking, and Pap testing in the US (33), and differences in sexual and reproductive risk factors in Costa Rica (34). Furthermore, regional differences in histopathology-specific incidence rates may reflect differences in disease etiology, since distinctive causal risk factors and HPV co-factors have been found for SCC and ADC (11-13).

While this study provides a detailed examination of cervical cancer incidence and histopathology among urban women in Peru, we were unable to examine cervical cancer patterns among rural women because of the lack of cancer registry coverage in these areas. Approximately 26% of Peruvians live in rural areas (25), where the risk of developing cervical cancer is thought to be higher than in urban areas. Based on our findings, we speculate that overall cervical cancer incidence would have been higher in rural Peru than in urban Peru, with rates of cervical SCC being higher in rural areas, and rates of cervical ADC being higher in urban areas. Urban-rural differences in socioeconomic status, and sexual and reproductive behaviors may account for the proposed urban-rural disparities in cervical cancer incidence; rural Peruvian women are more likely than urban women to live in poverty, initiate sexual activity at an earlier age, marry at an earlier age, and have more children, all of which are risk factors for cervical cancer (25, 35, 36).

In this study, we observed declines in overall and SCC-specific cervical cancer incidence rates in both Lima and Trujillo over time; however, statistically significant

declines were found in Trujillo only. Despite having no organized cervical screening program in either Lima or Trujillo, declining rates of cervical SCC could be partly explained by the existence of opportunistic cervical screening since cases would be diagnosed earlier as dysplasia rather than invasive cervical cancer (4). We believe that the lack of statistically significant trends in Lima may have been due to the limited number of years of data available for analysis, since we would not necessarily expect much change in cervical cancer incidence rates within the nine-year time span covered by this registry. In contrast, the Trujillo registry provided 19 years of data, which likely improved our ability to detect significant changes over time.

We also found evidence suggesting a rise in the burden of cervical ADC, particularly among young women in Trujillo, Peru. Upon examining changes in the proportion of each cervical carcinoma type, we saw that the proportion of carcinomas diagnosed as ADC increased significantly over time in Trujillo. We also observed slight trends toward increasing incidence rates of cervical ADC in Lima and Trujillo; however, these trends were not statistically significant. When time trends were examined for each age group, we found that rates of cervical ADC were increasing primarily among young women in both Lima and Trujillo; however, these trends were only marginally significant in Trujillo and non-significant in Lima. Nonetheless, these findings indicate that a change is occurring in the cervical cancer burden among urban Peruvian women.

Similar increases in the incidence of cervical ADC have been found among urban Brazilian women (9). As with the present study, population-based cancer registry data were used to examine time trends in the incidence of cervical ADC among women in Goiânia, Brazil. From 1988 to 2002, the age-standardized incidence of ADC increased

75%, from 1.47 to 2.84 per 100,000 women; however, mortality rates remained stable. To our knowledge, no other published studies have examined recent time trends in cervical ADC among women in less-developed countries. Among women in more-developed countries, the increasing incidence of ADC has been documented (5), particularly among young women, implying that economic development may somehow shift cervical cancer histopathology patterns.

We suggest that the rise in cervical ADC burden may reflect, at least in part, the limitations of current cytology-based screening. Pap test screening may not adequately detect ADC precursor lesions because these lesions are typically located higher in the endocervical canal, making them less accessible than SCC lesions for Pap testing (13, 14, 37). In addition, Pap test sensitivity for the detection of ADC has been estimated to be rather low (45% - 76%), and has been attributed to the higher rate of false-negatives compared to SCC lesions (14, 38). The inability to adequately detect ADC precursor lesions ultimately allows invasive cervical ADC to develop without early detection in some patients, and is a limitation of conventional screening practices. Newer technologies, such as HPV vaccination and HPV DNA testing, may serve as a solution but would be best used in combination with current Pap test screening (16, 39).

We utilized cancer registry data from Peru, a developing country, and saw the need to evaluate the quality of the data provided. Hence, a cervical cancer-specific data quality assessment was conducted for each Peruvian cancer registry. The results of the assessment showed that cervical cancer data quality was high among registries in Lima and Trujillo; however, in Arequipa we found a high proportion of cases microscopically verified (99.3%). While a MV% close to 100% is desirable in developed countries, it is

problematic in developing countries where it typically suggests an over-reliance on

pathology laboratories in diagnosing cervical cancer cases, and/or an inability to locate

cases diagnosed by other methods (40). In developing countries, the likelihood is greater

that cervical cancer cases never enter the health care system; therefore, the identification

of cases by other means, such as death certificates, is particularly important. Given the

paucity of available cervical cancer data in Peru, we included Arequipa in our analyses

even though it did not meet international data quality requirements; however, the issue of

data quality should be taken into account when interpreting the data.

Even though the Trujillo cancer registry met international data quality

requirements, we observed large fluctuations in age-specific cervical cancer incidence

rates over time, indicating potential data quality issues. Large spikes in cervical cancer

incidence were found in Trujillo from 1990-1994, especially among older age groups,

and may be explained by local attempts at introducing cervical cancer screening

programs targeting older women in the early 1990's, which would have led to a

subsequent increase in the number of diagnosed cervical cancers among older women.

Furthermore, the incidence rates for Trujillo were based on relatively small numbers

(compared to Lima), which may have contributed to the variability in incidence rates over

time.

This study had some additional limitations. The cancer registries analyzed in this

study may not be representative of all Peruvian women, since only urban areas were

examined. As is the case with all cancer registry data, any changes in the number of

cases, the presence of missing data, and even the misclassification of diagnoses (e.g.,

histopathology) would be capable of altering the numerators and, hence, the rates

provided in this analysis (41). As for population denominators, we assumed no error in the population counts provided by the Peruvian census and assumed linear population growth between censuses. For the time trend analyses, we did not have sufficient data to adequately assess time trends for Arequipa, and had little overlap in registration time periods across the three registries. Only Lima and Trujillo shared the nine-year registration period 1990-1998, which prevented us from making direct comparisons across registries. Even so, combined with our cervical cancer-specific data quality assessment, we believe that this study provides an informative evaluation of cervical cancer histopathology across the three Peruvian cancer registries.

One of the primary strengths of this study is its novelty. Few studies have been published using cancer registry data from developing countries, such as Peru, to describe the intra-country variation in cervical cancer incidence and histopathology. Typically, these analyses have been reserved for cancer registries in more-developed countries, such as the US (5, 6, 42); however, these registries tend to have extensive data of higher quality than those of less-developed countries. We found that utilizing existing data from population-based cancer registries allows for a time- and cost-efficient method of describing cancer burden in a population, which is especially beneficial in low- and middle-income countries. Cancer registry data can be used to guide current and future cancer control programs not only by demonstrating cancer burden, but also by monitoring primary prevention measures and influencing health care planning (32).

In conclusion, cancer registry data showed that overall and histopathology-specific cervical cancer incidence rates varied across regions of Peru, and over time in certain registries and age groups. We found trends suggesting an increase in cervical

ADC burden among young women, especially in Trujillo. Utilizing existing cancer registry data proved to be an efficient method for evaluating cervical cancer histopathology patterns among Peruvian women once data quality had been established. We suggest that the results from this study be used to guide future policy recommendations regarding population-based cervical cancer screening in Peru. Since cervical ADC rates may be increasing among young women in urban areas of Peru, we recommend supplementing current Pap test screening with newer technologies, such as universal HPV vaccination and HPV DNA testing, which are likely to be more capable of reducing the cervical cancer burden than cytology-based methods alone (15-17, 39). To confirm our findings that suggest a rising burden of cervical ADC among young women in Peru, similar studies should be conducted over longer periods of time and in other regions of Peru, and also in other Latin American countries.

Table 3.1. Cervical cancer-specific data quality assessment of cancer registries in Peru.

Registry	Registration Time Period	Population Coverage, Females, 2007 (N)	Cervical Cancer Cases (N)	Microscop-ically Verified (MV%)	Death Certificate Only (DCO%)	Unknown Basis of Diagnosis (UB%)	Unknown Age (UA%)
				Acceptable Range			
				75% - 98%	≤ 10%	≤ 10%	≤ 20%
Lima	1990-1998	4,338,566	4,554	90.1	3.1	N/A	0.2
Trujillo	1984-2002	355,202	1,529	93.6	3.5	0.2	0
Arequipa[1]	2004-2006	413,208	357	99.3	0.5	0	0

[1]Despite the MV% being high, we included data from Arequipa in our analyses because of the paucity of available cervical cancer data in Peru.

Table 3.2. Cervical cancer incidence rates and 95% confidence intervals in Peru, by histopathologic type and registry.

	Lima (1990-1998)[2]			Trujillo (1984-2002)[2]			Arequipa (2004-2006)[2]		
	N	Rate[1]	95% CI	N	Rate[1]	95% CI	N	Rate[1]	95% CI
Overall									
Crude rate	6,142	18.9	(18.4,19.3)	1,837	36.1	(34.5,37.8)	567	47.2	(43.4,51.2)
Age-specific rate									
15-29 years	212	2.07	(1.80,2.37)	46	2.86	(2.10,3.82)	10	2.85	(1.36,5.23)
30-44 years	1,761	26.0	(24.8,27.2)	500	50.4	(46.1,55.1)	146	54.4	(45.9,64.0)
45-59 years	2,205	61.8	(59.3,64.5)	658	119.5	(110.6,129.0)	212	128.3	(111.6,146.8)
60-74 years	1,427	77.6	(73.6,81.8)	447	163.4	(148.6,179.3)	140	167.1	(140.5,197.1)
75+ years	521	76.1	(69.7,82.9)	186	166.9	(143.8,192.7)	59	148.6	(113.2,191.7)
SCC									
Crude rate	4,554	14.0	(13.6,14.4)	1,529	30.0	(28.6,31.6)	357	29.7	(26.7,33.0)
Age-specific rate									
15-29 years	134	1.31	(1.10,1.55)	43	2.68	(1.94,3.60)	6	1.71	(0.63,3.72)
30-44 years	1,346	19.9	(18.8,21.0)	430	43.4	(39.4,47.7)	89	33.2	(26.6,40.8)
45-59 years	1,674	46.9	(44.7,49.2)	532	96.7	(88.6,105.2)	131	79.3	(66.3,94.1)
60-74 years	1,041	56.6	(53.2,60.2)	383	140.0	(126.4,154.8)	92	109.8	(88.5,134.6)
75+ years	350	51.1	(45.9,56.8)	141	126.5	(106.5,149.2)	39	98.3	(69.9,134.3)
ADC									
Crude rate	700	2.15	(1.99,2.32)	134	2.63	(2.21,3.12)	39	3.25	(2.31,4.44)
Age-specific rate									
15-29 years	25	0.24	(0.16,0.36)	1	0.06	(0.00,0.35)	1	0.28	(0.01,1.59)
30-44 years	226	3.34	(2.92,3.80)	44	4.44	(2.23,5.96)	13	4.84	(2.58,8.28)
45-59 years	268	7.51	(6.64,8.47)	61	11.1	(8.48,14.2)	15	9.08	(5.08,15.0)
60-74 years	137	7.45	(6.26,8.81)	18	6.58	(3.90,10.4)	8	9.55	(4.12,18.8)
75+ years	44	6.43	(4.67,8.63)	10	8.97	(4.30,16.5)	2	5.04	(0.61,18.2)

Abbreviations: N, case count; CI, confidence interval; SCC, squamous cell carcinoma; ADC, adenocarcinoma.
[1]Rate per 100,000 women per year.
[2]Registration time period.

Table 3.3. Proportion of cervical carcinomas in Peru, by histopathologic type and registry.

	Lima (1990-1998)[1]	Trujillo (1984-2002)[1]	Arequipa (2004-2006)[1]
SCC	0.827 [a,c]	0.895 [c,e]	0.724 [a,e]
ADC	0.127 [b,c]	0.078 [c]	0.079 [b]
Other carcinoma	0.046 [a,d]	0.027 [d,e]	0.197 [a,e]

Abbreviations: SCC, squamous cell carcinoma; ADC, adenocarcinoma.
Significant differences: [a]L vs. A (p<0.0001); [b]L vs. A (p<0.05); [c]L vs. T (p<0.0001); [d]L vs. T (p<0.05); [e]A vs. T (p<0.0001).
[1]Registration time period.

Figure 3.1. Age distribution of the female Peruvian population, by census year and region.

1993 Census

2007 Census

Lima

Lima

Trujillo

Trujillo

Arequipa

Arequipa
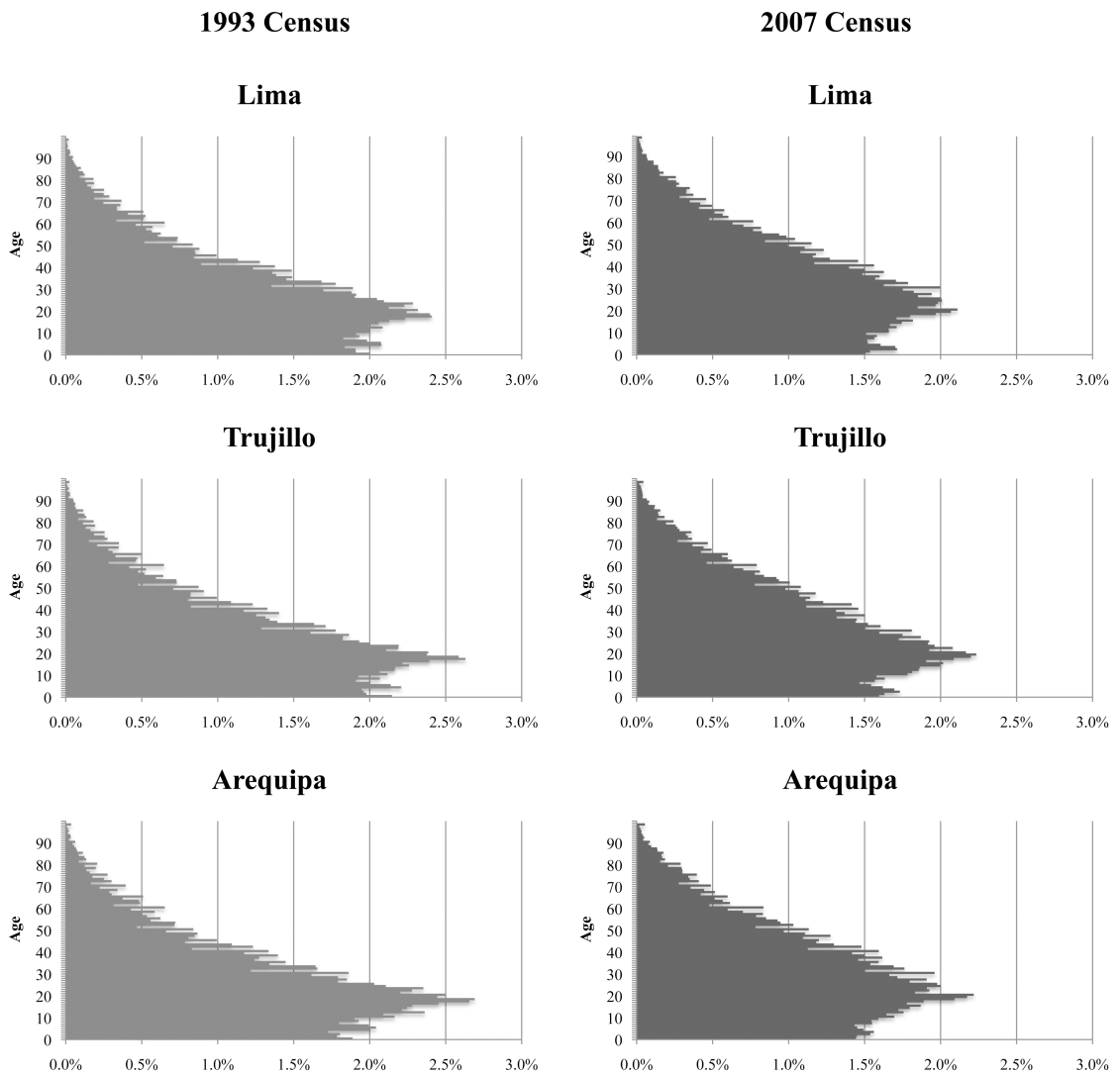
Figure 3.2. Trends in histopathology-specific cervical cancer incidence rates in Peru, by registry.

Lima

Trujillo
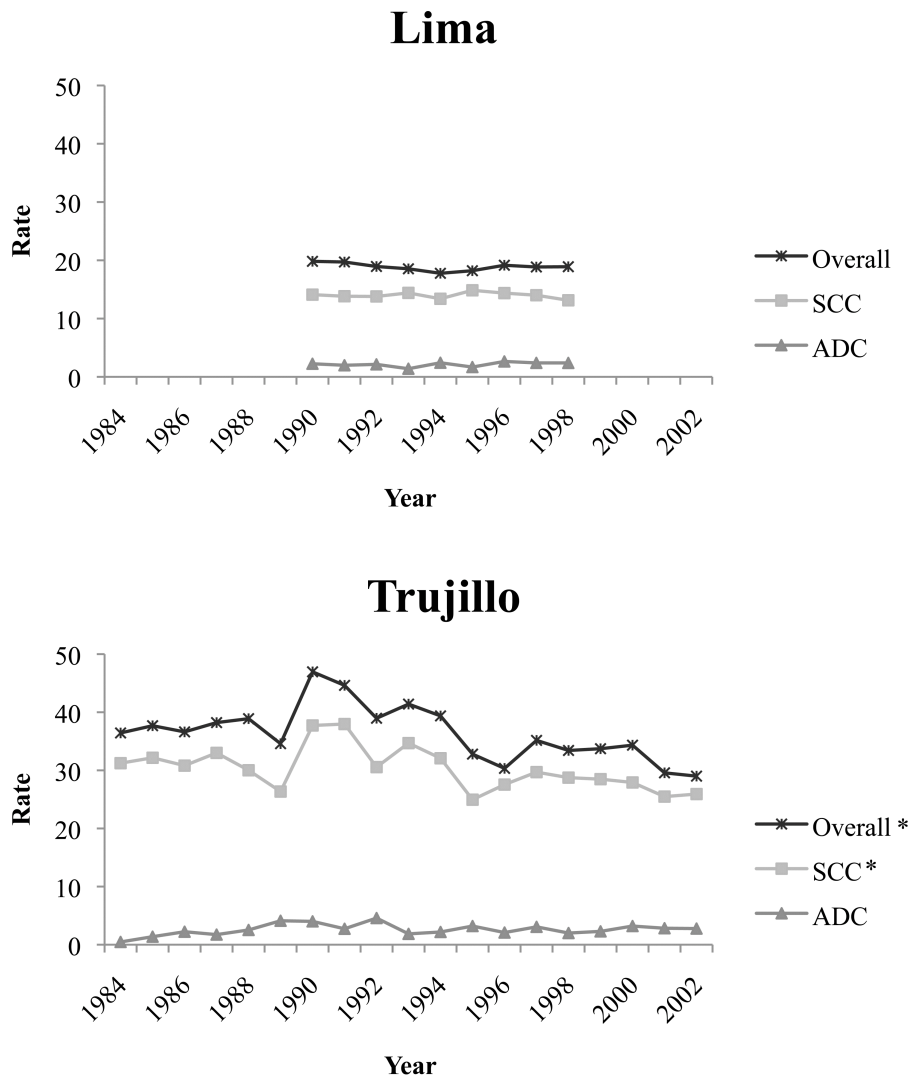
Abbreviations: SCC, squamous cell carcinoma; ADC, adenocarcinoma.
Note: Rate per 100,000 women per year.
*Significant decrease over time (p<0.05).

Figure 3.3. Trends in cervical cancer incidence rates in Peru, by age group, histopathology, and registry.

| **Overall** | **Squamous cell carcinoma (SCC)** | **Adenocarcinoma (ADC)** |
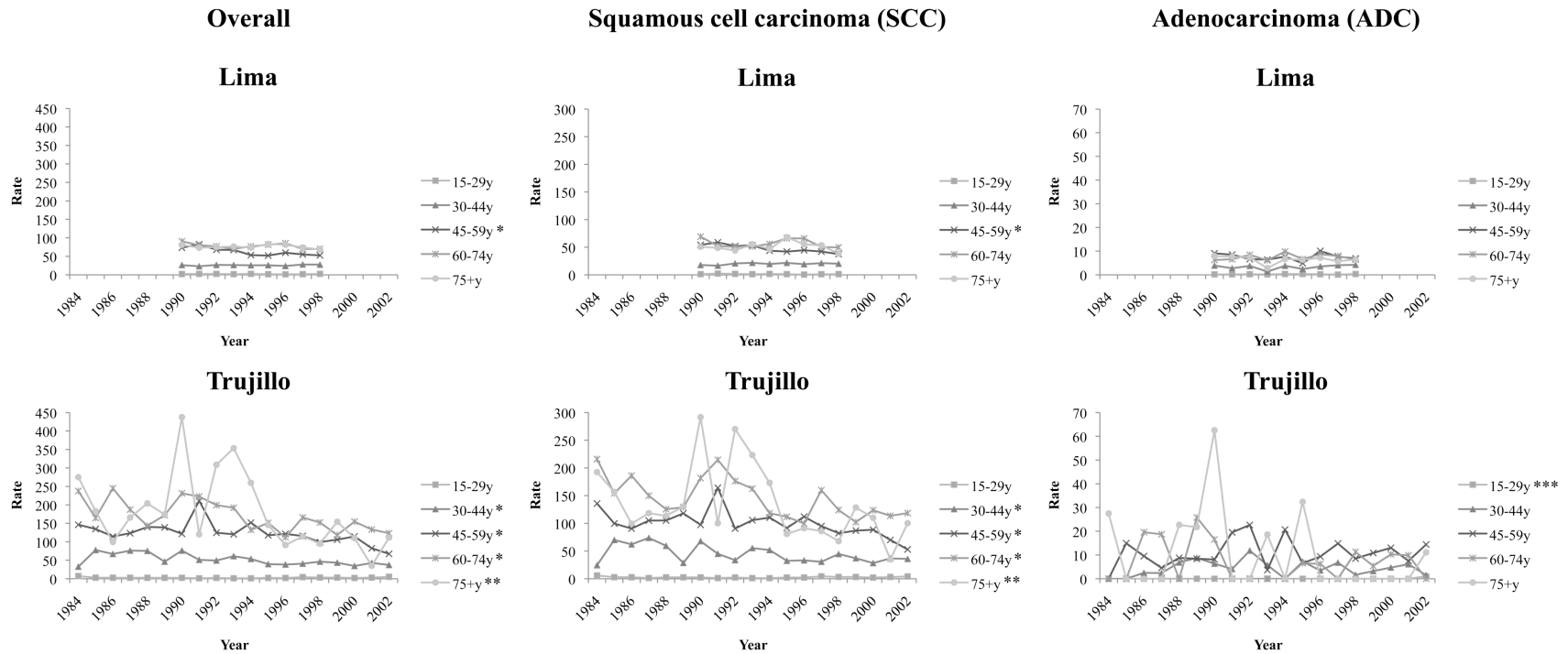
Note: Rate per 100,000 women per year.
*Significant decrease over time (p<0.05).
**Marginally significant decrease over time (p<0.10).
***Marginally significant increase over time (p<0.10).

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Chapter 4

Racial and Ethnic Disparities in Cervical Cancer Screening Prevalence and Predictors of Screening in Michigan

Introduction

Despite recent declines in incidence and mortality rates, cervical cancer ranks as the 13th most common cancer among women in the United States (US) (1, 2). In 2009, an estimated 11,270 incident cases of invasive cervical cancer and 4,070 deaths were due to the disease (3). Since the mid-20th century, cervical cancer mortality rates have declined 73%, from 26.2 per 100,000 in 1950 to 7.2 per 100,000 in 2000 (4). These dramatic declines in the US have been primarily attributed to the widespread implementation of cervical cancer screening, and success of the Papanicolaou (Pap) test in detecting cervical cancer and its precursor lesions (1, 4). However, despite an overall decline in incidence and mortality rates for the population as a whole, marked racial and ethnic disparities persist.

The disproportionately higher cervical cancer incidence rates in racial and ethnic minorities compared to non-minority white women are well documented (5-10). In the US between 2002-2006, approximately 8.3 per 100,000 women were diagnosed with invasive cervical cancer annually. However, disparities emerge when this rate is stratified based on race and ethnicity: Hispanics (12.7), African Americans (11.1), American Indians (9.4), whites (7.9), and Asians/Pacific Islanders (7.6) (2).

Research suggests that Hispanic women in the US suffer the greatest burden of cervical cancer, with incidence rates up to twice those of non-Hispanic white women (2, 6, 9, 11). While invasive cervical cancer ranks as the 13th most common cancer among white women in the US, it ranks as 7th among Hispanics (2). In 2009, an estimated 2,000 incident cases of invasive cervical cancer and 500 deaths occurred among Hispanic women (11). Incidence rates of cervical adenocarcinoma, the second most prevalent histopathologic type of cervical cancer, are also significantly higher among Hispanic women compared to non-Hispanic women (5-7, 9); furthermore, Hispanic women are more frequently diagnosed with cervical cancer at later stages, resulting in higher mortality rates (9, 12, 13). These estimates of cervical cancer incidence and mortality for Hispanics may even be underestimated since women without legal status may not seek medical care, and women may return to their country of origin for treatment or to die (14-16).

Disparities in cervical cancer incidence are largely due to differences in the utilization of cervical cancer screening. In the US, lack of Pap test screening is the most influential factor in the development of invasive cervical cancer (17), with 60-80% of women diagnosed with advanced cervical cancer having not been screened in the five years prior to diagnosis (18). Hispanic women are more likely to experience barriers to cancer screening, and consequently utilize cervical cancer screening at significantly lower rates than non-Hispanic women (19-24).

Many complex factors determine whether or not women will utilize cervical cancer screening. Among Hispanic women, major barriers to screening are sociodemographic, institutional, and cultural or personal. Sociodemographic barriers

include low educational attainment (25-28); low income (26, 27, 29, 30); being unmarried (24, 26, 30-32); and lack of health insurance coverage (26, 27, 29, 32, 33). Institutional barriers include a lack of cancer- and screening-related knowledge (28, 34); lack of access to quality health care (14); not having a usual source of care (24, 26, 27, 29, 32, 35); and not having doctor recommendation for screening (35, 36). Lastly, cultural or personal barriers include traditional cultural values and beliefs (34); feelings of embarrassment, fear, or fatalism (14, 21, 32, 36-38); foreign birth (33, 39, 40); non-citizen status (29); low level of acculturation (29, 41); and limited English language proficiency (36, 41, 42).

The National Breast and Cervical Cancer Early Detection Program (NBCCEDP) and Michigan Breast and Cervical Cancer Control Program (MBCCCP) have provided free breast and cervical cancer screening to low-income and uninsured women for the past 20 years. While increasing access to free screening sites is essential, more is needed to encourage women to be screened. Cervical cancer screening programs, such as the NBCCEDP and MBCCCP, address only a portion of the sociodemographic and institutional barriers faced by Hispanic women. Community-based cervical cancer education intervention programs have been successful at reducing cultural and personal barriers, and increasing cervical cancer screening use, among Hispanic populations across the US (43, 44). Many of these interventions utilize promotoras (community health workers) to promote utilization of care, and incorporate effective strategies in encouraging cancer screening among Hispanic women include having a physician recommendation, using Spanish-language print materials, and using culturally specific media (36, 43, 44). Given their success, community-based education interventions may

68

be the best method for promoting cervical cancer awareness, reducing barriers to screening, promoting positive cues to undergo screening, and encouraging early screening, especially among Hispanic women.

By the year 2050, Hispanic populations in the US are projected to grow from 49 million in 2010 to 111 million by 2050, a 128% increase (versus 11% among non-Hispanics), and will constitute 27.8% of the US population (an increase from 15.8% in 2010) (45, 46). If these estimates are accurate and racial/ethnic disparities in cervical cancer incidence and mortality persist, culturally sensitive community-based cervical cancer education interventions will be imperative in reducing the burden of this preventable disease. However, the development of cancer control strategies and interventions require local assessments of screening behaviors and underlying barriers to screening among women in the community of interest.

In this study, we provide a local assessment of cervical cancer screening behaviors among Michigan residents aged 40 years and older, with a particular emphasis on Hispanic women. The specific objectives of this study were to examine differences in the prevalence of reported cervical cancer screening by race and ethnicity, and identify significant predictors of screening. We hypothesized that disparities in reported cervical cancer screening prevalence would exist across racial/ethnic ethnic groups in Michigan, and anticipated that Hispanic women would have low prevalence, as has been documented elsewhere.

Materials and methods

<u>Data source and study population</u>

Data were obtained from the Michigan Special Cancer Behavioral Risk Factor Survey (SCBRFS), a population-based cross-sectional telephone survey funded by the Michigan Department of Community Health (MDCH) (47). The SCBRFS was designed to monitor change in screening behaviors and measure progress toward achieving state public health objectives for cervical, breast, colorectal, and prostate cancers. The first SCBRFS was conducted in 2001-2002, targeting adults aged 50 years and older. The survey was repeated in 2004, 2006, and 2008, and broadened to include adults aged 40 years and older.

The survey instrument, sampling design, and data collection process for the SCBRFS closely followed those of the Centers for Disease Control (CDC) Behavioral Risk Factor Surveillance System (BRFSS), a state-based annual telephone survey collecting information from adults on health behaviors and preventive practices (48). The SCBRFS sampling design was a disproportionate stratified, random-digit dial telephone sample (47). The survey was also designed to oversample racial/ethnic minority populations to obtain a sufficient number of respondents from each racial/ethnic group, thereby facilitating analyses among these groups and allowing for more precise estimates.

For the purposes of this study, we examined reported cervical cancer screening behaviors among Michigan women aged 40 years and older who responded to the 2004, 2006, or 2008 SCBRFS. Data were initially examined for each year individually; however, because the same core questions were asked in each survey year, stacking the datasets allowed us to include all survey years for the purpose of obtaining a larger

sample size for each racial/ethnic group. A sub-analysis of data from the 2008 survey was also conducted to examine supplemental questions that had been included that year. The focus of this study was on Hispanic women's cancer screening behavior, with other racial/ethnic groups included for comparative purposes. The final unweighted sample consisted of 8,023 women (2,316 in 2004, 2,611 in 2006, and 3,096 in 2008).

<u>Measures</u>

We assessed three self-reported cervical cancer screening outcomes. Two were based on the following questions: "Have you ever had a Pap smear?" (yes or no), and "How long has it been since you had your last Pap smear?" (<1 year, 1-2 years, 2-3 years, 3-5 years, or >5 years ago). If a woman reported having a Pap test within the last 3 years we considered her recently screened based on current recommendations for women over 40 years of age (49). The third outcome was frequency of reporting abnormal Pap tests, and was based on the question, "During the past 10 years, have you ever had a Pap test result that showed a problem in the cervix that required further testing?" (yes or no).

Independent variables were grouped into three categories: 1) sociodemographics, 2) cervical cancer knowledge, and 3) beliefs about cervical screening. Sociodemographics included age (40-49, 50-59, or $\geq$ 60), education (< high school, high school, some college, or $\geq$ college), marital status (married/living with partner or unmarried), employment status (employed or not employed), household income (< $15k, $15-25k, $25-35k, $35-50k, or $\geq$ $50k), health care coverage (yes or no), and race/ethnicity. Five mutually exclusive racial/ethnic categories were constructed: Hispanics, African Americans, American Indians, Asians/Pacific Islanders, and whites. For this analysis, respondents indicating Hispanic ethnicity were categorized as Hispanic,

71

regardless of the race chosen. All other respondents who did not identify themselves as Hispanic were grouped according to race. Asians and Pacific Islanders were not evaluated separately because there were too few survey respondents within the Pacific Islander group (n=24). Survey year (2004, 2006, or 2008) was also included as an independent variable.

Cervical cancer knowledge referred to the correct identification of cervical cancer risk factors and was based on the question, "What do you think is the most important thing that increases a woman's risk of getting cervical cancer?" Variables were constructed to identify women who responded with the human papillomavirus (HPV) and not having regular Pap tests, and also for women who did not know of any risk factors. Beliefs about cervical screening referred to the statement, "Every woman should be screened for cervical cancer regardless of her age" (agree or disagree).

In the 2008 survey, supplementary questions on knowledge, beliefs, preferred sources of information, and health status were asked. Additional measures of cervical cancer knowledge were based on the question, "From what you know about cervical cancer, what are the warning signs and symptoms?" Variables were constructed to identify women who responded that there are no signs or symptoms, and who did not know of any signs or symptoms. An additional belief measure referred to the statement, "Every girl or women between the ages of 9 and 26 should receive the newly available HPV vaccine for preventing cervical cancer" (agree or disagree). Variables were also constructed to identify women whose preferred source of cancer prevention information was a doctor/nurse, print materials, or the Internet. Lastly, general health status (excellent, very good, good, fair, or poor) was included.

<u>Statistical methods and analysis</u>

To account for the complex sampling design of the SCBRFS, data were analyzed using the survey procedures in SAS/STAT software (Version 9; SAS Institute, Cary, NC). Data were weighted to adjust for the unequal probabilities of selection and survey non-response, and to obtain unbiased estimates of standard errors. Descriptive analyses were first conducted to estimate the prevalence of reported sociodemographic characteristics, cervical cancer knowledge, beliefs, and screening, by race/ethnicity. Rao-Scott chi-square test statistics and associated p-values were used to examine differences in prevalence across racial/ethnic groups. Simple logistic regression was used to calculate prevalence odds ratios (OR) comparing prevalence estimates for Hispanics to other racial/ethnic groups.

Multiple logistic regression models were used to identify significant predictors of each cervical screening outcome. If a variable was significantly associated with reporting cervical cancer screening in all survey years, that variable was included in the model as potential predictor. Survey year, age, and race/ethnicity were included in all models, irrespective of the association with screening. Important predictors that were previously identified in the literature (education, marital status, and health care coverage) were also included in each model (26, 27, 32). Since colinearity existed between level of education and household income, and education was a stronger predictor of cervical cancer screening than income, we did not include household income in our models. Another set of multiple logistic regression models were used to identify predictors of reporting cervical screening among Hispanic women only. Finally, a sub-analysis was conducted

on data from the 2008 survey year; however, the smaller sample size prevented us from fitting models for Hispanic women separately in the sub-analysis.

Results

Sociodemographic characteristics of the study sample are presented, by race/ethnicity, in Table 4.1. The majority of survey respondents were non-Hispanic white (55.1%), and Hispanics comprised 7.8% of the sample population. The largest non-Hispanic minority group was African American (24.8%), followed by American Indian (7.4%), and Asian (5.0%). Apart from age, all sociodemographics presented in Table 4.1 were significantly different across racial/ethnic groups (p<0.01). Hispanics had the highest proportion of women with less than a high school degree (20.0%), whereas Asians had the highest proportion of women with a college degree or higher (54.2%). African Americans had the largest proportion of unmarried women (67.3%), whereas Asians had the largest proportion of married women (76.7%). American Indians had the highest proportion of women not employed (78.9%) and the lowest proportion of women covered by health insurance (80.4%).

Cervical cancer knowledge and beliefs

Table 4.2 shows the estimated prevalence of cervical cancer knowledge and beliefs about screening, by race/ethnicity. While knowledge varied across racial/ethnic groups, differences were not statistically significant. The odds of identifying not having regular Pap tests as a risk factor for cervical cancer were significantly higher among Hispanic women compared to Asian women (OR=7.69; 95% CI=2.27, 25.00). African American (OR=1.89; 95% CI=1.19, 3.02) and white (OR=1.69; 95% CI=1.07, 2.67)

74

women were significantly more likely than Hispanics to not know of any cervical cancer risk factors. Hispanics had the highest proportion of women identifying HPV as a cervical cancer risk factor (7.4%); however, this was not significantly higher than any other group.

The belief that every woman should be screened for cervical cancer regardless of age varied significantly across racial/ethnic groups (p<.0001). The racial/ethnic group with the highest proportion of women agreeing to this belief was Hispanics (89.2%). Furthermore, Hispanics were more likely to agree to this belief than Asians (OR=2.56; 95% CI=1.16, 5.56) and whites (OR=2.33; 95% CI=1.42, 3.82).

Cervical cancer screening

The prevalence of reporting ever being screening varied significantly across racial/ethnic groups (p=0.025) (Table 4.3). Over 99% of African American women reported being screened at least once in their lifetime. Compared with Hispanic women, the odds of reporting ever being screened were nearly five times higher among African American women (OR=4.87; 95% CI=1.44, 16.43) and slightly higher among white women (OR=1.51); however, this difference was not statistically significant. The odds of reporting ever being screened were 65% lower in American Indian women and 54% lower in Asian women compared to Hispanic women, but not significantly lower. The prevalence of reporting recent screening is also found in Table 4.3. Compared with Hispanics, the odds of reporting recent screening were lower in white (OR=0.87) and Asian (OR=0.89) women, but higher in African American (OR=1.25) and American Indian (OR=1.10) women; however, none of these differences were statistically significant.

The prevalence of reporting abnormal Pap tests in the last 10 years varied significantly across races/ethnicities (p=0.027) (Table 4.3). The racial/ethnic group with the highest proportion of women reporting an abnormal Pap test was Hispanics (26.0%). The odds of reporting an abnormal Pap test were significantly higher in Hispanic women compared to African American (OR=2.44; 95% CI=1.09, 5.26) and Asian (OR=4.00; 95% CI=1.10, 14.29) women, and slightly higher compared to white women (OR=2.18); however, this difference was not significant.

Predictors of cervical cancer screening

In Table 4.4 we provide results of the logistic regression analyses used to identify predictors of self-reported cervical screening behaviors among all women in the study population. Race/ethnicity proved to be a significant predictor of reporting ever having had a Pap test, even after controlling for age, education, marital status, employment status, health care coverage, and cervical cancer knowledge. Compared with Asian women, Hispanic women were 11 times more likely to report ever having had a Pap test (OR=11.11; 95% CI=1.75, 100.00). For all women, being aged 50-59 years, having some college education, and having health care coverage were significant predictors of reporting ever having had a Pap test. When the model was fit specifically for Hispanic women, we found that being aged 50-59 years, having a high school degree or some college education, being married, and having health care coverage were significantly predictive of reporting ever having had a Pap test, after also adjusting for cervical cancer knowledge (Table 4.5).

Analyses for having had a recent Pap test show that race/ethnicity was not predictive of reporting recent screening, after adjusting for age, education, marital status,

employment status, health care coverage, cervical cancer knowledge, and having a history of abnormal Pap tests (Table 4.4). Among all women, the likelihood of reporting a recent Pap test was significantly higher among those who were younger (40-49 years), had health care coverage, identified not having regular Pap tests as a risk factor for cervical cancer, and reported a history of abnormal Pap test results. Among Hispanic women in particular, being younger (40-49 years), having health care coverage, and reporting a history of abnormal Pap test results were significantly predictive of reporting recent screening, after also controlling for education and marital status (Table 4.5).

When we examined women who reported a history of abnormal Pap tests, we found that race/ethnicity was not associated with this screening outcome, after adjusting for age, education, marital status, employment status, health care coverage, cervical cancer knowledge, and having had a recent Pap test (Table 4.4). Among all women, the odds of reporting a history of abnormal Pap tests were higher among those who had a high school education and reported having had a recent Pap test; however, the odds were lower among those who were older (50-59 years and ≥60 years) and could not identify any cervical cancer risk factors. In the model fit specifically for Hispanic women, the likelihood of reporting a history of abnormal Pap tests was higher among those who had a high school education, agreed to the belief that all women should be screened regardless of age, and reported having had a recent Pap test; however, the likelihood was lowest among women who did not know of any cervical cancer risk factors, after also adjusting for age, marital status, health care coverage, and other measures of cervical cancer knowledge (Table 4.5).

Table 4.6 presents the estimated prevalence of each supplemental variable

included in the 2008 survey, by race/ethnicity. Significant racial/ethnic differences

existed only in general health status (p<.0001) and reporting the Internet as a preferred

source of cancer prevention information (p=0.001). Hispanics constituted the largest

proportion of women who agreed that every female aged 9-26 years should get the HPV

vaccine (74.2%). The odds of agreeing to that statement were significantly higher in

Hispanic women compared to African American (OR=2.78; 95% CI=1.23, 6.25) and

white (OR=2.36; 95% CI=1.08, 5.15) women. Hispanic women were more likely to

prefer a doctor or nurse as a source of cancer prevention information than any other

racial/ethnic group; however, this was not significant. Hispanic women were also 75%

less likely than Asian women to prefer the Internet (OR=0.25; 95% CI=0.06, 0.99).

Lastly, Hispanic women were significantly more likely than white women to not know of

any signs or symptoms of cervical cancer (OR=2.27; 95% CI=1.05, 4.88). The most

notable finding from the logistic regression analysis was that women who disagreed that

young females should get the HPV vaccine were significantly more likely to report ever

having had a Pap test (OR=5.35; 95% CI=1.25, 22.73), after controlling for age,

race/ethnicity, education, marital status, health care coverage, and measures of cervical

cancer knowledge, beliefs, and preferred sources of information (data not shown). No

supplemental variables were significantly predictive of recent screening or reporting

abnormal Pap test results.

Discussion

This study examined differences in self-reported cervical cancer screening prevalence by race/ethnicity, and subsequently identified significant predictors of screening among Michigan women aged 40 and older, with an emphasis on Hispanics. We found that the proportion of Hispanic women who reported ever being screened (97.2% ± 1.5) was not statistically different from that of whites (98.1% ± 0.5); moreover, the proportion of Hispanic women reporting being recently screened (83.0% ± 3.8) was not statistically different from that of whites (80.9% ± 1.6). While these results contradict much of the literature, similar findings have been found elsewhere (26, 29). Such high screening rates suggest that interventions and campaigns for improved cervical cancer screening among women in Michigan may have been successful in reducing racial and ethnic disparities in screening, and improving cervical cancer screening behaviors over time among Hispanic women in Michigan.

Given the abundance of research suggesting Hispanic women in the US underutilize cervical cancer screening, we expected Hispanic women to report lower screening prevalence than non-Hispanic white women (19-23). Several factors may have influenced our finding that Hispanic women in Michigan reported similar levels of screening as non-Hispanic whites. First, screening prevalence in non-Hispanic white women may have been underestimated. In the SCBRFS, information was unavailable on hysterectomy status; therefore, we were unable to exclude women who had a hysterectomy from the analyses. By including women who were not utilizing screening because they had hysterectomies, prevalence estimates would have been underestimated, and this would have been especially problematic among white women since the

likelihood of hysterectomy is higher in whites compared to Hispanics (50). Second, Hispanic women may have over reported Pap test utilization. Validation studies have shown that racial and ethnic minorities are less likely to accurately report cancer screening behaviors, with Hispanics being most likely to over report by responding affirmatively (51, 52). In one study of Mexican-American women in El Paso, Texas, only two-thirds of self-reported Pap smears in the previous three years were able to be verified with medical records (53). Over reporting of screening behaviors among Hispanic women may be related to a cultural emphasis on cooperation and avoidance of conflict, or to gain social approval (53). Furthermore, screening use may be over reported if women mistake a routine gynecologic exam without a Pap test as being screened (52). If Hispanic women truly overestimated the reporting of cervical cancer screening behaviors in this study, then racial/ethnic differences would have been masked; however, we are unable to confirm whether or not Hispanic women over reported their screening behaviors in our study.

The racial/ethnic group with the largest proportion of women reporting abnormal Pap test results in the last 10 years was Hispanics ($26.0\% \pm 7.6$), which was twice that of non-Hispanic whites ($13.9\% \pm 1.1$). In addition to having high cervical cancer incidence rates, studies have shown that Hispanic women have high rates of cervical precursor lesions, though rates have been similar to those of whites (10). Racial/ethnic disparities in reporting abnormal Pap results may reflect cultural differences in responding to the survey question. Hispanic women may have over reported abnormal results because they are more likely to respond affirmatively to survey questions, as mentioned above (51).

Moreover, it has been found that survey questions using the yes/no response format tend to increase cross-cultural disparities (54).

Our results suggest that significant racial/ethnic disparities existed in reporting ever being screened for cervical cancer. Despite controlling for age, education, marital status, employment status, health care coverage, and cervical cancer knowledge, race/ethnicity continued to be significantly predictive of reporting ever having had a Pap test. Yet, racial/ethnic disparities did not exist in reporting recent screening, or reporting abnormal Pap results upon controlling for sociodemographic variables. It should be noted that the use of race/ethnicity as a predictor of screening was not meant to imply biological differences, but was included as a proxy for social and health system determinants of health behavior (17). Therefore, we suggest that the observed racial/ethnic differences in reporting ever being screened for cervical cancer may actually be due to additional factors that were not measured or accounted for in this study, including place of birth, level of acculturation, having a usual source of care, or having recent contact with a health care provider, among others.

Age, education, and health care coverage were identified as significant predictors of self-reported cervical cancer screening in most models. In our study, older women were less likely than younger women to report utilizing Pap screening and to report abnormal Pap test results, similar to previous studies (15, 16). Older Hispanic women approach cervical cancer screening differently than younger women, experiencing more personal barriers to screening, such as embarrassment, fear, stigma associated with Medicaid coverage, and prior negative experiences with cancer prevention (55). We found that higher levels of education increased the likelihood of reporting cervical

screening use, and decreased the likelihood of reporting abnormal Pap test results. In the literature, educational attainment has been consistently regarded a strong predictor of cancer screening use (17, 21, 26, 36). In all models of ever and recent screening, having health care coverage was significant. Since Hispanics are more likely to be uninsured or underinsured, they are less likely to have a regular source of medical care, and, consequently, are more likely to go unscreened (21, 23).

Measures of cervical cancer knowledge (identifying not having regular Pap tests as a risk factor and not knowing of any risk factors) were significantly associated with reporting recent screening and reporting abnormal Pap test results. Lack of cancer- and screening-related knowledge has been associated with inadequate understanding of disease and reduced screening behaviors (17, 34). Women who lack such knowledge may be more likely to be unaware of the purpose of Pap tests and to not be screened (17). In our study, one measure of cervical cancer knowledge (identifying HPV as a risk factor) was not predictive of self-reported screening; however, a previous study found that knowledge about cervical cancer etiology predicted Pap use among Hispanics (34). The way in which the question was asked in the survey, or coded in the data analysis, may have impacted the validity of this variable. Education interventions designed to improve cervical screening utilization among high-risk women should emphasize public health literacy in relation to HPV, the role of the virus in the development of cervical cancer, primary and secondary prevention options, and the importance of regular screening despite being asymptomatic (34, 56).

Several limitations should be considered when interpreting these results. Although the SCBRFS is a population-based survey, selection bias may have been present. Cervical

cancer screening behaviors among women surveyed may not adequately reflect the experiences of women who were not surveyed. Specifically, our concern lies with Hispanic women since those who responded to the survey may represent a select group of wealthier, more acculturated, US citizens, and may not reflect all Hispanic women, especially those who are most vulnerable and at highest-risk of cervical cancer, including low-income and migrant women who have less access to the health care system. There is also the potential for response or coverage bias since the SCBRFS only contacted households with landline telephones, excluding wireless-only households or those without telephone service. In Michigan, 29% of households were wireless-only and 1.8% had no telephone service, with racial/ethnic minorities and low-income households more likely to be wireless-only (57). Current telephone surveys, including the SCBRFS and BRFSS, are in need of methodological improvements to ensure that high-risk populations are being surveyed.

Furthermore, the SCBRFS lacked information regarding place of birth for Hispanic women, which may have masked disparities within Hispanic ethnicity. Variation in cervical cancer screening behaviors has been found among Hispanic subgroups, with Mexican-American and Puerto Rican women most likely be recently screened (24, 58) and Central American women least likely to be recently screened (58). Lastly, the interpretation of our findings may also be limited by self-reported screening measures, which may differ from information obtained from medical records, resulting in recall bias. Validation studies have suggested that minority women, and particularly Hispanic women, over report screening frequency and underestimate the time since their

83

last screen (23, 51-53). Future studies should focus on more reliable and accurate assessments of cervical cancer screening behaviors among Hispanic women in Michigan.

Typically, studies examining racial/ethnic disparities in cervical cancer screening are limited by a small number of observations within each racial/ethnic group; however, the sample size of this survey contained a sufficiently large number of racial and ethnic minority women. The decision to oversample minority populations as a part of the study design allowed for meaningful analyses across racial/ethnic groups, and valid estimates of the standard error. Moreover, the decision to combine data from the three available survey years led to an even larger number of respondents from each racial/ethnic group.

Even though Hispanic women in our study reported similar cervical cancer screening rates to non-Hispanic whites, screening rates were still well below the *Healthy People 2020* national target set forth by the US Department of Health and Human Services. This initiative aims to increase the proportion of women who receive cervical cancer screening every three years; the target for cervical cancer screening is 93.0% by 2020 (59). In our study, only 83.0% of Hispanic women and 80.9% of white women reported being screened within the last three years. These findings suggest the need for continued efforts to improve cervical cancer awareness, knowledge, and screening utilization among Michigan women.

Despite efforts to reduce cervical cancer burden in Michigan through cytology-based screening, adherence to such screening programs is less than desired. Given the numerous barriers to cytology-based screening faced by Hispanic women, alternative cervical cancer prevention and control methods, including the HPV vaccine and HPV DNA testing, may be particularly suitable for this high-risk population since fewer visits

to health care providers are needed. However, culturally appropriate, community-based educational interventions will remain essential in promoting cervical cancer awareness, improving HPV-related knowledge, encouraging HPV vaccine uptake, and reducing barriers to HPV vaccination or HPV testing. This study broadens our understanding of the local cervical cancer screening behaviors in Michigan, which will enable policy makers to design and implement more effective, region-specific, methods of primary and secondary cancer prevention and control interventions to combat the rising cervical cancer burden.

Table 4.1. Sociodemographic characteristics of the study population, by race/ethnicity, Michigan SCBRFS 2004-2008 (N=8,023).

	Hispanic			African American (NH)			American Indian (NH)			Asian/Pacific Islander (NH)			White (NH)			p[2]
	n=626[1]			n=1,989[1]			n=590[1]			n=401[1]			n=4,417[1]			
	n[1]	%	(SE)	n[1]	%	(SE)	n[1]	%	(SE)	n[1]	%	(SE)	n[1]	%	(SE)	
Age																0.958
40-49 years	246	38.5	(6.0)	528	36.9	(2.2)	202	39.4	(8.8)	216	39.8	(7.8)	1,286	34.4	(1.7)	
50-59 years	194	24.9	(5.3)	630	28.0	(1.6)	177	22.3	(7.0)	111	31.5	(8.0)	1,251	28.3	(1.7)	
≥ 60 years	186	36.6	(6.6)	819	35.1	(1.9)	210	38.3	(8.4)	70	28.6	(8.8)	1,877	37.3	(1.5)	
Education																**<.0001**
< High school	180	20.0	(3.4)	227	9.9	(1.0)	87	17.0	(6.8)	20	5.7	(2.2)	485	6.2	(0.7)	
High school	172	40.8	(7.1)	618	31.3	(1.9)	242	29.2	(7.7)	48	14.9	(6.3)	1,440	33.5	(1.5)	
Some college	152	26.5	(4.7)	686	32.3	(1.8)	160	37.9	(8.7)	57	25.2	(9.7)	1,284	32.7	(1.7)	
≥ College	122	12.7	(2.7)	447	26.5	(2.2)	99	15.9	(6.0)	274	54.2	(8.8)	1,189	27.6	(1.6)	
Marital status																**<.0001**
Married	332	54.0	(6.5)	445	32.7	(2.1)	324	58.3	(8.4)	316	76.7	(8.9)	2,572	72.8	(1.3)	
Unmarried	293	46.0	(6.5)	1,531	67.3	(2.1)	265	41.7	(8.4)	84	23.3	(8.9)	1,829	27.2	(1.3)	
Employment status																**0.002**
Employed	293	39.6	(5.6)	777	46.5	(2.2)	283	21.1	(4.7)	223	43.5	(8.2)	1,832	45.3	(1.7)	
Not employed	310	60.4	(5.6)	1,108	53.5	(2.2)	280	78.9	(4.7)	174	56.5	(8.2)	2,470	54.7	(1.7)	
Household income																**<.0001**
< $15,000	97	21.5	(7.7)	370	18.8	(1.5)	92	29.0	(9.2)	23	7.7	(2.7)	542	9.4	(0.9)	
$15,000-24,999	143	21.0	(5.6)	426	20.6	(1.5)	144	21.9	(7.8)	46	18.7	(7.5)	694	17.7	(1.7)	
$25,000-34,999	92	25.6	(6.5)	316	19.0	(1.8)	80	16.6	(7.3)	27	13.1	(5.7)	489	12.6	(1.1)	
$35,000-49,999	67	10.4	(3.1)	258	13.6	(1.2)	76	8.4	(3.7)	40	5.8	(1.6)	583	16.1	(1.3)	
≥ $50,000	130	21.6	(4.5)	345	27.9	(2.4)	125	24.0	(7.3)	200	54.8	(8.0)	1,337	44.2	(1.9)	
Health care coverage																**0.006**
Yes	529	85.4	(4.8)	1,824	92.0	(1.1)	518	80.4	(8.3)	371	96.3	(1.1)	4,081	93.0	(1.2)	
No	97	14.6	(4.8)	157	8.0	(1.1)	70	19.6	(8.3)	29	3.7	(1.1)	323	7.0	(1.2)	

NOTE: Data were weighted to adjust for unequal probabilities of selection and survey non-response.

Abbreviations: NH, non-Hispanic; SE, standard error.

[1]Unweighted sample size.

[2]P-value based on Rao-Scott chi-square test of homogeneity across races/ethnicities; bolded p-value signifies statistical significance (p<0.05).

Table 4.2. Variation in cervical cancer knowledge and beliefs about screening, by race/ethnicity, Michigan SCBRFS 2004-2008 (N=8,023).

	Hispanic			African American (NH)			American Indian (NH)			Asian/Pacific Islander (NH)			White (NH)			p^2
	n=626[1]			n=1,989[1]			n=590[1]			n=401[1]			n=4,417[1]			
	n[1]	%	(SE)	n[1]	%	(SE)	n[1]	%	(SE)	n[1]	%	(SE)	n[1]	%	(SE)	
Cervical cancer knowledge																
Risk factors identified																
HPV	25	7.4	(2.9)	64	3.9	(1.2)	32	3.6	(1.9)	9	4.1	(3.3)	253	5.6	(0.6)	0.710
Not having regular Pap tests	81	13.8	(5.6)	276	14.2	(1.5)	68	14.9	(7.1)	22	2.1	(0.8)	407	9.0	(0.7)	0.086
Did not know of any risk factors	269	31.3	(4.8)	936	46.3	(2.1)	277	35.8	(8.3)	160	39.6	(8.2)	1,942	43.4	(1.7)	0.197
Beliefs about screening																
Every woman should be screened regardless of age																**<.0001**
Agree	524	89.2	(2.3)	1,715	88.4	(1.1)	483	94.4	(2.1)	264	76.2	(6.0)	3,399	78.1	(1.5)	

NOTE: Data were weighted to adjust for unequal probabilities of selection and survey non-response.

Abbreviations: NH, non-Hispanic; SE, standard error.

[1] Unweighted sample size.

[2] P-value based on Rao-Scott chi-square test of homogeneity across races/ethnicities; bolded p-value signifies statistical significance (p<0.05).

Table 4.3. Variation in reported cervical cancer screening, by race/ethnicity and age, Michigan SCBRFS 2004-2008 (N=8,023).

	Hispanic [1] n=626			African American (NH) [1] n=1,989			American Indian (NH) [1] n=590			Asian/Pacific Islander (NH) [1] n=401			White (NH) [1] n=4,417			p [2]
	n [1]	%	(SE)	n [1]	%	(SE)	n [1]	%	(SE)	n [1]	%	(SE)	n [1]	%	(SE)	
Cervical screening outcomes																
Ever had a Pap test																**0.025**
Yes	608	97.2	(1.5)	1,961	99.4	(0.2)	573	92.3	(6.9)	366	94.0	(2.1)	4,251	98.1	(0.5)	
Age-specific																
40-49 years	236	38.2	(6.1)	526	37.2	(2.2)	196	34.2	(8.2)	197	41.7	(8.6)	1,241	34.8	(1.7)	
50-59 years	190	25.4	(5.5)	628	28.2	(1.7)	176	24.4	(7.5)	100	29.3	(8.4)	1,209	28.7	(1.8)	
≥ 60 years	182	36.5	(6.8)	796	34.7	(1.9)	200	41.4	(8.7)	65	29.0	(9.6)	1,800	36.6	(1.5)	
Had a Pap test in last 3y																0.810
Yes	507	83.0	(3.8)	1,630	85.9	(1.5)	483	84.2	(5.0)	322	81.2	(10.1)	3,473	80.9	(1.6)	
Age-specific																
40-49 years	211	42.6	(7.4)	491	41.0	(2.4)	180	39.3	(9.6)	182	50.7	(8.6)	1,132	38.8	(1.9)	
50-59 years	165	28.3	(6.6)	542	29.3	(1.8)	148	20.9	(8.1)	89	34.6	(9.1)	1,048	30.2	(1.9)	
≥ 60 years	131	29.1	(8.0)	590	29.6	(1.9)	154	39.9	(9.9)	47	14.7	(3.4)	1,293	30.9	(1.4)	
Abnormal Pap test in last 10y																**0.027**
Yes	80	26.0	(7.6)	248	12.7	(1.2)	99	11.9	(4.2)	34	8.1	(3.9)	546	13.9	(1.1)	
Age-specific																
40-49 years	43	48.7	(18.7)	128	63.8	(4.2)	55	69.0	(14.5)	22	68.6	(17.0)	241	51.9	(4.4)	
50-59 years	26	29.3	(17.7)	82	25.8	(3.6)	28	26.0	(14.2)	10	25.7	(14.8)	182	30.5	(4.2)	
≥ 60 years	11	21.9	(17.5)	37	10.4	(2.1)	16	5.0	(2.2)	2	5.7	(5.2)	123	17.6	(2.9)	

NOTE: Data were weighted to adjust for unequal probabilities of selection and survey non-response.
Abbreviations: NH, non-Hispanic; SE, standard error.
[1] Unweighted sample size.
[2] P-value based on Rao-Scott chi-square test of homogeneity across races/ethnicities; bolded p-value signifies statistical significance (p<0.05).

Table 4.4. Adjusted prevalence odds ratios for predictors of reported cervical cancer screening among all women using multiple logistic regression, Michigan SCBRFS 2004-2008 (N=8,023).

All women	Ever had a Pap test			Had a Pap test in last 3 years			Had abnormal Pap test in last 10 years		
	OR[1]	(95% CI)	p[4]	OR[2]	(95% CI)	p[4]	OR[3]	(95% CI)	p[4]
Sociodemographic characteristics									
Age									
40-49 years	1.00			1.00			1.00		
50-59 years	2.76	(1.19, 6.39)	**0.018**	0.51	(0.30, 0.88)	**0.015**	0.59	(0.43, 0.83)	**0.002**
≥ 60 years	0.64	(0.27, 1.50)	0.300	0.18	(0.10, 0.30)	**<.0001**	0.31	(0.17, 0.56)	**0.001**
Race/ethnicity									
Hispanic	1.00			1.00			1.00		
African American (NH)	2.06	(0.45, 9.54)	0.353	1.50	(0.85, 2.64)	0.165	0.52	(0.25, 1.06)	0.072
American Indian (NH)	0.19	(0.04, 1.03)	0.054	1.52	(0.57, 4.02)	0.403	0.40	(0.14, 1.14)	0.087
Asian/Pacific Islander (NH)	0.09	(0.01, 0.57)	**0.011**	0.91	(0.27, 3.03)	0.878	0.29	(0.08, 1.02)	0.053
White (NH)	0.46	(0.11, 1.93)	0.292	0.97	(0.57, 1.66)	0.906	0.61	(0.28, 1.34)	0.220
Education									
< High school	1.00			1.00			1.00		
High school	2.47	(0.87, 6.98)	0.088	1.15	(0.71, 1.88)	0.567	2.59	(1.24, 5.38)	**0.011**
Some college	25.33	(7.81, 82.20)	**<.0001**	1.05	(0.63, 1.76)	0.860	1.51	(0.81, 2.83)	0.194
≥ College	2.24	(0.49, 10.30)	0.300	1.37	(0.78, 2.39)	0.269	1.65	(0.86, 3.17)	0.135
Marital status									
Married	1.59	(0.70, 3.61)	0.272	1.19	(0.84, 1.69)	0.330	1.02	(0.68, 1.52)	0.936
Unmarried	1.00			1.00			1.00		
Employment status									
Employed	1.71	(0.64, 4.56)	0.287	1.19	(0.82, 1.72)	0.365	1.13	(0.81, 1.60)	0.469
Not employed	1.00			1.00			1.00		
Health care coverage									
Yes	14.25	(6.28, 32.34)	**<.0001**	4.51	(2.38, 8.52)	**<.0001**	0.85	(0.45, 1.62)	0.622
No	1.00			1.00			1.00		

Table 4.4. (continued)

All women	Ever had a Pap test			Had a Pap test in last 3 years			Had abnormal Pap test in last 10 years		
	OR[1]	(95% CI)	p[4]	OR[2]	(95% CI)	p[4]	OR[3]	(95% CI)	p[4]
Cervical cancer knowledge									
Identified HPV as a risk factor									
Yes	5.52	(0.68, 44.85)	0.110	--	--		--	--	
No	1.00			--	--		--	--	
Identified not having regular Pap tests as a risk factor									
Yes	2.92	(0.49, 17.59)	0.242	2.87	(1.65, 4.99)	**0.001**	--	--	
No	1.00			1.00			--	--	
Did not know of any risk factors									
Yes	0.52	(0.26, 1.04)	0.063	--	--		0.59	(0.42, 0.83)	**0.002**
No	1.00			--	--		1.00		
Cervical cancer screening behavior									
Had abnormal Pap test in last 10 years									
Yes	--	--		3.2	(1.60, 6.40)	**0.001**	--	--	
No	--	--		1.00			--	--	
Had a Pap test in last 3 years									
Yes	--	--		--	--		3.14	(1.65, 5.99)	**0.001**
No	--	--		--	--		1.00		
Survey year									
2004	1.00			1.00			1.00		
2006	2.57	(0.78, 8.54)	0.122	1.36	(0.93, 2.00)	0.117	0.65	(0.42, 1.02)	0.054
2008	2.40	(1.19, 4.87)	**0.015**	1.02	(0.67, 1.54)	0.941	0.77	(0.50, 1.20)	0.235

NOTES: Data were weighted to adjust for unequal probabilities of selection and survey non-response; dashed lines indicate that the variable was not included in the model.

Abbreviations: NH, non-Hispanic; OR, odds ratio; CI, confidence interval.

[1]Adjusted for sociodemographic characteristics, knowledge (HPV, regular Pap tests, did not know any risk factors), and survey year.

[2]Adjusted for sociodemographic characteristics, knowledge (regular Pap tests), screening behavior (abnormal Pap tests), and survey year.

[3]Adjusted for sociodemographic characteristics, knowledge (did not know any risk factors), screening behavior (Pap test in last 3 years), and survey year.

[4]P-value; bolded value signifies statistical significance (p<0.05).

Table 4.5. Adjusted prevalence odds ratios for predictors of reported cervical cancer screening among Hispanic women using multiple logistic regression, Michigan SCBRFS 2004-2008 (N=626).

Hispanic women	**Ever had a Pap test**			**Had a Pap test in last 3 years**			**Had abnormal Pap test in last 10 years**		
	OR[1]	(95% CI)	p[4]	OR[2]	(95% CI)	p[4]	OR[3]	(95% CI)	p[4]
Sociodemographic characteristics									
Age									
40-49 years	1.00			1.00			1.00		
50-59 years	35.78	(5.68, 225.61)	**0.001**	0.75	(0.25, 2.21)	0.596	1.10	(0.35, 3.45)	0.866
≥ 60 years	0.93	(0.16, 5.47)	0.933	0.06	(0.02, 0.21)	**<.0001**	0.38	(0.07, 2.02)	0.255
Education									
< High school	1.00			1.00			1.00		
High school	23.80	(3.44, 164.93)	**0.001**	2.08	(0.57, 7.63)	0.269	14.99	(2.69, 83.55)	**0.002**
Some college	60.92	(5.29, 702.06)	**0.001**	0.76	(0.22, 2.65)	0.669	1.39	(0.30, 6.42)	0.671
≥ College	1.47	(0.33, 6.57)	0.617	0.46	(0.12, 1.76)	0.257	1.08	(0.20, 5.72)	0.929
Marital status									
Married	14.48	(3.41, 61.58)	**0.001**	1.30	(0.54, 3.14)	0.566	1.80	(0.57, 5.72)	0.321
Unmarried	1.00			1.00			1.00		
Health care coverage									
Yes	5.09	(1.10, 23.62)	**0.034**	7.74	(2.46, 24.4)	**0.001**	0.62	(0.17, 2.30)	0.470
No	1.00			1.00			1.00		
Cervical cancer knowledge and beliefs									
Identified HPV as a risk factor									
Yes	--	--		--	--		0.12	(0.01, 1.04)	0.055
No	--	--		--	--		1.00		
Identified not having regular Pap tests as a risk factor									
Yes	17.21	(0.83, 356.12)	0.066	--	--		--	--	
No	1.00			--	--		--	--	
Did not know of any risk factors									
Yes	--	--		--	--		0.28	(0.11, 0.73)	**0.010**
No	--	--		--	--		1.00		

Table 4.5. (continued)

Hispanic women	Ever had a Pap test			Had a Pap test in last 3 years			Had abnormal Pap test in last 10 years		
	OR^1	(95% CI)	p^4	OR^2	(95% CI)	p^4	OR^3	(95% CI)	p^4
Every woman should be screened regardless of age									
Agreed	--	--		--	--		4.35	(1.36, 13.93)	**0.013**
Disagreed	--	--		--	--		1.00		
Cervical cancer screening behavior									
Had abnormal Pap test in last 10 years									
Yes	--	--		14.37	(2.80, 73.85)	**0.001**	--	--	
No	--	--		1.00			--	--	
Had a Pap test in last 3 years									
Yes	--	--		--	--		10.98	(2.71, 44.53)	**0.001**
No	--	--		--	--		1.00		
Survey year									
2004	1.00			1.00			1.00		
2006	1.35	(0.16, 11.06)	0.782	3.25	(0.98, 10.81)	0.055	0.14	(0.03, 0.73)	**0.020**
2008	0.16	(0.02, 1.60)	0.119	0.55	(0.19, 1.57)	0.263	0.89	(0.28, 2.84)	0.850

NOTES: Data were weighted to adjust for unequal probabilities of selection and survey non-response; dashed lines indicate that the variable was not included in the model.

Abbreviations: NH, non-Hispanic; OR, odds ratio; CI, confidence interval.

[1]Adjusted for sociodemographic characteristics, knowledge (regular Pap tests), and survey year.

[2]Adjusted for sociodemographic characteristics, screening behavior (abnormal Pap tests), and survey year.

[3]Adjusted for sociodemographic characteristics, knowledge (HPV, did not know any risk factors), belief (every woman should be screened), screening behavior (Pap test in last 3 years), and survey year.

[4]P-value; bolded value signifies statistical significance (p<0.05).

Table 4.6. Supplemental variables included in the 2008 sub-analysis, by race/ethnicity, Michigan SCBRFS 2008 (N=3,096).

	Hispanic			African American (NH)			American Indian (NH)			Asian/Pacific Islander (NH)			White (NH)			p[2]
	n=227[1]			n=715[1]			n=209[1]			n=232[1]			n=1,713[1]			
	n[1]	%	(SE)	n[1]	%	(SE)	n[1]	%	(SE)	n[1]	%	(SE)	n[1]	%	(SE)	
Cervical cancer knowledge and beliefs about screening																
Signs and symptoms identified																
There are no signs/symptoms	15	2.7	(0.9)	13	2.4	(0.9)	8	1.4	(0.8)	5	1.8	(1.0)	77	4.4	(1.7)	0.200
Did not know of any signs/symptoms	118	62.4	(8.7)	342	44.9	(4.0)	114	53.3	(15.5)	108	57.9	(9.6)	809	42.3	(2.9)	0.259
Every female 9-26y should get HPV vaccine																0.190
Agree	129	74.2	(7.2)	327	50.8	(4.5)	122	40.8	(15.5)	130	58.0	(11.8)	815	54.9	(3.3)	
Preferred source of information on cancer prevention																
Doctor/nurse	76	47.9	(10.7)	281	43.1	(4.2)	70	20.3	(9.0)	34	26.7	(10.6)	529	31.5	(2.7)	0.119
Print materials	68	26.7	(7.3)	179	27.1	(3.3)	44	24.3	(13.1)	59	18.7	(6.8)	466	27.7	(2.5)	0.915
Internet	28	11.1	(4.8)	75	10.0	(1.6)	42	4.3	(1.5)	70	33.0	(11.1)	281	22.2	(3.0)	**0.001**
General health status																**<.0001**
Excellent	28	8.3	(2.8)	71	16.6	(4.6)	27	8.0	(5.6)	47	23.9	(9.8)	290	17.7	(2.1)	
Very good	54	32.7	(10.7)	188	28.7	(3.3)	65	21.3	(12.0)	81	34.5	(9.3)	633	38.6	(3.0)	
Good	76	28.5	(7.8)	269	34.4	(3.7)	69	12.6	(5.1)	80	36.7	(10.3)	490	30.7	(2.9)	
Fair	53	15.7	(4.6)	155	17.2	(2.0)	31	17.1	(11.9)	12	2.2	(0.9)	228	9.9	(1.5)	
Poor	15	14.8	(10.5)	30	3.0	(0.7)	16	41.0	(16.2)	11	2.7	(1.1)	69	3.0	(0.7)	

NOTE: Data were weighted to adjust for unequal probabilities of selection and survey non-response.

Abbreviations: NH, non-Hispanic; SE, standard error.

[1]Unweighted sample size.

[2]P-value based on Rao-Scott chi-square test of homogeneity across races/ethnicities; bolded p-value signifies statistical significance (p<0.05).

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Chapter 5

Conclusions

Summary of Findings

As a whole, this dissertation expands upon the international and domestic cervical cancer literature by examining the incidence and histopathologic types of invasive cervical cancer in LAC and cervical cancer screening practices among women in Michigan. In spite of recent progress in reducing incidence and mortality rates worldwide, cervical cancer remains a major global health problem. Over the next few decades, demographic changes, primarily population growth and aging, will lead to an increase in the number of cervical cancer cases, disproportionately affecting women across LAC and Hispanics in the US. Understanding the local magnitude and nature of the cervical cancer burden, along with cervical cancer screening behaviors, will enable policy makers to develop more effective, region-specific methods for primary and secondary prevention strategies aimed at high-risk populations.

Chapter 2, the descriptive epidemiological study using CI5-IX data, examined differences in cervical cancer incidence rates across 14 population-based cancer registries in the LAC region. Prior to conducting this comprehensive analysis, a cervical cancer-specific data quality assessment was conducted. Overall, we found significant geographical heterogeneity in cervical cancer incidence rates across LAC. From 1998-2002, average age-standardized incidence rates for overall cervical cancer ranged from

14.6 to 44.0 per 100,000, cervical SCC ranged from 9.1 to 37.3 per 100,000, and cervical

ADC from 1.1 to 3.6 per 100,000. This heterogeneity is likely influenced by differences

in the availability and utilization of regional cervical cancer screening programs, as well

as in the underlying prevalence of HPV infection (1). Regional variation in health care

system efficiency and access to diagnostic and treatment facilities may also contribute to

the heterogeneity found in this study (2).

To our knowledge, this was the first investigation of the variation in cervical

cancer incidence among this large number of cancer registries in the LAC region for the

time period studied. The existence of marked disparities in the LAC region emphasizes

the importance of examining data from as many registries as possible when

characterizing cancer risk across a region. As shown in this study, reliable cancer registry

data from less-developed countries can be a valuable resource for understanding the local

cancer burden and providing region-specific recommendations on cancer control and

prevention activities.

Chapter 3 also used population-based cancer registry data; however, data were

obtained directly from Peruvian cancer registries. We examined cervical cancer incidence

patterns among three cancer registries in Peru, specifically for the most prevalent

histopathologic types of cervical cancer (SCC and ADC), and assessed changes in

incidence over time. Similar to findings in Chapter 2, significant geographical variation

in overall cervical cancer incidence rates existed across registries in Peru, with rates

ranging from 47.2 per 100,000 in Arequipa, to 36.1 per 100,000 in Trujillo, and 18.9 per

100,000 in Lima. Histopathologic results showed heterogeneity in incidence rates for

cervical SCC, but not for cervical ADC. Differences in the incidence of histopathologic

types may indicate differences in disease etiology, as distinct risk factors and HPV co-factors exist for SCC and ADC (3-5).

Over time, cervical cancer incidence rates fluctuated, particularly in Trujillo. Overall and SCC-specific cervical cancer incidence rates in Trujillo decreased significantly, whereas ADC-specific rates increased, though not significantly. In Lima, overall and SCC-specific rates increased and ADC-specific rates decreased, but none of these trends were statistically significant. However, when time trends were examined by age, significant trends appeared. Among several age groups in Lima and Trujillo we observed significant declines in both overall and SCC-specific incidence rates. Even though the cervical cancer screening programs in Peru are not well developed, declining rates of cervical SCC could be partly explained by the existence of opportunistic screening which would identify dysplasia rather than invasive cervical cancer (6). Finally, we observed trends that suggest increasing rates of ADC among young women in Trujillo and Lima, though these trends were not significant. This finding has important implications for screening since ADC is not well detected by Pap tests. Alternative methods of cervical cancer prevention and screening may be more effective in averting an increase in cervical ADC burden. Furthermore, the finding that cervical ADC incidence may be increasing among young women confirms results from Brazil (7) and many developed countries (5, 8-11).

We believe that this study was the first to use cancer registry data to examine variation in the cervical cancer histopathologic profile among Peruvian women. In this analysis, existing cancer registry data proved to be an efficient source, once data quality had been established. Therefore, the use of cancer registry data may be used as a reliable

source for exploring potential changes in the cervical cancer burden in LAC or other low-to middle-income countries. Furthermore, results may guide future cancer prevention policies regarding cervical cancer screening in Peru. Since cervical ADC rates may be increasing among young women in Trujillo, we recommend supplementing current screening methods with HPV vaccination and HPV DNA testing, once they become affordable for Peruvian women, as these methods are predicted to be more capable of reducing the cervical cancer burden than Pap tests alone (1, 12).

Chapter 4, the local assessment of screening behaviors using data from the SCBRFS survey, investigated differences in reported cervical cancer screening prevalence by race/ethnicity, and subsequently identified significant predictors of screening among Michigan women aged 40 and older, with a focus on Hispanics. Based on an extensive literature review, we anticipated that Hispanic women would underutilize cervical cancer screening compared to non-Hispanic whites (13-17); however, in our study, Hispanic women reported being screened (ever screened and recently screened) at prevalence rates similar to non-Hispanic whites. This finding has been documented in other Hispanic populations in the US (18, 19). The high screening prevalence reported among Hispanics in our study may indicate successful cervical cancer screening campaigns targeting Hispanic women in Michigan. However, this finding may also reflect possible over reporting of screening behaviors among Hispanics (20-22), or underestimation of screening prevalence among non-Hispanic whites as a result of not excluding women based on hysterectomy status (23). Regardless of similar screening behaviors to non-Hispanic white women, recent screening rates among Hispanic and non-Hispanic women were still well below the Healthy People 2020 national target (93.0%),

suggesting the need for improved screening among all racial/ethnic groups in this study (24).

We observed differences in the reported prevalence of ever being screened for cervical cancer by racial/ethnic group. After adjusting for age, education, marital status, employment status, health care coverage, and cervical cancer knowledge, race/ethnicity persisted as a significant predictor of reporting ever being screened. Observed racial/ethnic differences in reporting ever screening may be attributable to factors that were not measured or accounted for in this study, including cultural, attitudinal, or social factors, and may not imply valid biological differences (25). Furthermore, younger age, higher education, having health care coverage, and cervical cancer knowledge (identifying not having regular Pap tests as a risk factor and not knowing of any risk factors) were identified as significant predictors of cervical cancer screening in most models, confirming prior literature (16, 17, 19, 25-30).

Given the expected increase in size and age of Hispanic populations in the US over the next few decades (31), the number of cervical cancer cases will rise if disparities in screening persist and Pap testing remains underutilized. Alternative methods of cervical cancer prevention and control, including HPV vaccination and HPV DNA testing, may be able to further reduce cervical cancer incidence and mortality rates among US women, regardless of race/ethnicity. By evaluating local cervical cancer screening behaviors among Michigan women, we hope to aid policy makers in designing and implementing more effective, region-specific, methods of cervical cancer control to prevent a future rise in cervical cancer cases.

Limitations and Strengths

Some potential weaknesses of this dissertation research must be acknowledged. Cancer registry data are subject to certain limitations, such as under reporting of cervical cancer cases and missing data, while survey data may be subject to recall bias due to self-reported measures; these limitations have been previously addressed in Chapters 2, 3, and 4. Nevertheless, we are convinced that the incidence rates estimated reflect true differences in cervical cancer risk among populations, although the magnitude of the differences may not be accurate due to differences in data quality, reporting, and cervical cancer screening.

Incidence rates were calculated using the entire female population as the population-at-risk (Chapters 2 and 3); however, women who have had a hysterectomy for non-cancerous gynecological conditions, such as uterine fibroids and endometriosis, are not at risk of developing cervical cancer, and should have been excluded from the population-at-risk (32). Obtaining this information is problematic, though, as the prevalence of hysterectomy is typically unknown (32). In this study, we were unable to correct for this error, leading to a probable impact on incidence rates estimated in Chapters 2 and 3. Likewise, by not excluding women who have had a hysterectomy from our calculations of screening prevalence in Chapter 4, we may have underestimated the screening prevalence of those populations at higher risk of hysterectomy, such as non-Hispanic white women (23).

Lastly, these dissertation analyses were limited by the countries (Chapter 2), cancer registries (Chapters 2 and 3), and populations (Chapter 4) for which data were

available, and may not be generalizable elsewhere. Chapter 2 included data from 14 cancer registries in seven LAC countries that submitted data for inclusion in CI5-IX. All cancer registries were located in upper middle- or lower middle-income countries, and most covered only urban populations; therefore, it is reasonable to assume that some areas of LAC that were not adequately represented (e.g., rural populations) may have very different patterns of cervical cancer risk. For instance, data from Mexico were unavailable, and given its geographical proximity to the US, we might expect the cervical cancer burden to be different from that of other countries in LAC. Chapter 3 only included data from three cancer registries, all of which were urban centers located on the Peruvian coast. We would expect substantial differences in cervical cancer patterns among women living in more rural regions of the country. In Chapter 4, we included data from five racial/ethnic groups in Michigan. Despite the SCBRFS being a population-based survey, selection bias may have been present. Cervical cancer screening behaviors among women who were selected and subsequently responded to the survey may not adequately reflect the experiences of those women who were not selected or did not respond. Nonetheless, this dissertation research provides a broader understanding of the cervical cancer burden in LAC and Peru, and of screening behaviors among Hispanics in Michigan, than has been available previously.

Nonetheless, this dissertation research has many strengths. Utilizing existing data from cancer registries (Chapters 2 and 3) and surveys (Chapter 4) allowed a time- and cost-efficient means of describing cervical cancer burden among various populations, which is especially beneficial in low- and middle-income countries and other disadvantaged populations. Cancer registry and survey data are two valuable sources that

105

can be used to guide current and future cancer control initiatives not only by demonstrating cancer burden, but also by monitoring primary and secondary prevention interventions and influencing cancer prevention and control policies.

Another strength of this dissertation is its assessment of cervical cancer-specific data quality for each cancer registry (Chapters 2 and 3). We were able to include a more diverse group of registries in our analyses, including those from low- to middle-income countries, without compromising data quality. Utilizing this approach allowed us to examine cervical cancer burden from countries that otherwise would have had no means to publish their data. Moreover, we were able to observe variation in histopathologic cervical cancer incidence and time trends for a developing country (Peru) (Chapter 3); whereas, this type of analysis is typically reserved for more-developed countries. Similar analyses could be conducted for other cancer sites, particularly if those cancers are preventable and of high public health priority. The comparative nature of this dissertation is also a strength. A great deal can be learned about cervical cancer prevention and control by comparing cervical cancer incidence rates within such geographically diverse regions (Chapters 2 and 3), and comparing cervical cancer screening behaviors across culturally diverse populations (Chapter 4).

Future Research Directions

This dissertation research offers some insight into the international burden of cervical cancer and cervical screening behaviors among Hispanic women, internationally and domestically; however, much remains unknown. Future research should aim to provide more accurate and precise estimations of cervical cancer incidence, mortality,

and screening behaviors, particularly among high-risk populations worldwide. As local cervical cancer screening programs develop, accurate assessments of local cervical cancer risk will be essential in effectively targeting those populations in greatest need.

In our international studies, we demonstrated that patterns of cervical cancer incidence vary widely across LAC. Although the analyses presented here provide a broader understanding of cervical cancer incidence in LAC than has been previously published, our findings may not be representative of all women. While there are a few nationwide cancer registries operating in LAC, most are regional registries covering only urban populations (33). Furthermore, many countries in LAC still lack a well-developed cancer registry (33). As a result, cancer incidence in rural populations, and even in some countries, must be speculated. The lack of knowledge regarding cervical cancer burden in rural populations is particularly problematic since research on urban-rural differences in cervical cancer risk has been limited in LAC. One study in Mexico found that the risk of dying from cervical cancer was three times greater for women living in rural areas compared to those living in urban areas (34). This increased risk in rural areas may be due to limited access and availability of diagnostic and treatment facilities, or to the higher prevalence of various sociodemographic, sexual, and reproductive risk factors for cervical cancer, such as low level of education, poverty, early age at sexual initiation, and high parity (35, 36).

Population-based cancer registries can be used to aid public health professionals and policy makers in understanding and addressing the local burden of cancer. To better recognize cervical cancer incidence patterns among all women in LAC, monitor trends, and facilitate future epidemiological studies, we propose that regional cancer registries be

established in all LAC countries and in some rural areas. However, cancer control must first be made a government priority, and there should be adequate infrastructure, experienced staff, and funding in place, otherwise the cancer registry may not be sustainable.

In our domestic study, we showed that self-reported cervical cancer screening rates among Hispanics in Michigan were similar to those of non-Hispanic whites, suggesting an improvement in cervical cancer disparities among Michigan women; however, screening remained underutilized in all racial/ethnic groups. In light of an expected increase in the number of cervical cancer cases among US Hispanics (immigrants and non-immigrants), we suggest that future research examine the effect of migration on cervical cancer incidence, mortality, and screening practices among Hispanic women. Migration studies that examine multiple generations of immigrants may better elucidate the relationship between migration and cervical cancer. Migration from less- to more-developed countries has been found to decrease the risk of developing cervical cancer (37); however, most available migration studies have focused on the experiences of Asian immigrants to the US. There is a paucity of research examining cervical cancer risk and screening behaviors in Hispanic immigrants (18, 38), and to the best of our knowledge, none have examined the process of migration specifically or the effect of immigrant generation. To better address the health concerns of Hispanic immigrants, it is imperative that we understand the cervical cancer burden and screening practices affecting women in their native countries prior to immigrating to the US, and also the experiences of first- and second-generation immigrants.

Since substantial geographical variation in cervical cancer risk was documented in our international studies, we advocate for future domestic research that focuses on identifying cervical cancer burden and screening behaviors among different Hispanic subgroups (e.g., Mexican, Cuban, Peruvian) in the US. Although Hispanics are typically classified as a single ethnic group, they represent a variety of national origins and are culturally, politically, socioeconomically, and genetically heterogeneous (39). Differences in cervical cancer screening practices have been found across Hispanic subgroups (40, 41). In an analysis of National Health Interview Survey data from 1992, Mexican-American women aged 18 years and older had the highest rates of recent Pap screening (80%), followed by Puerto Rican (77%), Cuban (73%), and Mexican (72%) women (41); however, all other Hispanic subgroups had to be aggregated because of limited sample sizes for each group. Additional research needs to be performed with larger sample sizes for each Hispanic subgroup in order to confirm these findings. Furthermore, building upon our suggestion above, conducting migration studies in different Hispanic subpopulations may provide additional clues, especially regarding issues of culture, socioeconomics, and genetics, in explaining cervical cancer risk and screening behaviors within this diverse population.

Public Health Policy Implications

In LAC, most countries continue to experience cervical cancer incidence rates that are much higher than those of more-developed countries. Despite efforts to control cervical cancer through cytology-based screening, few countries in LAC have successfully implemented cytology-based screening programs. Although organized

screening programs have had a greater impact on reducing cervical cancer burden than opportunistic screening, most LAC countries have only been able to offer opportunistic screening, with services located primarily in urban areas (42). Many countries in LAC have developed national cervical cancer screening policies or guidelines in an attempt to establish well-organized screening programs; however few have implemented them successfully: Chile (national), Brazil (regional), and Mexico (regional) (1). The unsuccessful nature of most screening programs in LAC stems from the fact that Pap tests depend on high-quality samples, skilled cytologists, adequate follow-up and diagnosis of women with positive results, and extensive coverage of women at risk (1); these requirements may be difficult to meet in low-resource countries.

With the limited success of cytology-based screening in LAC, newer technologies have emerged as promising cancer control alternatives. Primary prevention of cervical cancer through HPV vaccination of young women is the most encouraging, with the potential to significantly reduce the incidence of cervical cancers and precursor lesions. The Pan American Health Organization has already made universal HPV vaccination of young women a public health priority in the LAC region; however, no country has yet to implement an official policy on the matter (43). High-risk HPV DNA testing is the most promising new method of secondary cervical cancer screening, with many advantages over cytology-based screening. HPV DNA tests have higher sensitivity, reduced quality control issues, allow for longer screening intervals, and ultimately reduce costs (1). Results from a randomized, controlled trial conducted in a low-resource setting showed that a single round of HPV DNA testing was the most objective, reproducible, and effective screening method in reducing the incidence of advanced cervical cancer and

cervical cancer mortality (44). In rural Amazonian Peru, HPV DNA testing was found to be the most sensitive cervical cancer control method, performing better than cytology and VIA, and offered the best prospect for screening in this region (45). However, low- and middle-income countries may not have the resources to obtain and implement current HPV DNA testing technology. In LAC, a few countries have begun to create policies concerning the implementation of HPV DNA testing, and several more have begun using HPV testing as an opportunistic screening method, but only because of local physicians' preference (43). Thus far, cost has limited the use of these screening methods; however, there is strong political support for HPV vaccination and HPV DNA testing in LAC.

Region-specific recommendations for cervical cancer control policies have been proposed for LAC. To lessen the costs associated with newer cervical cancer prevention technologies, primary (HPV vaccination) and secondary (screening) cervical cancer control activities should be integrated into one system. Franco et al. suggest implementing a policy for universal HPV vaccination among young women in LAC countries, and a policy recommending HPV DNA testing as the principal method of screening, where only HPV-positive women would receive cytology screening (Pap test) (43). This approach would provide maximum impact and be the most cost-effective strategy for LAC (46).

In the US, Hispanic women experience high cervical cancer incidence rates compared to non-Hispanic whites, and in spite of efforts to reduce cervical cancer burden through cytology-based screening, adherence to such screening programs has been relatively low (13-17). Given that numerous barriers to cytology-based screening exist that discourage screening use among Hispanic women, alternative methods of cervical

cancer prevention and control, such as HPV vaccination and HPV DNA testing, may be particularly suitable for this high-risk population. The recommendations for cervical cancer control policies proposed by Franco et al. could be adapted for use among racial and ethnic minority populations in the US (primary cervical cancer prevention through universal HPV vaccination in young women, and the use of HPV DNA testing as the main screening test, followed by Pap tests in HPV-positive women) (43). However, community-based educational interventions remain essential in promoting cervical cancer and HPV-related knowledge, improving HPV vaccine acceptance, and reducing barriers to HPV vaccination or HPV testing.

Primary prevention is the ultimate goal in cervical cancer prevention and control. Public health policies should concentrate on universal HPV vaccination among young adolescent women worldwide since this strategy may have the largest, long-term impact on reducing disparities in global cervical cancer incidence and mortality. However, since the complete effect of vaccination will not be seen for decades, public health policies may also need to emphasize the use of HPV DNA testing, especially among women at highest risk of developing cervical cancer.

Conclusions

Cervical cancer is, and will likely continue to be, a major global health problem. This dissertation expands upon current knowledge of cervical cancer incidence, histopathology, and cervical cancer screening behaviors among Hispanic women in LAC and Michigan. The findings that cervical cancer incidence demonstrated substantial geographical heterogeneity across LAC, that cervical ADC may be increasing among

young women in Trujillo, Peru, and that cervical cancer screening utilization may have

improved among Hispanics in Michigan, all emphasize the importance and benefit of

utilizing available, population-based data to monitor cancer burden, time trends, and the

effectiveness of cancer control interventions. This research will have important

implications in the development of future research studies and public health policies

aimed at reducing the burden of cervical cancer across the Americas.

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