CERVICAL CANCER INEQUITIES IN COLOMBIA

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Silvia Bermedo-Carrasco

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ABSTRACT

Cervical cancer (CC) is the second most common cancer and third in cancer-related deaths among women. Developing countries account for most CC-related deaths and are highly impacted by CC mortality in young women. In South America, CC is the second most incident cause of cancer and first cause of cancer deaths among women 15-44 years. In Colombia, CC is the second most common cause of cancer mortality among women. Previous studies conducted in Colombia have shown inequities in CC prevention and mortality by different socio-demographic factors; however, there is a lack of nationwide studies evaluating these factors specifically in young Colombian women. The goal of this thesis was to identify socio-demographic characteristics associated with awareness of CC primary prevention, access to secondary prevention for CC, and CC mortality among young women in Colombia.

The educational level, type of health insurance, having a rural or urban residence, and region of residence of women were common factors related to inequities in CC prevention and mortality in Colombia. Women with limited or no education had a reduced probability of having heard of HPV vaccination, with differing effects of education by age and region of residence. In the case of Pap testing, having a rural residence decreased the odds of Pap testing compared to having an urban residence, with wider differences in the odds among women with limited-to-no education compared to those with higher education. Additionally, a higher prevalence of no education in the neighbourhood where women lived resulted in lower odds of Pap testing in both rural and urban areas, especially when comparing women with limited-to-no education to women with a secondary or higher education. Measured at the administrative divisions or department level, a high prevalence of no education was associated with a low prevalence of Pap testing, specifically for departments being at or above the national prevalence of women living in rural areas. Similarly, mortality rates were higher among women with limited or no education compared to women with higher education, observing wider differences in younger age groups.

Having subsidised insurance and not having insurance were associated with a decreased awareness of HPV vaccination. The effect of type of health insurance on Pap testing varied by whether women had a rural or urban residence. Departments with higher prevalences of women with subsidised insurance were associated with not having heard of HPV vaccination and not having had a Pap test. No significant differences in CC mortality were observed between women

with subsidised insurance and those with no insurance. Also, mortality rates for different types of health insurance varied for some age groups.

Women living in rural areas had a reduced awareness of HPV vaccination with variations by regions. Having a rural residence also decreased the probability of having Pap testing, particularly in some regions of Colombia and among women with no insurance or subsidised health insurance. Furthermore, increments in the department percentage of women living in rural areas increased the risk ratio of having women who had not had a Pap test in departments classified as at or above the national prevalence of no education. In contrast, living in rural areas was associated with lower CC mortality rates.

Women from the Amazon-Orinoquía region had high rates of CC mortality and were less likely to have heard of HPV vaccination and have had a Pap test. Several departments located in the Amazon-Orinoquía region and a few departments from the Pacific, and Atlantic regions (e.g. Chocó, Sucre, and La Guajira) had a high risk of women not having access to primary and secondary CC prevention, after accounting for other risk factors.

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AIDS	Acquired immune deficiency syndrome
AIC	Akaike's information criterion
AOR	Adjusted odds ratio
ASMR	Age-standardised mortality rate
CAR	Conditional autoregressive
CC	Cervical cancer
CODA	Convergence diagnosis and output analysis
DANE	*Departamento Administrativo Nacional de Estadística* (National Administrative Department of Statistics of Colombia)
Fig.	Figure
GDP	Gross domestic product
GLMM	Generalised linear mixed models
HIV	Human immunodeficiency virus
HPV	Human papillomavirus
IRR	Incidence rate ratio
INVIMA	*Instituto Nacional de Vigilancia de Medicamentos y Alimentos* (National Institute of Drug and Food Surveillance)
NDHS	National Demographic and Health Survey
NDP	National Development Plan
NHrd-Vac	Not heard of HPV vaccination
NHd-Pap	Not had Pap testing
OR	Odds ratio
Profamilia	*Asociación Probienestar de la Familia Colombiana*
REB	Research Ethics Board
Ref.	Reference category
RR	Risk ratio
RRR	Risk ratio ratio
RRR_M	Median risk ratio ratios
RSR	Restricted spatial regressions

ROC	Receiving operating characteristic
SD	Standard deviation
SDOH	Social determinants of health
SGSSS	*Sistema General de Seguridad Social en Salud* (General Social Security System in Health)
STI	Sexually transmitted infection
UOR	Unadjusted odds ratio
VPC	Variance partition coefficient
YLL	Years of life lost
95%CI	95% confidence interval
95%Cr.I.	95% credible interval

CHAPTER 1 – INTRODUCTION

1.1. Background

Cervical cancer (CC) is the result of a persistent infection by oncogenic human papillomaviruses (HPV) (1, 2). High-risk HPV infections related to CC include a number of different HPV types, such as HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59 (3). Sexually active individuals are at risk of contracting HPV (4), with a global estimated prevalence of infection among women between 2% and 35% (5). The number of lifetime sexual partners, co-infection with the human immunodeficiency virus (HIV) and other sexually transmitted infections (STIs), smoking, long-term oral contraceptive use, and having a high parity have been associated with an increased risk of CC (6).

Despite being highly preventable (7), CC was ranked globally as the second most common cancer as measured by incidence and third in cancer-related deaths for women in 2012 (8). More than half a million new cases of CC were diagnosed and more than a quarter million women died due to the disease worldwide in 2012 (9). Developing countries are differentially impacted by CC mortality (10, 11). While the 2012 age-standardised mortality rate (ASMR) of CC was 3.3 per 100,000 in more developed regions, in less developed areas the ASMR reached 8.3 per 100,000 (9). Compared to the world ASMR, higher rates were reported in 2012 for Africa with the exception of Northern Africa, Melanesia, South-Central Asia, Central and South America, the Caribbean, and South-Eastern Asia (9). Deaths of young women due to CC are also a concern in developing countries (10, 11). Out of the more than 200,000 total CC deaths reported worldwide in 2010, 78% corresponded to women living in developing countries (11). In the same year, 55,900 women between 15 and 49 years of age died due to CC globally; 83% of them were from developing countries (11).

In Latin America, CC is the second most common cancer among women (12) and one of the main causes of mortality (13). Also, in this region, CC is ranked as the first cause of cancer deaths among women between 15 and 44 years (10). Measured as years of life lost (YLL), CC is the most important cause of YLL in Latin America and the Caribbean, contributing to more YLL than the acquired immune deficiency syndrome (AIDS) (14). The highest incidence rates of CC are in Bolivia, Paraguay, Peru, Venezuela, Ecuador, Brazil, and Colombia (10). Countries located in Central America and the Andean region also have high mortality rates due to CC (15).

Cervical cancer affects women and their families worldwide. Physical (16) and psychological (7) sequelae are common among women living with CC. The sequelae of CC treatment, including infertility (16) or mental health problems (17), could affect the willingness of women to continue with proper cancer follow-up (17). In many countries, CC also poses a substantial financial burden on families. This burden includes the loss in productivity for the women affected by CC (18), high costs associated with medical care (19), and the need for caregivers to quit or reduce working hours to look after women affected by CC (20). Cervical cancer impacts society due to the loss of mothers (19) and caregivers for other family members (7) who are in many cases important contributors to family income (21). Maternal deaths from CC could further affect children by impacting their nutritional status (20) or decreasing opportunities to access education due to prioritisation of other family needs (21). These effects perpetuate the social impact that CC has on education, gender equity, and poverty, especially among women (21). Furthermore, it has been estimated that CC is the cancer with the third highest disability-adjusted life-years worldwide (22). In the Americas region alone, about US$3.3 billion are lost each year due to the economic loss associated with CC deaths (23).

The purpose of this chapter is to highlight international inequities in CC prevention, with a focus on the importance of the disease in Colombia. Published reports of inequities related to primary and secondary prevention strategies for CC and mortality due to CC are described with background information on the social context of Colombia.

1.2. Cervical Cancer Prevention

Cervical cancer and deaths due to CC can be prevented at different stages through primary, secondary, or tertiary strategies (4).

The goal of primary prevention in CC is to prevent disease occurrence among susceptible individuals (24) by stopping infection with HPV (4). Given that individuals can be infected with

HPV at any time after sexual debut (25), to be effective, primary prevention must begin before first sexual activity. Education is key to create awareness (26) and promote CC prevention in the population (27). Measures to decrease the risk of infection include educating individuals about HPV, risk factors for acquiring a HPV infection, and vaccination against HPV (25, 28). Vaccination of women before their exposure to high-risk HPV types has been associated with a reduction of pre-invasive cervical lesions (28-30). Indeed, estimates predict a potential 70% reduction of CC cases through HPV vaccination (19).

There are three vaccines against HPV available on the market. The quadrivalent vaccine (Gardasil®) was licensed in 2006 and protects against HPV 6, 11, 16, and 18. This vaccine could be administered to girls and boys starting at 9 years of age (31). The bivalent vaccine (Cervarix®) offers protection against HPV 16 and 18 (29) and could be administered to girls from 9 years of age (31). Both vaccines should be ideally administered in multiple doses (31, 32). Recently, a vaccine with nine strains (Gardasil®9) has been approved for market in the United States (33), Canada (34), and the European Union (35). Gardasil®9 offers protection against HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 (36). Administration of this vaccine follows the same dosage schedule as Gardasil® (37).

Secondary prevention focuses on reducing complications resulting from HPV infection and new cases of CC (25) by identifying the disease at early stages through screening and provision of timely treatment (38). Secondary CC prevention includes visual screening, tests to detect HPV infection, and the conventional cytological screening test or Pap test (39). The Pap test identifies early-stage lesions in exfoliated cells collected from the cervix (40) and is one of the most popular techniques used for CC screening worldwide (41). Education about the importance of CC screening that considers the expectations and concerns of the population is fundamental to the success of CC screening programmes (19).

The objective of tertiary CC prevention is timely treatment of invasive CC (4) to limit disability in women at late stages of the disease (24). The objectives for three of the four chapters of this thesis are focused on primary and secondary prevention of CC.

1.3. Inequities in Cervical Cancer

The health status of individuals varies across populations. Inequities in health occur when these variations are unnecessary and avoidable, as well as unfair and unjust (42). Inequities in health are closely related to the socioeconomic and political conditions where people live and die (43). These conditions are known as the social determinants of health (SDOH) (43). The SDOH include factors such as education and housing, as well as access to health care (44). The presence of inequities in health is associated with an unfair distribution of the SDOH (45) that systematically impact the health of the most socially disadvantaged groups (46). Inadequate social policies, economic conditions, and politics between and within countries result in unfair distribution of the SDOH (43).

Reducing inequities in health requires eliminating avoidable and unfair factors by "creating equal opportunities for health (42)." This reduction could be achieved through the development of public policies to address the SDOH (47). Such healthy public policies should help improve living and working conditions of people by creating environments where making healthy decisions is easy and health care is accessible for all who need it (42). Evidence regarding the impact of policies on the SDOH is crucial to reduce inequities in health (43).

Inequities in health are not randomly distributed (48), as is the case of CC. Cervical cancer has been described as a disease of poverty (49), given its high impact on women living in socially disadvantaged circumstances (50). Despite being preventable, thousands of young women are affected by CC globally (10). Cervical cancer disproportionally affects women from developing countries who do not seek help until the advanced phases of the disease (7), often because inadequate access to CC screening programmes (51). The effects of CC in developing countries perpetuate poverty, impacting negatively on education and gender inequity; problems which are central to the Millennium Development Goals (21).

1.3.1. Inequities in Cervical Cancer Prevention

Studies conducted in different countries have associated socio-demographic factors with inequities in primary and secondary strategies to prevent CC (4, 19, 38, 40, 41, 52-80). These studies have identified variations in the distribution of risk factors associated with HPV knowledge, HPV infection, and HPV vaccination.

Studies of primary prevention of CC consistently report that socio-demographic characteristics of individuals increase their risk for exposure to HPV infection. For example, sexual debut is earlier for women in low-resource countries (19). Studies conducted in developed countries have shown a lower age for sexual debut has also been associated with ethnicity (52-54); while socioeconomic status has been associated with a younger age of sexual debut in both developed and developing countries (53-55).

Other studies conducted in different countries have identified factors associated with knowledge of HPV and the importance of HPV vaccination, showing variations according to educational level (56-61), health insurance (56), income (58, 62), age (63, 64), race (63), and type of job (63). Having a limited awareness of CC prevention and HPV vaccination decreases the uptake of HPV vaccination (65-67). Rates of HPV vaccination are reported as low among girls from socially deprived groups (68, 69) and some ethnic backgrounds (70, 71). Rates of HPV vaccination also vary based on geographic area of residence (70), health insurance status (70), and socioeconomic status (70, 71).

Secondary prevention is important in minimising the impact of HPV infection. Cervical cancer screening programmes have been associated with a decrease in CC incidence and mortality in developed countries (40, 41, 72). It has been estimated that, in countries where CC screening programmes have been successfully implemented, CC mortality has been reduced by at least 50% (73). This achievement is associated with women having access to repeated screening (73) and well organised CC screening programmes (40). In contrast, women living in low-resource regions usually have limited access to both Pap testing and proper follow-up once diagnosed with CC (38). While more than 75% of women in developed nations participate in CC screening programmes, less than 5% of women in developing countries have access to CC screening (19). Inadequate infrastructure and resources, competing priorities in health care, and fragile health systems are factors affecting the implementation of CC screening programmes in developing countries (4). In areas where CC screening is available, there are also groups of women with no access to CC screening programmes (19).

Reports from countries around the world have linked poor participation rates in CC screening to age (74), ethnic background (53, 74-78), limited education (53, 74, 78-80), living in rural or less developed areas (74, 79), lack of health insurance or access to health care (74, 75, 77, 78, 80), poor socioeconomic conditions (74, 78), and a lack of knowledge of HPV and CC (79). Lack of CC screening, as well as late and inappropriate CC treatment are failures in health services that could lead to further socio-demographic disparities in CC mortality (76).

1.3.2. Inequities in Cervical Cancer Mortality

Mortality due to CC is highest in women living under disadvantaged socio-demographic conditions (49). The impact of CC mortality is particularly concerning in young women from developing nations (19). Mortality rates in these countries are three times higher than rates observed in developed nations (81). Differences in CC mortality between developing and developed areas could be attributed to a late diagnosis (82) and limited access to screening and treatment (19).

Studies conducted in different countries have shown variations in mortality associated with socio-demographic factors including poverty, ethnicity, education, geographic area of residence, and health insurance coverage. A CC mortality study that included 184 countries showed that increments in the proportion of population living in extreme poverty resulted in more deaths from CC, while an increase in health expenditure was associated with reductions in CC mortality (81). Studies conducted in Europe and the United States have reported that mortality rates increase with decreasing socioeconomic or income status of women (83-85) and in the United States with increasing levels of neighbourhood poverty (76). An increasing trend in CC mortality rates was found between 1980 and 2000 in Brazilian regions with poor socioeconomic conditions (86). Studies in the United States have shown high CC mortality among women who belong to certain ethnic groups, such as non-Hispanic black or Hispanic women (76, 87, 88). In contrast, studies from the United States, Argentina, and Brazil have reported a lower CC mortality among more educated women compared to those with no or limited education (88-90). Also, differences in CC mortality have been studied among areas of residence (84, 85, 89) and health insurance status (91). A study conducted in the United States revealed that women living in the south eastern and south western regions had higher CC mortality rates compared to other parts of the country (85). Another study in the United States showed that the hazard ratio for dying due to CC was highest among women who had Medicaid and those with no insurance compared to insured women (91). This study also found that women with limited or no insurance coverage usually started treatment for CC in more advanced stages of the disease (91).

1.4. Context of This Research

This thesis will focus on CC in Colombia. Colombia is located in the northern area of South America. The country has a total area of 2,070,408 Km^2 and is bordered by Panama, Venezuela, Ecuador, Peru, and Brazil, sharing maritime borders with Costa Rica, Haiti, Jamaica, the Dominican Republic, and Nicaragua (92). Colombia has 32 political administrative divisions called departments which, along with the capital district of Bogotá D.C., account for a total of 33 administrative territories (92) (Fig. 1-1).

Colombia had an estimated population of 48,747,708 in 2016 (93), most (75%) of whom resided in urban areas (94). The life expectancy at birth of Colombians in 2015 was 74.8 years, with females (78.4 years) having longer average lifespans than males (71.2 years) (95).

Colombia is one of the most inequitable countries in Latin America, where the distribution of income varies greatly (96). A 2015 report from the Economic Commission for Latin America and the Caribbean revealed that, in Colombia, the richest 1% of the population captures 20% of the total income (97). The per capita gross domestic product (GDP) varies largely by department (98). Casanare had the highest per capita GDP in 2009, similar to Saudi Arabia, while the 2009 GDP in Vaupés was similar to Moldova (98). In spite of reductions in poverty levels reported in recent years, 21.9% of Colombians lived in deprived conditions in 2014 (99). The proportion of the population living in poverty ranges from 25% in the capital of the country to 87% in the department of Chocó, with variations within departments and municipalities (98). High poverty levels are present in rural areas and in the Atlantic and Pacific regions (100). Most Colombians

(85%) report having an income just adequate to cover basic living expenses and 42% consider themselves as poor (101).

Fig. 1-1. Map of Colombia

While the level of literacy in the country is high (94%) (101), there are regional differences. For example, illiteracy rates in Chocó and most of the departments located in the Atlantic coast are higher (>16%) than the rest of the Colombian departments (98).

As a result of the historical exclusion of the rural population (102), the quality of life for people living in these areas of Colombia is poor. Inequities observed in rural areas have been influenced by a number of factors, such as the limited presence of the Colombian state in these territories, a scattered population, poor political representation, a lack of education and formal work opportunities (102), as well as limited access to services, like sanitation (103). Poverty rates in rural areas (44%) (103) are higher than urban areas, resulting in higher numbers of socially vulnerable people (104). Also, education is more limited in rural areas (104). Data from the 2014 Colombian Census of Agriculture, revealed that 20% of the population between 5 and 16 years and 76% of individuals between 17 and 24 years living in rural areas were not enrolled in school (103).

More than 40% of the Colombian population live in big cities, such as Bogotá, Medellín, Cali, Barranquilla, and Cartagena (94). In contrast, the departments located in the Amazon-Orinoquía region account for less than 3% of the total national population (94). Decisions made in the capital control policy (100) and the state has a very limited presence in the more remote Colombian territories (105). This fragile situation limits the efficacy and credibility of governmental institutions (105), creating the necessary conditions for groups, other than governmental agencies, to control certain areas of the country through corruption or violence (98).

The Colombian internal armed conflict is one of the oldest of this kind in the world (106). Rooted in the 40s and 50s (107), this conflict has impacted the economic and social welfare of Colombian society. Homicides, kidnappings, injuries due to landmines, and forced displacements are some consequences of the conflict for the population (108). Given the length and intensity of the conflict, Colombia is ranked second as the country with the highest number of internally displaced persons worldwide (109). More than 6 million Colombians have been forced to leave their homes (109) and have settled mainly in urban areas (94). The loss of individuals due to the conflict and the need to accommodate displaced individuals have had an impact on health and social services in Colombia (94).

The internal conflict has impacted the quality of life and socioeconomic status of the displaced population (110). Children, women, and ethnic minorities are the most affected groups (108). Displaced children and adolescents suffer from infectious and malnutrition-associated diseases and lack access to vaccination programmes (108). Moreover, about 35% of displaced teenagers are mothers (108). Among the adult population, women are the most vulnerable group (108). Compared to the national distribution of women (51%), displaced women represent 54% of the total displaced persons (111). The proportion of displaced women between 25 and 49 years is higher than the proportion of displaced males in the same age group (111). Displaced women are more likely to have lower literacy levels, a higher number of children, as well as more responsibilities at the family level due to being the household head (108). Other challenges to the wellbeing of displaced women include mental health issues, nutritional or gynaecological diseases, and a lack of access to health care (112).

Barriers to accessing health care affect both displaced people and the rest of the Colombian population, with the greatest impact on the most disadvantaged groups (113-115). These barriers are related to a lack of specialised health care, long waiting lists, restrictions in accessing medical appointments and tests, out-of-pocket payments or co-payments, the suspension of health insurance coverage due to lack of payment, and the distance to health care centres (113). Furthermore, Colombians have to deal with escalating health care costs and poor quality of health services, as a consequence of a lack of regulation of the health care system and corruption (116).

1.4.1. Health Care in Colombia

The Colombian health care system is an insurance-based model system, known as the *Sistema de Seguridad Social en Salud* (SGSSS), that was established in 1993 by Law 100 (117). The model comprises the contributory and subsidised health insurances (118, 119) in which individuals are insured according to their capacity to pay (120). Formal employees and people who can directly pay, as well as their beneficiary group, are affiliated to the contributory system (119). Individuals who cannot pay and are eligible for governmental benefits become part of the subsidised system (119). In addition to the beneficiaries of the SGSSS, there are special health care plans for individuals who belong to the military and police, as well as for public teachers and employees of the Colombian Oil Company (121).

Despite achievements of the SGSSS related to increased numbers of Colombians with health insurance coverage (118) and improved access to free and population-based services (119), almost 10% of the population in 2012 did not have health care coverage (101). Furthermore, health care benefits differ between the subsidised and the contributory health systems. Compared to the contributory system, individuals in the subsidised system obtain up to 40% less health care benefits (118). This difference has created equity concerns, since formally employed individuals enjoy more benefits than people living with limited resources (120). In rural areas, limitations to access health services are common; in some cases, people living in rural areas opt to be treated using traditional medicine, given the difficulties in obtaining health services (122). Issues with authorisation for medical procedures or treatments, the control of clinical practice by health insurance companies, a fragmentation of services, a high turn-over of health care professionals, and a lack of clarity about services covered are examples of other barriers to access health care faced by Colombians (113).

1.4.2. Cervical Cancer and HPV Infection in Colombia

Cervical cancer is ranked as the second most common incident cancer among women in Colombia (123). Age-standardised incidence rates in Colombia (18.7 per 100,000) are higher than rates estimated for the Americas region as a whole (14.9 per 100,000) and countries such as Costa Rica (11.4 per 100,000), Chile (12.8 per 100,000), or Brazil (16.3 per 100,000) (9). Cervical cancer poses a high economic burden for Colombia, given the high direct costs associated with its treatment (124). Cancer of the cervix is one of the top ten most preventable causes of death in Colombia, accounting for 3% of the total economic costs associated with avoidable mortality (125).

Despite the reported decrease in mortality between 1984 and 2008 in Colombia (126), CC is the second cause of cancer deaths among women in the country (123). It was estimated that about five women died each day due to CC between 2000 and 2006 (127). Age-standardised mortality rates in Colombia (8 per 100,000) are higher than the Americas region and the rates estimated for Costa Rica, Chile, and Brazil (5.9 per 100,000, 4.4 per 100,000, 6 per 100,000, and 7.3 per 100,000, respectively) (9). It has been suggested that late diagnosis and lack of access to treatment might explain 50% of CC deaths in Colombia (128). Inadequate or delayed access to CC treatment has been related to administrative formalities imposed by health insurance companies (129).

Limited access to prevention programmes may be reflected in the distribution of the risk factors for CC, as shown in different Colombian reports. The 2010 National Demographic and Health Survey (NDHS) (122), a national representative survey, described that the median age of sexual onset reported by women aged 25-49 years was 18 years. However, this survey revealed that 11% of women reported being sexually active before they were 15 years of age and 48% started sexual intercourse before the age of 18. The NDHS also revealed that 17% of women aged 15-49 years did not have information about STIs other than HIV/AIDS (122), although most of the people seeking treatment for STIs in Colombia are women and individuals between 20 and 29 years of age (130).

A study that included women 15-69 years attending CC programmes from four regions of Colombia found that 49.6% were HPV positive and 64.8% of those who were positive had a co-infection with multiple HPV types (131). A cohort study reported that during the follow-up period younger women and those with a new partner were more likely to be infected with high-risk types of HPV (132). Another study found a higher odds of detecting high-risk HPV among women with a normal Pap test who were <35 years compared to women 35-44 years, as well as higher odds of detecting any type of HPV infection among those who reported two or more sexual partners compared to women who reported only one partner (133). Also, this study showed that women <30 years had higher odds of having infection by multiple HPV types compared to older women (133). Another study conducted in the Colombian capital found that

HPV infection affected more than 350,000 women, 54% of whom were <30 years (134). In 74% of the cases these infections were caused by high-risk HPV types (134).

Having an infection by other sexually transmitted agent is also a co-factor for CC (6). A report on the distribution of STIs in Colombia between 2009-2011 showed that most Colombians who sought medical advice due to a STI were women and individuals aged 20-29 years (130). An international review reported an increased risk for CC among women infected by *Chlamydia trachomatis* and women with antibodies for herpes simplex virus type 2 (135). A recent study in various Colombian regions showed that women infected by multiple HPV types were also infected by *Chlamydia trachomatis*, especially among those who reported a greater number of sexual partners (136). A Brazilian study showed that women infected by gonorrhoea and *Trichomona vaginalis* had an increased risk for high grade cervical lesions (137).

Given the increased risk for CC associated with other STIs, the reported data on the frequency of other STIs in women from Colombia were obtained and summarised. Data from the Colombian Ministry of Health show that *Chlamydia trachomatis* infection was most prevalent among Colombians aged 15-49 years (130). A 2003 study in Bogotá determined that 5% of women aged 18+ participating in the study were positive for *C. trachomatis* (138). Another study among female and male students between 14 and 19 years in a province of the department of Cundinamarca, showed that 2.2% of participants had a *Chlamydia* infection (139). In regards to herpes type 2, a multicentre study including Colombian women found that 57% of participants were seropositive to the virus (140). Additionally, gonorrhoea in Colombia is one of the most common STI, with more than 8,000 cases reported between 2009 and 2011 (130). The Colombian Ministry of Health also reported 6,200 cases of *T. vaginalis*, between 2009 and 2011 (130). However, given a limited knowledge regarding STIs in Colombia (130), official rates of STIs could be affected by underreporting of cases.

Decreasing the risk of HPV infection and increasing the chance that cervical lesions are detected before they become malignant require educational initiatives to improve awareness of HPV infection (25, 28). Despite the Colombian National Policy of Sexuality, Sexual, and

Reproductive Rights emphasises the need for sexual education (141), few programmes for education about sexuality have been implemented in the country (142).

1.4.3. National Efforts to Prevent Cervical Cancer

The National Programme for Cervical Cancer Control started in Colombia in 1990 with the objective of increasing screening rates and encouraging women to continue participating in the programme through follow-up and treatment (143). However, following Law 100, the programme became fragmented and dependent on health insurance companies (143). As a result, Colombian efforts to prevent CC are mainly centred in achieving a certain Pap test coverage instead of a programme offering appropriate treatment and follow-up to women with CC (144). Further complicating the issue of CC prevention in Colombia, leaders of both health services and health insurance companies lack information regarding the epidemiologic profiles for the populations they serve (129). This deficiency in information has been related to the lack of prioritisation of CC as a public health concern in Colombia (129), affecting the implementation of CC prevention programmes.

Problems in the implementation of CC screening services in Colombia include inadequate training to interpret Pap tests, lack of infrastructure, difficulties for women to get to appointments, and lack of protocols to follow-up with women who have abnormal Pap tests (129). These problems exist in the context of a Colombian health care system which is centred primarily in curing rather than in preventing disease in the population (145).

Recognising the limitations in existing CC programmes, Colombia, together with other countries in the Americas, agreed in 2008 to ensure prevention and control of CC through the Declaration of the Human Papilloma Virus Meeting held in Mexico (146). The Colombian government also agreed to reducing mortality rates from CC based on increasing screening coverage and guaranteed access of women to treatment, among other strategies (147). Furthermore, the government has launched the 2014-2018 National Development Plan (NDP), which aims to reduce the number of preventable deaths due to non-transmissible diseases, including cancer, guarantee sexual and reproductive rights, and increase the detection of CC (148). Given the emphasis in Colombia on treating rather than preventing disease occurrence

(145), the NDP proposes a change in this paradigm by increasing prevention as one of the pillars to reduce morbidity and mortality. Additionally, the Plan emphasises the importance of reducing social inequalities between urban and rural areas through ensuring equal opportunities for rural people (148).

The importance of addressing these inequalities are outlined in the following sections examining inequities and challenges in primary prevention of CC, secondary prevention of CC, and mortality due to CC in Colombia.

1.4.4. Inequities in Cervical Cancer in Colombia

1.4.4.1.Inequities in primary prevention of cervical cancer

Knowledge of HPV infection and of HPV vaccination has consistently been demonstrated as poor in Colombia (149-154). Between 34% and 72% of individuals participating in different Colombian studies have reported poor knowledge or no knowledge of HPV infection (149-151, 154). A study among professors and students of a university located in the Central region (149), found significant variations in the knowledge of HPV according to the age of professors and the number of years that students had been in their university programme using Chi-square tests. No significant differences in the knowledge of HPV were found based on the type of health insurance of students. In contrast, other reports from Colombia have identified differences in HPV awareness by health insurance and education, using bivariate (154) and multivariable (151) analysis. Results of a descriptive study conducted in a Colombian university located in the Central region indicated that older students, women, and individuals with a better socioeconomic status were more likely to know about HPV (150).

Other Colombian studies have found low levels of both knowledge of the relationship between CC and HPV infection (151, 152), and the association between CC and awareness of HPV vaccination (154). In a study conducted in Medellín, 86% of women 18+ years were unaware of the role of HPV in the development of CC (151). Another study among adolescent women in the city of Cartagena, located in the Atlantic region, reported 24% of women with knowledge of the link between HPV infection and CC (152). All participants in this study were unfamiliar with preventing HPV infection through vaccination (152). Chi-square tests also showed no significant differences in the knowledge of HPV by type of health insurance and socioeconomic status (152). A study in Bogotá showed that only 26.4% of men and 48.4% of women were aware of the HPV vaccine (154). Based on Chi-square tests, this study also reported that having more education and contributory health insurance increased awareness of HPV vaccination (154). The problem of limited information about HPV extends also to health care professionals. A qualitative study among physicians from different specialities working in several cities of Colombia, showed that general practitioners exhibited lower levels of knowledge about the role of HPV on CC compared to gynaecologists and paediatricians (153).

The results of the studies about inequities in primary CC prevention in Colombia reveal that efforts are needed in the country to educate the general population and health care professionals about HPV infection. Having adequate knowledge of HPV-related topics among health care practitioners is crucial, especially considering that they are a source of information about HPV and that they could promote HPV vaccination in the population (59).

1.4.4.2. Inequities in secondary prevention of cervical cancer

Socio-demographic factors in Colombia have also been linked to inequities in access to secondary prevention of CC. Although in 2005 more than 75% of women reported having had a Pap test in the previous three years (155), access to Pap testing in Colombia varied according to socio-demographic characteristics. For example, compared to older groups, younger women were less likely to participate in CC screening programmes (155-158). Living in rural areas has been suggested as another factor impacting CC screening in Colombia. The results of an unconditional analysis from a study that included women 16+ years from a rural municipality located in the Eastern region, reported that living in rural areas decreased the odds of having Pap testing (156).

Education and access to health insurance have also been identified as risk factors limiting access to secondary prevention of CC. Other studies conducted in Colombia have found that, after controlling for other socio-demographic factors, women with less education have lower odds of having a Pap test compared to women with higher levels of education (155, 157, 158). Furthermore, having a low socioeconomic status has been associated with decreased odds of having Pap testing. The results presented in the study of Piñeros et al (155) among women aged 25-49 years showed that the odds of not having had a Pap test in the three previous years to the study decreased as the socioeconomic status of women increased. Moreover, having health insurance has been reported to increase access to CC screening (158), with differences according to the type of health insurance of women (155).

1.4.4.3.Inequities in mortality due to cervical cancer

In addition to the inequities described for primary and secondary prevention of CC, inequities in CC mortality have also been reported in Colombia. For example, differences in CC mortality rates among departments have been identified. Higher age-adjusted CC mortality rates were reported in the Colombian departments of Meta, Tolima, Arauca, and Caquetá from 2000 to 2006 (127). These results coincide with another study analysing CC mortality data of women aged 15+ years in the period 2005-2008, which found the highest mortality rates in the departments of Arauca, Meta, Tolima, Caquetá, and Quindío (159). The results of this study also suggested that CC mortality rates were higher in urban than in rural areas (159). In contrast, Chocontá-Piraquive et al (160) reported high CC mortality rates between 2000 and 2004 among women of all ages in the departments of Caldas, Tolima, Quindío, and Risaralda.

Socioeconomic status has also been suggested as an important predictor of CC mortality in Colombia. An ecological study using 2000-2007 mortality data from women of all ages in the department of Antioquia, located in the Central region of Colombia, showed an association between CC mortality rates and social variables in the department, such as poverty, illiteracy, and unmet basic needs (161). High levels of poverty and unmet needs were related to higher mortality rates due to CC; in contrast, lower levels of illiteracy were associated with lower CC mortality rates (161).

Again, similar to the observations for primary and secondary prevention of CC, education and insurance have been suggested as important risk factors CC mortality in Colombia. A recent Colombian study about mortality and educational level among women between 25 and 64 years who died from CC, found that women with primary and secondary education had an increased risk of dying due to CC compared to women with higher education (162). In relation to health insurance, one study reported an association between the proportion of uninsured women and mortality rates, finding higher mortality rates when the proportion of women with no health insurance increased (160). Furthermore, this study showed that CC mortality decreased about 40% when a high proportion of women complied with their follow-up after having an abnormal Pap test.

1.5. Rationale

The rationale for investigating factors associated with the primary and secondary prevention of CC and mortality due to CC in Colombia in this thesis included access to national data that provided a unique opportunity to build on previous research that could lead to reducing inequities in health.

The results presented in this thesis are based on data from the 2010 NDHS, a nationwide and representative household survey (122), as well as the Colombian official mortality records. The 2010 NDHS assessed different aspects of women's health and their households collected to guide policy (122). In the 2010 NDHS, women were asked, among other topics, about HPV, CC prevention, and associated risk factors (122). Official mortality records from 2005 to 2013 were obtained from the Colombian National Administrative Department of Statistics (*Departamento Administrativo Nacional de Estadística* - DANE). The Colombian DANE has been gathering, processing, analysing, and disseminating statistical information for about 60 years (163), including the collection of mortality data at the national level.

Colombia is one of the most inequitable countries in Latin America (96). Colombians have to deal with high levels of inequity in the distribution of the SDOH, such as income (97-101) and education (98, 103, 104). Also, the country has experienced a long internal armed conflict, with millions of displaced individuals, who are primarily women (111). In this social context, CC is ranked as the second most common incident cancer and the second most common cause of cancer deaths among Colombian women (123), affecting a large number of women and their families. Added to these problems, health inequities have grown in Colombia after the implementation of a health system that provides inequitable care for the poor compared to the wealthy (120).

Although inequities in primary (149-154) and secondary CC prevention (155-158), as well as inequities in CC mortality (127, 159-162) have been reported in Colombia, nationwide studies evaluating how socio-demographic factors relate to primary and secondary prevention of CC and CC mortality specifically in young Colombian women are lacking in the country.

There are many opportunities to build on the existing literature regarding knowledge of HPV and primary CC prevention strategies. Previous Colombian reports have not focused explicitly on young women and the results of analyses are sometimes limited based on the number and type of variables examined and the comprehensiveness of statistical analysis conducted. To date, there are no nationwide studies evaluating multiple factors associated with awareness of HPV vaccination among young women in Colombia. For example, studies assessing knowledge of HPV or HPV vaccination have included both males and females or females only of various age ranges living in several Colombian cities (149-154). Also, most of these studies used descriptive (150), bivariate (149, 152) or qualitative analysis (153). Two studies that assessed knowledge of HPV, measured the role of type of health insurance using simple bivariate analysis (149) and descriptive statistics (152). One study conducted in the city of Medellín to assess the knowledge of HPV among women aged 18-69 years included age and education as the independent variables of interest (151). Results of another study conducted in Bogotá that measured awareness of HPV and HPV vaccine, stated that a multivariable model was tested to assess confounding; however, the results of this analysis were not included in the published version of the study (154).

There are similar opportunities to build on the existing understanding of factors influencing secondary prevention strategies. In relation to Pap testing, although access to CC screening among women has been reported to be good in Colombia (155), there are no studies assessing the socio-demographic factors associated with Pap testing taking into account the effect of the context where women live (e.g. neighbourhood) on the probability to access this test. Most of the studies available have been conducted among women aged 13+ years living in specific cities

(155-158). There are limitations in the two studies investigating the role of health insurance in Pap testing (155, 158). The authors of the only nationwide study used a simple logistic regression to assess the effect of health insurance on the probability of having a recent Pap test among women 25-49 (155). Women aged 18-24 years were not included in this study, and contextual effects were not assessed. The study of Lucumí Cuesta et al (158) conducted in Bogotá considered affiliation status of women as a dichotomous variable without specifying the type of insurance.

Furthermore, spatial variations in accessing primary and secondary CC preventing strategies have not been examined among young women, despite the diversity in socio-demographic factors among Colombian departments. The application of tests for global and local clustering could be useful to the detect a lack of randomness in the spatial distribution in the outcome variables of interest (164, 165). Furthermore, modelling of spatial data could be helpful to evaluate factors related to the spatial variability in the access to primary and secondary CC prevention in Colombia beyond that explained by fixed effects, such as education and insurance (164, 165). These kinds of analyses could help examine geographical differences in risk of accessing CC prevention and identify areas where further study is needed to best optimize the use of limited resources for CC prevention.

Regarding mortality, previous studies evaluating factors associated with CC mortality have focused on a broad range of ages (159-162). Results of these studies do not provide explicit evidence on how socio-demographic factors are associated with premature CC mortality in young women. Similarly, no studies to date have examined factors associated with variations in mortality rates by assessing interactions between other risk factors and age. In relation to risk factors and mortality, the study of de Vries et al (162) assessed the relevance of education in CC mortality among women aged 25-64 years; however, women with no formal education were not included in the analysis. Women with no education were included in a study by Baena et al (161) that evaluated variations in CC mortality rates according to percentage of literacy in a specific department of Colombia. There is only one previous study that evaluated the role of health insurance in CC in Colombia (160). This study did so by evaluating the association between the percentage of uninsured women and CC mortality rates and, therefore, did not include comparisons among different types of health insurance.

Moreover, considering the limitations to access health care faced by women living in rural areas of Colombia (122), only one study included rural residence as a risk factor for having Pap testing in a multivariable regression analysis (156). However, this study was limited to a municipality located in the department of Santander. Similarly, despite the diversity of Colombian regions (98), just two studies have reported the distribution of Pap testing (155) and CC mortality rates (127) by departments. There are no nationwide studies conducted in Colombia showing associations between either Pap testing or CC mortality and both rural residence and region or department of residence.

1.6. Goals and Objectives of This Research

The goals of this thesis are to identify individual and department socio-demographic characteristics associated with awareness of primary prevention programmes and access to secondary prevention programmes for CC in Colombia. The goals of this thesis also include examining the relationships among socio-demographic factors in young Colombian women and CC mortality.

The specific questions that guided this research were as follows:

a. What socio-demographic factors are associated with having heard about HPV vaccination among women between 13 and 49 years in Colombia?
b. What socio-demographic characteristics of women aged 18 to 49 years in Colombia are associated with having ever had a Pap test?
c. Is there a spatial pattern in the department frequencies of women not having heard of HPV vaccination and the department frequencies of not having had Pap testing that could be explained by variations in socio-demographic factors in Colombia?
d. Are there differences in CC mortality rates of women aged 20 to 49 years in Colombia associated with their socio-demographic factors?

To answer each of the questions, this thesis has been organised into a series of four chapters.

Article 1, presented in Chapter 2, used data from the 2010 NDHS. Using a multivariable logistic regression model, this paper examined differences in the socio-demographic factors associated with the probability of having heard of HPV vaccination among women aged 13-49 years.

Article 2, presented in Chapter 3, also used data from the 2010 NDHS. The goal of this paper was to identify the socio-demographic factors related to ever having had a Pap test among women aged 18 to 49 years. Using a generalised linear mixed model, this article also explored the influence that neighbourhood and municipality where women live had on the probability of having had Pap testing.

Article 3, presented in Chapter 4, used data from both the 2010 NDHS and the DANE. Global and local tests for detecting clustering, as well as Bayesian Poisson hierarchical models were used to identify spatial patterns in having heard of HPV vaccination and not ever having had a Pap test, as well as department factors associated with the outcomes of interest.

Article 4, presented in Chapter 5, used CC mortality records from 2005 to 2013 and population projection data made available by DANE. The study also made use of the 2010 NDHS to characterise the population at risk. Associations between socio-demographic factors and mortality due to CC were explored using multivariable negative binomial regression models.

The papers presented in Chapters 2 to 5 have been previously published in peer-reviewed journals. Full citations are given at the beginning of each chapter. The permissions to include the reformatted papers in this thesis are included in Appendix A.

Because this thesis used secondary data, the University of Saskatchewan Research Ethics Board (REB) provided an exemption from ethics review. A formal letter and e-mail with the REB document exempting these studies from ethics review are included in Appendix B.

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CHAPTER 2 – PREDICTORS OF HAVING HEARD ABOUT HUMAN PAPILLOMAVIRUS VACCINATION: CRITICAL ASPECTS FOR CERVICAL CANCER PREVENTION AMONG COLOMBIAN WOMEN

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This chapter describes risk factors associated with having heard about the human papillomavirus (HPV) vaccine among young Colombian women, including socio-demographic factors, such as age, educational level, socioeconomic and working status, type of health insurance, having rural or urban residence, and region of residence. This is the first nationwide study in Colombia among women aged 13-49 years examining socio-demographic factors associated with a primary prevention strategy for cervical cancer (CC). In addition to the identified low prevalence of HPV vaccination awareness, this work demonstrates the presence of inequities and a social gradient in CC primary prevention, showing a key role of education and rural residence. The study results could guide the development of CC prevention programmes to educate women about HPV vaccination, focussing on young women and those living in socially disadvantaged conditions.

2.1. Introduction

Cervical cancer (CC) is responsible for over 275,000 female deaths each year, with more than 500,000 new cases diagnosed worldwide (1). Persistent infection of the anogenital tract with high-risk human papillomavirus (HPV), which is a sexually transmitted disease (2), has been established as a necessary cause for cervical intraepithelial neoplasia and CC (3, 4). Factors such as being sexually active, young age, oral contraceptive use, socioeconomic status, high parity, smoking status, and previous HPV infections, among others, have been associated with the transmission of HPV (2).

Vaccination against certain high-risk HPV types among women without previous exposure to these viruses and ideally before their sexual debut has been associated with a reduction of pre-invasive cervical lesions (2, 5). HPV vaccination provides a potential cost-effective way to prevent CC (6). Currently, two vaccines are available against HPV: the bivalent vaccine protects against HPV types 16 and 18; the quadrivalent one protects against HPV types 6, 11, 16, and 18 (5). Awareness of prevention of CC is key to support HPV vaccination (7) and raising knowledge about the role of HPV in the development of CC is central in CC prevention (8). Previous studies have shown that a low intention of HPV vaccination is associated with limited awareness and poor knowledge of HPV vaccination (7, 9, 10). Therefore, measuring awareness of HPV vaccination is critical for CC prevention programmes.

In Colombia, CC is the cancer most frequently affecting women (11, 12). It has been estimated that about 15% of Colombian women will develop a HPV infection during their lifetime (12). The Colombian *Instituto Nacional de Vigilancia de Medicamentos y Alimentos* (INVIMA) approved the quadrivalent and bivalent HPV vaccines in 2006 and 2007, respectively (13); then, the HPV vaccines were available for women who were willing to pay for them. The quadrivalent HPV vaccine is an insured service for girls aged 9 years and older since 2012 (14). However, a lack of knowledge about HPV infection and HPV vaccination has been reported in Colombia, especially among less educated and low income groups (8, 15). Indeed, these disadvantaged groups have been highly affected by the structure of the Colombian *Sistema General de Seguridad Social en Salud* (SGSSS), which is an insurance-based health care system (16). This system has increased barriers to access health care (16) and obtain equal health benefits for individuals unable to pay (subsidised health insurance) (16, 17) compared to those who can contribute to the system (contributory health insurance) (16, 18) and those who belong to groups with special health care plans (public teachers, workers of public universities, military forces, police, and employees of the Colombian Oil Company) (19).

To the best of our knowledge, there are no nationwide studies in Colombia evaluating socioeconomic and personal factors associated with having heard about HPV vaccination among women. Therefore, our objectives were to determine: (1) the prevalence of Colombian women having heard about HPV vaccination; (2) whether the probability of having heard about HPV vaccination differs by age group, educational level, socioeconomic (wealth quintile) and working status, type of health insurance, region and rural/urban area of residence, women having experienced intercourse, type of contraceptive method used, and women who have had children; and (3) whether the effect of predictors for having heard about HPV vaccination differs at different educational levels and rural/urban area of residence.

2.2. Methods

The data were drawn from the 2010 National Demographic and Health Survey (NDHS), a national representative survey conducted among women between 13 and 49 years old living in Colombia. In total, 53,521 out of 56,886 women participated in the NDHS (response rate = 94%) (20). This survey evaluated socio-demographic characteristics of participants, as well as different aspects of their health.

All women were asked whether they had heard about the HPV and also if they had ever heard about a vaccine to prevent CC. Women who reported having heard about HPV and having heard about a vaccine to prevent CC were classified as “1 = have heard about HPV vaccination;” otherwise, they were classified as “0 = have not heard about HPV vaccination.” This was the dependent variable of our study. Self-reported factors considered as independent variables in the study were age group, educational level, wealth quintile, working status, type of health insurance, having experienced intercourse, type of contraceptive method used, having children, and region and rural/urban area of residence. Atlantic, Amazon-Orinoquía, Central, Eastern, and Pacific were the regions established in the Colombian NHDS; Bogotá (the capital) was included in the Eastern region. Chi-square tests were performed to test differences in the distribution of women in different categories of the independent variables.

A logistic regression model was built using the manual backward method at a 5% level of significance. Variables not included in the model were tested as confounders; the presence of confounding was considered if these variables changed the parameter estimates of predictors in the model by more than 10%. Additionally, educational level and rural/urban area of residence were tested as modifier effects.

Unadjusted (UORs) and adjusted odds ratios (AORs), 95% confidence intervals (95%CIs), and p-values were computed. Women with missing data were excluded from the multivariable analysis. Model diagnostics were examined through receiver-operating characteristic (ROC) curves and assessment of residuals. The analyses were performed using SAS software version 9.3 (SAS Institute Inc., Cary, NC, USA).

The Ethical Committee of the *Asociación Probienestar de la Familia Colombian*a (Profamilia) provided ethical approval for the 2010 NDHS; participants gave their consent before the administration of the survey. To use the 2010 NDHS data for the present study, the University of Saskatchewan Research Ethics Board provided an exception for ethics review.

2.3. Results

In total, data from 53,521 women aged 13–49 years were obtained. The mean age of the women was 29.2 years (SD=10.8). The distribution of women's characteristics is presented in Table 2-1. Of the total women, 14,363 (26.8%; 95%CI=26.3–27.1%) reported having heard about HPV vaccination. The proportion of women who heard about HPV vaccination by age group was: 13–18 years, 12.9% (95%CI=11.4–14.4%); 19–24 years, 16.6% (95%CI=15.1–18.1%); 25–32 years, 23.9% (95%CI=22.5–25.3%); 33–40 years, 21.7% (95%CI=20.3–23.1%); and 41–49 years, 24.9% (95%CI=23.5–26.3%). Among the 14,363 women who have heard about HPV vaccination, 49% had secondary education, 23.9% belonged to the highest wealth quintile, 83.8% were working, 50.7% had contributory health insurance, 84.2% were living in urban areas, 27.4% lived in the Eastern region, 88% had experienced intercourse, 38.7% were not using contraceptive methods, and 67.4% had children. Statistically significant differences were found when comparing socio-demographic and sexual factors among women who had heard about HPV vaccination and those who had not. Bivariate analyses indicated that all the predictors were significantly associated with the dependent variable (*p*-values<0.001); UORs and their 95%CI are shown in Table 2-1.

Table 2-1. Descriptive statistics for variables used in the model building, unadjusted odds ratios (UOR) and corresponding 95% confidence intervals (CI). National Demographic and Health Survey (NDHS), Colombia, 2010 (n=53,521).

Variable	**Categories**	**All women** [a]	**Have heard about human papillomavirus vaccination** [a,b]		**UOR (95%CI)**
			No (39,158)	Yes (14,363)	
Age group	41–49 years old	10,736 (20.1)	7164 (18.3)	3572 (24.9)	2.61 (2.45–2.79)
	33–40 years old	10,207 (19.1)	7089 (18.1)	3118 (21.7)	2.31 (2.16–2.46)
	25–32 years old	11,513 (21.5)	8075 (20.6)	3438 (23.9)	2.23 (2.10–2.38)
	19–24 years old	9508 (17.7)	7124 (18.2)	2384 (16.6)	1.76 (1.64–1.88)
	13–18 years old	11,557 (21.6)	9706 (24.8)	1851 (12.9)	Ref.
Educational level	None	1145 (2.1)	997 (2.6)	148 (1.0)	0.15 (0.13–0.18)
	Primary	13,550 (25.3)	11,524 (29.4)	2026 (14.1)	0.18 (0.17–0.19)
	Secondary	28,393 (53.1)	21,357 (54.5)	7036 (49.0)	0.34 (0.32–0.35)
	Higher	10,433 (19.5)	5280 (13.5)	5153 (35.9)	Ref.
Wealth quintile	Lowest	13,203 (24.7)	11,507 (29.4)	1696 (11.8)	0.15 (0.14–0.17)
	Lower	13,642 (25.5)	10,608 (27.1)	3034 (21.2)	0.30 (0.28–0.32)
	Middle	11,001 (20.6)	7908 (20.2)	3093 (21.5)	0.41 (0.38–0.43)
	Higher	8662 (16.2)	5554 (14.2)	3108 (21.6)	0.58 (0.55–0.62)
	Highest	7013 (13.1)	3581 (9.2)	3432 (23.9)	Ref.
Working status	No	12,061 (22.5)	9729 (24.8)	2332 (16.2)	0.59 (0.56–0.62)
	Yes	41,460 (77.5)	29,429 (75.2)	12,031 (83.8)	Ref.
Type of health insurance	Non-affiliated	6180 (11.5)	4739 (12.1)	1441 (10.0)	0.44 (0.42–0.48)
	Subsidised	27,970 (52.3)	22,864 (58.4)	5106 (35.6)	0.33 (0.31–0.34)

	Special	1454 (2.7)	917 (2.3)	537 (3.7)	0.86 (0.77–0.96)
	Contributory	17,917 (33.5)	10,638 (27.2)	7279 (50.7)	Ref.
Area of residence	Rural	14,636 (27.3)	12,366 (31.6)	2270 (15.8)	0.41 (0.39–0.43)
	Urban	38,885 (72.7)	26,792 (68.4)	12,093 (84.2)	Ref.
Region	Atlantic	11,474 (21.4)	8322 (21.3)	3152 (21.9)	0.79 (0.74–0.83)
	Amazon-Orinoquía	9117 (17.0)	7826 (20.0)	1291 (9.0)	0.34 (0.32–0.37)
	Central	13,096 (24.5)	9197 (23.5)	3899 (27.1)	0.88 (0.83–0.93)
	Pacific	7737 (14.5)	5651 (14.4)	2086 (14.5)	0.77 (0.72–0.82)
	Eastern	12,097 (22.6)	8162 (20.8)	3935 (27.4)	Ref.
Had experienced intercourse	Yes	44,249 (82.7)	31,607 (80.7)	12,642 (88.0)	1.76 (1.66–1.86)
	No	9272 (17.3)	7551 (19.3)	1721 (12.0)	Ref.
Contraceptive method	Condoms	3633 (6.8)	2440 (6.2)	1193 (8.3)	1.60 (1.48–1.73)
	Hormonal methods	8866 (16.6)	6305 (16.1)	2561 (17.8)	1.33 (1.26–1.40)
	Female sterilisation	11,790 (22.0)	8330 (21.3)	3460 (24.1)	1.36 (1.29–1.43)
	Other methods	5491 (10.3)	3898 (10.0)	1593 (11.1)	1.34 (1.25–1.43)
	Not using	23,741 (44.4)	18,185 (46.4)	5556 (38.7)	Ref.
Have had children	Yes	35,126 (65.6)	25,439 (65.0)	9687 (67.4)	1.12 (1.07–1.16)
	No	18,395 (34.4)	13,719 (35.0)	4676 (32.6)	Ref.

[a] n (%).
[b] Some percentages with rounding error.

In the model building, age was found to be not linearly related to the log odds of the outcome ($p<0.001$); therefore, it was included as a five-category variable which was created according to age distribution. Working status and having experienced intercourse were variables initially removed from the model (p-values>0.05); notwithstanding, working status was found to be a confounding variable and was included as a covariate in the model. Also, significant interactions were found between educational level and age group ($p=0.002$), educational level and region ($p<0.001$), and rural/urban area of residence and region ($p<0.001$).

Table 2-2 presents AORs and their corresponding 95% CIs of predictors not interacting in the logistic regression model. Regarding wealth quintile, women in the lowest (AOR=0.44; 95%CI=0.40–0.49) and lower (AOR=0.57; 95%CI=0.53–0.61) quintiles were less likely to have heard about HPV vaccination in comparison to women from the highest quintile. Similarly, women in the middle (AOR=0.64; 95%CI=0.59–0.68) and higher (AOR=0.74; 95%CI=0.69–0.79) wealth quintiles were less likely to have heard about HPV vaccination. The type of health insurance was also significantly associated with having heard about HPV vaccination. Women with subsidised health insurance (AOR=0.69; 95%CI=0.66–0.73) and those non-affiliated to any health insurance (AOR=0.73; 95%CI=0.68–0.79) were less likely to have heard about HPV vaccination than women in the contributory group. Women using condoms (AOR=1.19; 95%CI=1.10–1.29), hormonal methods (AOR=1.20; 95%CI=1.13–1.28), or who were sterilised (AOR=1.10; 95%CI=1.03–1.17) were more likely to have heard about HPV vaccination than those not using any contraceptive method. Furthermore, women with children were less likely to have heard about HPV vaccination compared to women with no children (AOR=0.87; 95%CI=0.81–0.92).

Table 2-2. Adjusted odds ratio (AORs) and corresponding 95% confidence intervals (CI) of having heard about human papillomavirus vaccination by non-interacting predictors (n=53,520). National Demographic and Health Survey (NDHS) Colombia, 2010.

Predictor	**Categories**	**AOR (95%CI)**
Wealth quintile	Lowest	0.44 (0.40–0.49)
	Lower	0.57 (0.53–0.61)
	Middle	0.64 (0.59–0.68)
	Higher	0.74 (0.69–0.79)
	Highest	Ref.
Working	No	1.05 (0.98–1.12)
	Yes	Ref.
Type of health insurance	Non-affiliated	0.73 (0.68–0.79)
	Subsidised	0.69 (0.66–0.73)
	Special	0.91 (0.81–1.02)
	Contributory	Ref.
Contraceptive method	Condoms	1.19 (1.10–1.29)
	Hormonal methods	1.20 (1.13–1.28)
	Female sterilisation	1.10 (1.03–1.17)
	Other methods	1.05 (0.97–1.13)
	Not using	Ref.
Have had children	Yes	0.87 (0.81–0.92)
	No	Ref.

Predictors interacting in the model are depicted in Fig. 2-1, Fig. 2-2 and Fig. 2-3. The probabilities of having heard about HPV vaccination were higher among older age groups and women with better levels of education; however, differences in these probabilities by age group were more evident among educated women compared to non-educated ones (Fig. 2-1). Comparing the level of education by region (Fig. 2-2), it was observed that women with no education had the lowest probabilities of having heard about HPV vaccination in all regions, and that the probability gap between these women and the highly educated ones was wider in the Eastern than in the Amazon-Orinoquía region. Also, among women with high educational levels, those living in the Amazon-Orinoquía region had the lowest probability of having heard about HPV vaccination; however, highly educated women of the Amazon-Orinoquía region were more likely to have heard about vaccination than those with lower levels of education in any other region. Furthermore, women living in rural areas had lower probabilities of having heard about HPV than those living in urban areas (Fig. 2-3); notwithstanding, women living in urban areas of the Amazon-Orinoquía region had similar probabilities than those living in rural areas of the Eastern region. Also, narrower gaps between women in rural and urban areas were observed in the Atlantic and Amazon-Orinoquía regions.

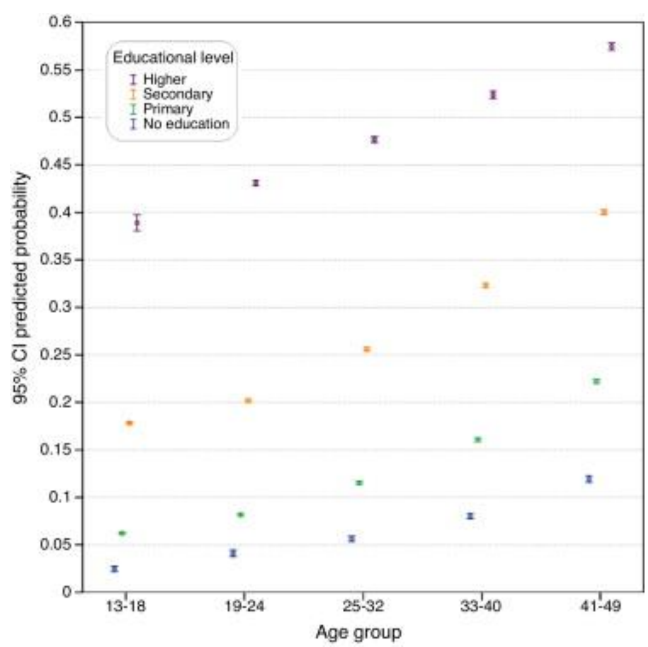

Fig. 2-1. Predicted probabilities and 95%CIs of having heard about HPV vaccination by age group and educational level; NDHS Colombia, 2010.

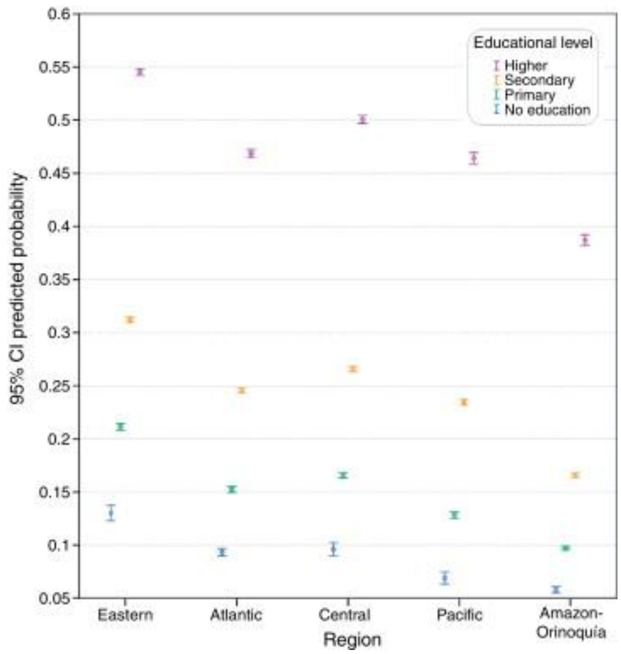

Fig. 2-2. Predicted probabilities and 95%CIs of having heard about HPV vaccination by region of residence and educational level; NDHS Colombia, 2010.

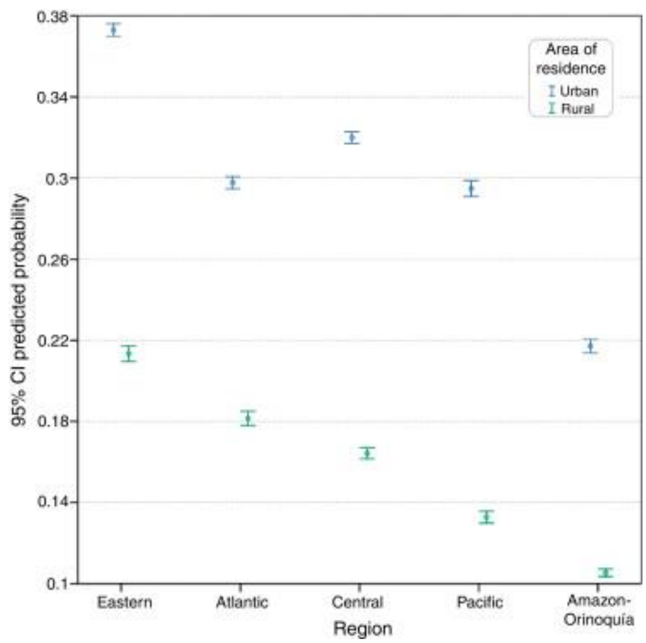

Fig. 2-3. Predicted probabilities and 95%CIs of having heard about HPV vaccination by region and rural/urban area of residence; NDHS Colombia, 2010.

In the model diagnostics, the ROC curve showed that the logistic model correctly classified 72.5% of the women who had heard about HPV vaccination, which could be considered as satisfactory. Also, the assessment of residuals showed that they were within an adequate range of ±3 standard deviations from zero.

2.4. Discussion

The low prevalence of women who had heard about HPV vaccination found in our results is in accordance with a previous study claiming a poor awareness of HPV vaccination among adolescents in Cartagena, Colombia (21). This lack of awareness of HPV vaccination in the country could be resulting from poor national "HPV educational efforts (8)." Other authors in Colombia have reported a higher proportion of individuals aware of HPV and HPV vaccination (8, 15); however, their samples included patients attending health care centres. The participants of these studies could have more access to HPV-related information which could increase their level of HPV awareness. Also, these studies did not include women below 18 years and data were drawn from larger cities, such as Medellín (8) and Bogotá (15). Our study included not only nationwide data of women aged 18–49 years but also incorporated data of women from 13 to 17 years which represented 18.2% of the total sample. We identified that women in the youngest age group had the lowest prevalence of having heard about HPV vaccination. Studies in other countries have reported higher awareness of HPV vaccination (22, 23). A recent study in developed countries identified that more than 80% of women had heard about HPV vaccination (23); in contrast, after a mass media advertisement campaign to promote HPV vaccination in Argentina, 36% of the women had an adequate knowledge about HPV vaccination (22).

Different studies have considered the existence of variations in the level of awareness of HPV vaccination by socioeconomic (8, 15, 21-25) and educational status (7-10, 15, 22, 24, 25). We identified that the prevalence of having heard about HPV vaccination was low among women who belonged to deprived socioeconomic levels, non-insured individuals, and women covered by the subsidised health insurance. These findings are in agreement with other studies showing socioeconomic disparities in knowledge of HPV vaccination in Colombia (8, 15, 21). A study conducted among individuals with genital warts in Bogotá identified that participants without health insurance coverage, and beneficiaries of the subsidised health insurance were less aware of HPV vaccination (15). In fact, individuals in the subsidised health insurance receive about 40% less health benefits than those in the contributory one (18), and most of the non-insured people belong to the lowest income group (17). Therefore, barriers to access health care experienced by disadvantaged groups in Colombia could be affecting knowledge about HPV and HPV vaccination, since health care professionals are an important source of information about HPV vaccination and a motivating factor for HPV vaccine intake (9, 10, 22, 24, 26).

Our results show novel information regarding modifier effects of education and rural/urban residence on the awareness of HPV vaccination. In Colombia, researchers have identified that individuals living in rural areas are more likely to report a poor health status (27), and that these individuals are highly impacted by economic, political, and social problems of the country compared to people living in urban areas (28). Furthermore, low educational levels and high poverty indicators have been reported in departments located in the Amazon-Orinoquía, Pacific, and Atlantic regions (29). These findings agree with our results that show low probabilities of having heard about HPV vaccination among women living in these three regions of Colombia, specifically if they have rural residence and low educational levels. Thus, there is a need to reduce these gaps when designing and implementing educational initiatives about HPV vaccination. Further programmes educating the general population about CC and its relation to HPV are critical to increase knowledge about HPV vaccination (8, 9, 15, 30).

Although it is known the role that parents have in approving participation of their daughters in HPV vaccination programmes (7, 9, 25, 31, 32), we identified that women with children were less likely to have heard about HPV vaccination compared to women with no children, adjusting by age and other factors. This lack of awareness suggests that parents could be experiencing limitations to obtain information about HPV vaccination. A qualitative study conducted in four Colombian regions showed that parents were unaware of HPV vaccination and that receiving information was central to decide vaccinating their daughters (31). Additionally, it needs to be recognised that the socioeconomic context of parents impacts on their ability to support HPV vaccination of their family members (25, 31). Given that discussions about HPV vaccination between parents and children are a starting point to approach sexuality issues (31, 32), continuous efforts to educate about CC prevention and HPV vaccination are definitely needed not only for young women (10, 30) but also for older populations (i.e., parents and grandparents). Women need multiple sources of information about HPV vaccination, including the advice that they could receive from other women they trust (30).

We propose that CC prevention and education programmes recognise and overcome existing inequities – "inequalities considered unfair or stemming from some form of injustice (33)"– in the awareness of HPV vaccination. Therefore, national and local campaigns should be encouraged to change the paradigm of insufficient commitment to improve prevention and health promotion programmes within the Colombian SGSSS (19). These campaigns should ensure the reception of educational messages about HPV vaccination in the general population, emphasizing socially disadvantaged groups (22, 24, 25). Furthermore, working with health care professionals, schools, and community organisations might help develop better health promotion and preventive strategies to overcome difficulties related to area and region of residence, educational level, and health insurance coverage. We also recommend studies that evaluate successful experiences about HPV vaccination awareness and CC prevention campaigns to adjust and replicate them across the country. These studies should also include an assessment of the knowledge about HPV infection and HPV vaccination using validated instruments (23, 34). Given that HPV vaccination is an insured service and that the Colombian Ministry of Health is leading CC prevention strategies (14), awareness of HPV vaccination in upcoming studies could be compared to our results to explore persistence of inequities.

Limitations of this study are primarily due to its cross-sectional design, which only provides information about associations. In addition, our study evaluated whether women had heard about HPV and a vaccine to prevent CC, which could be considered as a proxy of HPV vaccination knowledge. Also, it needs to be acknowledged that social desirability could have an impact on the findings.

In conclusion, almost three quarters of the women in Colombia had not heard about HPV vaccination. The socio-demographic variations found on having heard about HPV vaccination indicate the presence of inequities and a social gradient in the awareness of HPV vaccination in Colombia. These findings suggest that programmes raising awareness of vaccination to prevent

CC have had a poor impact and that they could be neglecting marginalised groups of women in Colombia. Hence, further educational programmes about CC prevention and HPV vaccination should target the general population, although specific strategies are also necessary to reach disadvantaged groups (low socioeconomic strata, individuals with subsidised health insurance, women with no education, and those living in isolated or rural regions).

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CHAPTER 3 – INEQUITIES IN CERVICAL CANCER SCREENING AMONG COLOMBIAN WOMEN: A MULTILEVEL ANALYSIS OF A NATIONWIDE SURVEY

Article reproduced with minor edits and with permission. Originally published as: "Bermedo-Carrasco S, Peña-Sánchez JN, Lepnurm R, Szafron M, Waldner C. Inequities in cervical cancer screening among Colombian women: a multilevel analysis of a nationwide survey. *Cancer Epidemiol*. 2015; 39:229-36. http://dx.doi.org/10.1016/j.canep.2015.01.011." My contributions to this study included the study design, data acquisition and analysis, interpretation of the results, and preparation of the manuscript.

This chapter builds on the inequities in primary cervical cancer (CC) prevention identified among Colombian women in Chapter 2 by describing socio-demographic risk factors for whether or not women aged 18 to 49 years have ever had Pap testing. Age, educational level, socioeconomic and working status, type of health insurance, having a rural or urban residence, region of residence, having children, and whether women make their own health care decisions were factors associated with having a Pap test. This study is the first in Colombia showing that a lack of education in the neighbourhood where women live was also an important factor associated with Pap test uptake, demonstrating that CC screening decreased as the prevalence of no education in neighbourhoods increased. The evidence presented in this chapter highlights that CC screening programmes should acknowledge not only individual socio-demographic attributes, but also the importance of education in all women who live nearby and may contribute to a local social network.

3.1. Introduction

Although cervical cancer (CC) is considered a preventable disease (1, 2), worldwide it is ranked third for incident cancer cases and fourth for cancer-related mortality (3-5). In South America, CC is the second most incident cancer and first for cancer mortality among women between 15 and 44 years (5). In Colombia, CC is the second most common cancer (6) and has a proportional mortality of 12%, making it the second most common cause of cancer mortality (7).

The Pap smear, or Pap test, is used globally to screen for pre-cancerous lesions of the cervix (8). Hence, failure to have a Pap test has been considered a risk factor for CC (9). The Colombian recommendations for CC screening state that women between 25 and 69 years (or younger who have experienced intercourse) should have free access to Pap testing; however, a Colombian committee of experts advised starting CC screening at 21 years of age (10). The recommended frequency of Pap testing in Colombia is 1-1-3 which means if two consecutive annual tests are negative, subsequent tests should be repeated every third year (10). In spite of these recommendations, Pap test coverage in Colombia is lower than in other Latin American countries (11). Furthermore, the CC screening programme is decentralised in Colombia; health insurance companies and their network of health care providers are responsible for Pap testing (12).

Studies conducted in Colombia have identified differences in access to Pap testing between rural and urban areas and among geographic region of residence (13, 14), educational level (15), wealth quintile (15), age group (15, 16), and type of health insurance (16). Colombia has an insurance-based health care system, the *Sistema General de Seguridad Social en Salud* (SGSSS – the General Social Security System in Health), with two schemes: contributory and subsidised (17). Workers and retired individuals with the ability to pay belong to the contributory system, and those unable to pay are part of the subsidised system (17, 18). Public teachers and universities workers, members of the military forces, police, and employees of the Colombian Oil Company have special health insurance plans (18). Differences in access to health care benefits between the contributory and subsidised systems have been reported (19-21) which mainly affect disadvantaged populations (19, 22, 23). The SGSSS has been criticised for not considering geographical, social, and cultural contexts, increasing barriers to access health care (24).

While residential context influences participation in Pap testing (25), previous studies exploring factors affecting Pap test uptake in Colombia (13, 15) have not considered the influence of contextual factors on the probability of having a Pap test. The aim of this study was to identify socio-demographic factors related to ever having had a Pap test among sexually active women aged 18–49 years in Colombia, considering the influence of neighbourhood and municipality where women live. The specific objectives of this study were to identify factors associated with whether women in Colombia have had a Pap test, evaluate differences in risk factors between rural and urban residence, and evaluate the contextual effect of the lack of education on having had a Pap test.

3.2. Material and Methods

3.2.1. Study Population and Data

Data for this study were part of the 2010 National Demographic and Health Survey (NDHS), a Colombian nationwide survey assessing different aspects of women's health. The NDHS included information from 53,521 women aged 13–49 years representing 51,447 households (13). The data were collected using random, cluster, and multistage sampling. Households were grouped with others of similar characteristics and proximity, creating groups of houses (hereinafter called neighbourhoods) with an average of ten households. The NDHS subdivided Colombia into five geographic regions (Amazon-Orinoquía, Pacific, Central, Atlantic, and Eastern).

In the NDHS, only women 18 years or older, who had not had a hysterectomy, and who had experienced intercourse, were eligible to answer questions about CC prevention. Consequently, this work is based on the responses of the 40,410 (out of the original 53,521) women who met this eligibility criterion for answering questions related to CC screening (Pap test). Women, who self-declared they had heard about Pap smears and have ever had a Pap test, were classified as “1

= have had a Pap test”; otherwise, they were classified as “0 = have not had a Pap test.” This was the outcome variable of interest for this study.

The Ethical Committee of the *Asociación Probienestar de la Familia Colombiana* (Profamilia) provided ethical approval prior to data collection. Also, Profamilia obtained consent from participants before the administration of the NDHS. To conduct the present analysis using the 2010 NDHS database, the University of Saskatchewan Research Ethics exempted the project.

3.2.2. Statistical Analysis

The frequencies of women who had a Pap test were calculated according to socio-demographic factors of interest, including age, whether women had children, whether they had the final say on their own health (who makes decisions related to the woman's health), educational level, wealth quintile, working status, rural/urban area of residence, region of residence, and type of health insurance (Table 3-1). Considering the sampling procedure and the resulting hierarchical structure of the data (Fig. 3-1), a three-level mixed model (first level: women, second level: neighbourhoods, and third level: municipalities) for a binomial outcome with a logit link function and Laplacian approximation was used. The errors for the second and third levels were considered as random effects to account for variation in the probability that women would have a Pap test among municipalities and neighbourhoods. Multilevel modelling has the advantage of examining how both group and individual factors impact the outcome variable (26), considering the potential clustering of outcomes within groups (27). This technique also allows an exploration of the potential contextual effects of group membership (28). The average number of observations and proportion of replications per level were examined for each of these random intercepts. The geographic region (group of departments) was considered as a predictor in the fixed portion of the model.

Table 3-1. Distribution of women who have and have not had a Pap test by socio-demographic factors and unadjusted odds ratios (UOR) with corresponding 95%CI computed in a three-level logistic model (n = 40,392).

	All women (*n* = 40,410)	Have had a Pap test [a]		UOR (95%CI)
		Yes	No	
		35,264 (87.3%)	5128 (12.7%)	
Age group				
41–49 years	9540 (23.61%)	9113 (25.84%)	423 (8.25%)	12.84 (11.48–14.37)
33–40 years	9799 (24.25%)	9315 (26.42%)	478 (9.32%)	11.85 (10.64–13.19)
25–32 years	11,251 (27.84%)	10,331 (29.3%)	915 (17.84%)	6.65 (6.10–7.24)
18–24 years	9820 (24.3%)	6505 (18.45%)	3312 (64.59%)	Ref.
Educational level				
No education	1029 (2.55%)	794 (2.25%)	233 (4.54%)	0.78 (0.65–0.93)
Primary	11,355 (28.1%)	10,203 (28.93%)	1150 (22.43%)	1.69 (1.54–1.86)
Secondary	18,722 (46.33%)	16,175 (45.87%)	2536 (49.45%)	1.03 (0.69–1.12)
Higher	9304 (23.02%)	8092 (22.95%)	1209 (23.58%)	Ref.
Wealth quintiles				
Lowest	9700 (24%)	7943 (22.52%)	1751 (34.15%)	0.60 (0.52–0.69)
Lower	10,335 (25.58%)	9033 (25.62%)	1298 (25.31%)	0.80 (0.70–0.91)
Middle	8474 (20.97%)	7530 (21.35%)	937 (18.27%)	0.87 (0.77–0.99)
Higher	6586 (16.3%)	5929 (16.81%)	656 (12.79%)	0.94 (0.82–1.07)
Highest	5315 (13.15%)	4829 (13.69%)	486 (9.48%)	Ref.
Working status				
No	4182 (10.35%)	3135 (8.89%)	1045 (20.38%)	0.38 (0.35–0.41)
Yes	36,228 (89.65%)	32,129 (91.11%)	4083 (79.62%)	Ref.
Type of health insurance				
Non-affiliated	4627 (11.45%)	3653 (10.36%)	973 (18.97%)	0.30 (0.27–0.33)
Subsidised	20,691 (51.2%)	17,630 (49.99%)	3049 (59.46%)	0.51 (0.47–0.55)
Special	1112 (2.75%)	1033 (2.93)	79 (1.54%)	1.21 (0.95–1.55)
Contributory	13,980 (34.6%)	12,948 (36.72%)	1027 (20.03%)	Ref.
Area of residence				
Rural	10,948 (27.09%)	9264 (26.27%)	1682 (32.8%)	0.86 (0.79–0.93)
Urban	29,462 (72.91%)	26,000 (73.73%)	3446 (67.2%)	Ref.
Region of residence				
Amazon-Orinoquía	6923 (17.13%)	5697 (16.16%)	1223 (23.85%)	0.69 (0.55–0.86)
Pacific	5875 (14.54%)	5190 (14.72%)	683 (13.32%)	1.00 (0.82–1.23)
Central	9948 (24.62%)	9028 (25.6%)	914 (17.82%)	1.28 (1.07–1.55)
Atlantic	8399 (20.78%)	7114 (20.17%)	1281 (24.98%)	0.70 (0.58–0.84)
Eastern	9265 (22.93%)	8235 (23.35%)	1027 (20.03%)	Ref.
Have had children				
Yes	33,294 (82.39%)	30,690 (87.03%)	2586 (50.43%)	10.22 (9.46–11.05)
No	7116 (17.61%)	4574 (12.97%)	2542 (49.57%)	Ref.
Final say on own health				
Someone else	4914 (12.16%)	3489 (9.89%)	1423 (27.75%)	0.30 (0.28–0.33)
Woman and other	4612 (11.41%)	4083 (11.58%)	529 (10.32%)	0.41 (0.83–1.01)
Woman alone	30,884 (76.43%)	27,692 (78.53%)	3176 (61.93%)	Ref.

Note: All χ^2 tests were significant (p-values < 0.0001).
[a] 18 missing values in the outcome variable (excluded from analysis).

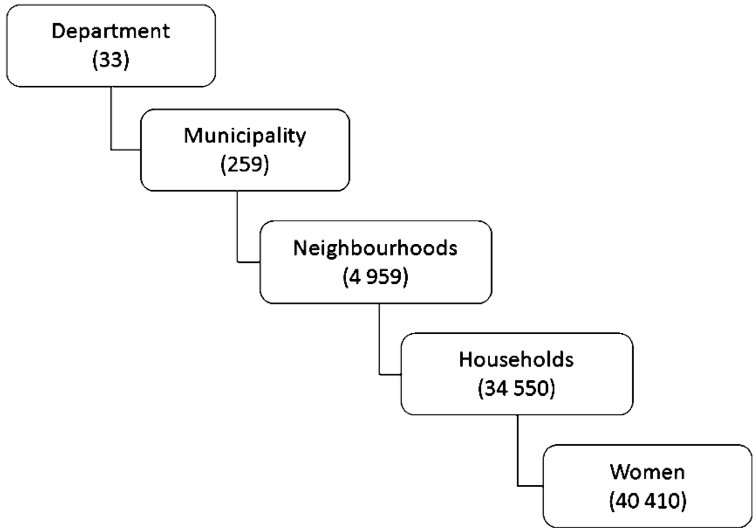

Fig. 3-1. Hierarchical structure of the 2010 NDHS data.

Unconditional analyses between each predictor and the outcome in the multilevel model were conducted and unadjusted odds ratios (UOR) were computed. Risk factors with unconditional *p*-values≤ 0.2 (27) were retained for consideration in the multivariable analysis. A manual backward selection strategy was used to build the multivariable model, removing the predictor with the highest *p*-value, one at a time until only variables with *p*<0.05 remained. Categorical variables with more than two categories were assessed using a type-3 likelihood ratio test. The linearity assumption of age was tested using a quadratic term. Age was used as a four-category variable given that the linearity assumption was not met (*p*<0.001). Observations with missing values were removed from the analysis. Potential confounders were retained in the final model if including the variable changed the coefficients of other variables of interest by >10%. Interactions were assessed between the retained main effects in the multivariable model and rural/urban residence; interactions were considered significant if *p*<0.05. Post hoc comparisons were used to explore differences across multiple categories. A contextual effect measuring the prevalence of no education in the neighbourhoods was examined for an association with having had a Pap test. Finally, an interaction was examined between the prevalence of no education within each neighbourhood and an individual woman's educational level.

Population-averaged odds ratios (OR) and their corresponding 95% confidence intervals (95%CI) were computed using population-averaged coefficients (β_{PA}) calculated from the final multivariable model. Using subject-specific coefficients (β_{SS}) from the final multivariable model, the following formula was employed: $\beta_{PA} \approx \beta_{SS}/\sqrt{(1 + 0.346[\sigma_v^2 + \sigma_\mu^2])}$ (27), where σ_v^2 was the municipality level variance and σ_μ^2 represented the neighbourhood level variance.

In the null model, the variance partition coefficient (VPC) was computed for the neighbourhood and municipality levels to measure clustering in the probability of having had a Pap test. The VPCs were computed using the latent response variables approach (29). For the neighbourhood level, the $VPC = \sigma_\mu^2/(\sigma_v^2 + \sigma_\mu^2 + 3.29)$, and for the municipality level, the $VPC = \sigma_v^2/(\sigma_v^2 + \sigma_\mu^2 + 3.29)$.

Akaike's Information Criterion (AIC) was used to compare the fit of competing models (27). The adequacy of the final model was assessed using plots of the standardised residuals for the neighbourhood and municipality levels, and receiver-operating characteristic (ROC) curves. Statistical analyses were completed in STATA 12 (StataCorp LP, College Station, TX, USA) at a 5% level of significance.

3.3. Results

The mean age of the 40,410 women, who provided information on CC screening, was 32.4 years (SD = 9.0); socio-demographic characteristics of the sample are presented in Table 3-1. In total, 87.3% of 40,392 women reported having had a Pap test. Only 18 women (<0.1%) had missing information about having had a Pap test.

The average numbers of women per neighbourhood and municipality were 8.2 and 156, respectively. Clustering by individual household was not included, as the average number of participating women per household was less than two and 72.9% (29,469/40,410) of units were not replicated. In the null multilevel model (including only the random intercepts), 4.8% and 5.6% of the total variability in the dependent variable was explained by the neighbourhood and municipality levels, respectively. All of the risk factors examined were unconditionally associated with the likelihood of having had a Pap test, *p*-values<0.0001 (Table 3-1). Similar associations were also identified in a sub-group analysis of women aged 25–49 years (data not shown).

3.3.1. Multilevel Multivariable Analysis

Rural/urban residence was initially removed from the model during the backward selection process; all other variables were retained. However, rural/urban residence was identified as a confounder of the variable describing whether the women had the final say on their own health. Additionally, rural/urban residence modified the effect of education (p=0.03), type of insurance (p=0.01), age group (p<0.001), and region of residence (p<0.001). The model with four interaction terms with rural/urban residence fit substantially better (AIC=22,691) than the model without rural/urban residence interactions (AIC=22,729).

The prevalence of no education within the neighbourhoods was a contextual factor also associated with having had a Pap test (p =0.005) (AIC=22,688). Finally, the interaction between the prevalence of no education within the neighbourhoods and the educational level of women was significant (p=0.009). Thus, the final model including the contextual effect and interactions, as described above, had the best fit of those examined (AIC=22,683); this model is presented in the Appendix C. Standardised residuals for the neighbourhoods and municipalities were within the acceptable range of ±3 standard deviations from zero. The ROC curve suggested the model had good discrimination power (area under the curve=0.87; 95%CI=0.87–0.88).

Table 3-2. Population-averaged odds ratios (OR), 95%CI, and *p*-values for risk factors for having had a Pap test among Colombian women from the final multivariable model. Effect estimates reported here were not modified by other variables but were adjusted for other factors in the final three-level logistic regression model (n = 40,392).

Predictors	OR	95%CI	*p**
Wealth quintiles			
Lowest	0.70	(0.58–0.84)	<0.001
Lower	0.85	(0.72–1.00)	0.05
Middle	0.91	(0.79–1.06)	0.23
Higher	0.90	(0.78–1.04)	0.14
Highest	Ref.		
Working status			
No	0.63	(0.57–0.69)	<0.001
Yes	Ref.		
Have had children			
Yes	5.52	(5.06–6.02)	<0.001
No	Ref.		
Final say on own health			
Someone else	0.62	(0.57–0.67)	<0.001
Woman and other	1	(0.90–1.11)	0.99
Woman alone	Ref.		

* *p*-values for subject specific coefficients.

As summarised in Table 3-2, being in the lowest wealth quintile decreased the likelihood of having had a Pap test when compared to being in the highest quintile (OR=0.7, p<0.001). Women whose final health decisions depended on somebody else were less likely to have had a Pap test than those who made their own health care decisions (OR=0.62, p<0.001). Also, Pap testing was less likely among those who were unemployed compared to those who were employed (OR=0.63, p<0.001). In contrast, women with children were more likely to have had a Pap test compared to those who did not have children (OR=5.52, p<0.001).

The difference in the odds of having a Pap test among age groups, type of insurance, and region of residence varied based on rural/urban residence. In both rural and urban areas, women in the youngest age group, living in the Amazon-Orinoquía and Atlantic regions, with subsidised insurance, and those with no insurance were less likely to have had a Pap test (Table 3-3). For instance, women living in rural (OR=0.63, p<0.001) and urban (OR=0.55, p<0.001) areas with subsidised insurance had lower odds of having Pap testing compared to women with contributory insurance.

After accounting for other risk factors, women living in rural areas were less likely to have a Pap test than women in urban areas (Fig. 3-2, Table 3-4). However, the difference between women with limited-to-no education and those with higher education was greater for those living in neighbourhoods with a higher prevalence of no education in both rural and urban areas (Table 3-4). For instance, among women living in neighbourhoods with 0% prevalence of no education, the odds of having a Pap test for women with no education living in rural areas were 0.32 (95%CI=0.20–0.49) times that of women with higher education living in rural areas.

Table 3-3. Population-averaged odds ratios, 95%CI, and p-values for risk factors for having had a Pap test from the final three-level multivariable model. Variables reported here include interactions between rural/urban residence and age group, type of insurance, and region.

Comparisons	OR	95%CI	*p**
Women living in rural areas			
Age group			
18–24 vs. 25–32 years	0.26	(0.22–0.30)	<0.001
18–24 vs. 33–40 years	0.20	(0.16–0.23)	<0.001
18–24 vs. 41–49 years	0.22	(0.18–0.27)	<0.001
25–32 vs. 33–40 years	0.76	(0.63–0.92)	<0.01
Type of health insurance			
Subsidised vs. contributory	0.63	(0.50–0.80)	<0.001
Subsidised vs. special	0.59	(0.44–0.78)	<0.001
Subsidised vs. non-affiliated	1.73	(1.47–2.04)	<0.001
Non-affiliated vs. contributory	0.37	(0.28–0.48)	<0.001
Non-affiliated vs. special	0.35	(0.19–0.65)	<0.001
Region of residence			
Amazon-Orinoquía vs. Eastern	0.63	(0.47–0.85)	<0.01
Amazon-Orinoquía vs. Central	0.38	(0.29–0.50)	<0.001
Atlantic vs. Central	0.48	(0.37–0.63)	<0.001
Atlantic vs. Pacific	0.60	(0.45–0.79)	<0.001
Eastern vs. Central	0.60	(0.46–0.80)	<0.001
Pacific vs. Central	0.47	(0.35–0.63)	<0.001
Women living in urban areas			
Age group			
18–24 vs. 25–32 years	0.29	(0.26–0.32)	<0.001
18–24 vs. 33–40 years	0.17	(0.15–0.20)	<0.001
18–24 vs. 41–49 years	0.14	(0.12–0.16)	<0.001
25–32 vs. 33–40 years	0.60	(0.52–0.70)	<0.001
25–32 vs. 41–49 years	0.47	(0.40–0.56)	<0.001
33–40 vs. 41–49 years	0.79	(0.66–0.94)	<0.01
Type of health insurance			
Subsidised vs. contributory	0.55	(0.50–0.61)	<0.001
Subsidised vs. special	0.59	(0.44–0.78)	<0.001
Subsidised vs. non-affiliated	1.23	(1.09–1.38)	<0.001
Non-affiliated vs. contributory	0.45	(0.40–0.51)	<0.001
Non-affiliated vs. special	0.48	(0.36–0.64)	<0.001
Region of residence			
Amazon-Orinoquía vs. Central	0.65	(0.50–0.84)	<0.001
Atlantic vs. Central	0.58	(0.47–0.72)	<0.001
Atlantic vs. Pacific	0.63	(0.49–0.80)	<0.001
Eastern vs. Central	0.61	(0.49–0.76)	<0.001
Eastern vs. Pacific	0.66	(0.51–0.86)	<0.01
Pacific vs. Central	0.70	(0.53–0.94)	<0.01

Note: Non-statistically significant comparisons ($p \geq 0.05$) are not presented in this table.
* p-values for subject specific coefficients.

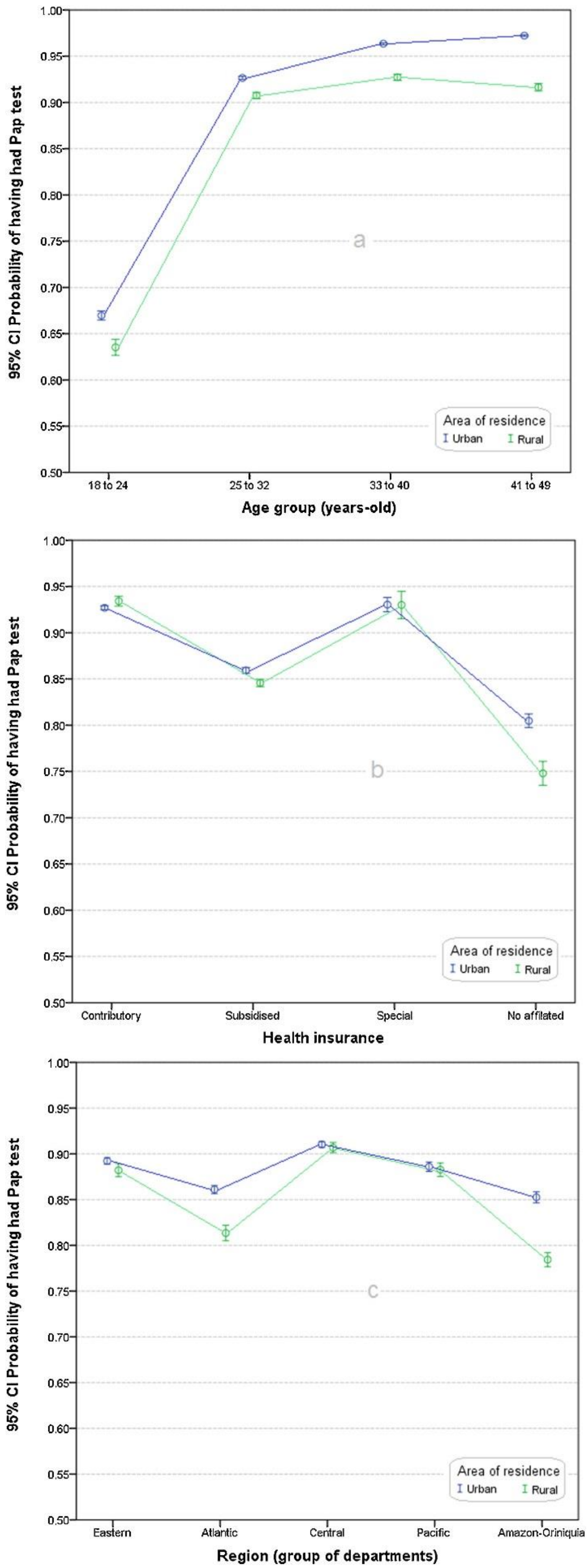

Fig. 3-2. Probability of having a Pap test among women living in rural and urban areas according to age group, type of health insurance, and region of residence. In most comparisons, living in rural settings decreased the probability of having had a Pap test, particularly among young women (a), those with no insurance or with subsidised health insurance (b), and women living in the Atlantic and the Amazon-Orinoquía regions (c).

Table 3-4. Population-averaged odds ratios, 95%CI, and *p*-values for risk factors for having had a Pap test from the final three-level multivariable model. Variables reported here include interactions between rural/urban residence and educational level, considering three scenarios of prevalence of no education in neighbourhoods.

Comparisons	Prevalence of no education in neighbourhoods where women lived								
	0%			20%			50%		
	OR	**95%CI**	***p****	**OR**	**95%CI**	***p****	**OR**	**95%CI**	***p****
Between urban and rural areas [a]									
No education vs. no education	2.14	(1.35–3.39)	<0.001	2.14	(1.35–3.39)	<0.001	2.14	(1.35–3.39)	<0.001
Primary vs. primary	1.39	(1.04–1.87)	0.03	1.39	(1.04–1.87)	0.03	1.39	(1.04–1.87)	0.03
Secondary vs. secondary	1.76	(1.34–2.31)	<0.001	1.76	(1.34–2.31)	<0.001	1.76	(1.34–2.31)	<0.001
Higher vs. higher	1.63	(1.14–2.35)	0.01	1.63	(1.14–2.35)	0.01	1.63	(1.14–2.35)	0.01
Within women living in rural areas									
No education vs. primary	0.43	(0.30–0.61)	<0.001	0.43	(0.34–0.55)	<0.001	0.44	(0.29–0.65)	<0.001
No education vs. secondary	0.43	(0.30–0.62)	<0.001	0.31	(0.24–0.42)	<0.001	0.20	(0.12–0.33)	<0.001
No education vs. higher	0.32	(0.20–0.49)	<0.001	0.19	(0.11–0.32)	<0.001	0.09	(0.03–0.27)	<0.001
Primary vs. secondary	0.99	(0.85–1.15)	0.88	0.73	(0.59–0.90)	0.003	0.46	(0.27–0.76)	0.003
Primary vs. higher	0.74	(0.55–0.98)	0.04	0.44	(0.27–0.72)	0.001	0.21	(0.07–0.63)	0.005
Secondary vs. higher	0.74	(0.57–0.97)	0.03	0.61	(0.37–0.99)	0.05	0.45	(0.14–1.41)	0.17
Within women living in urban areas									
No education vs. primary	0.66	(0.47–0.94)	0.02	0.66	(0.48–0.92)	0.01	0.67	(0.39–1.14)	0.14
No education vs. secondary	0.52	(0.37–0.73)	<0.001	0.38	(0.27–0.54)	<0.001	0.24	(0.13–0.44)	<0.001
No education vs. higher	0.42	(0.29–0.59)	<0.001	0.25	(0.15–0.42)	<0.001	0.12	(0.04–0.37)	<0.001
Primary vs. secondary	0.78	(0.69–0.89)	<0.001	0.57	(0.46–0.72)	<0.001	0.36	(0.21–0.62)	<0.001
Primary vs. higher	0.63	(0.54–0.73)	<0.001	0.38	(0.24–0.60)	<0.001	0.18	(0.06–0.54)	0.002
Secondary vs. higher	0.8	(0.72–0.89)	<0.001	0.66	(0.42–1.04)	0.07	0.49	(0.15–1.53)	0.22

* *p*-values for subject specific coefficients.

[a] Computed for women aged 18–24 years, living in the Amazon-Orinoquía region, and with no health insurance.

3.4. Discussion

The proportion of women who have had at least one Pap test varies across and within countries (14, 15, 30-33). In this 2010 study, we found that 87% of the women in Colombia have ever had a Pap test. Other Colombian studies have identified similar results. In 2006, in Medellín (Eastern region), about 85% of women reported having had a Pap test (32), and in 2005, in a nationwide sample, 90% of women between 25 and 69 years reported having a recent Pap test (15). In contrast, a 1998–1999 study found that 67% of women had a Pap test in a municipality located in the Eastern region (14), and another study in 2007 identified that 56% of university students living in a city located in the Pacific region had at least one Pap test (33). Notwithstanding, our results provide a recent nationwide figure of Pap testing among Colombian women, evaluating differences by socioeconomic and contextual factors.

Several Colombian (15, 16, 32) and Latin American studies (34) suggest the existence of substantial differences in Pap test access based on the socioeconomic conditions of women. Moreover, living in rural areas exacerbated other challenges to Pap testing. Soneji and Fukul (34) found that rural residence significantly decreased the probability of having a recent Pap test in Nicaragua, Ecuador, and Peru. In Colombia, women living in rural regions have a lower health status (35) and face high poverty levels, poor possibilities for having a job and receiving a fair income, and limited access to housing, education and health care (36). Other problems in rural Colombia are the distance between one's home and a health care centre (14, 24), violence and war, high vulnerability of youth and women (37), and a lack of knowledge about the SGSSS and the health care rights that citizens have (38).

We observed that having a rural/urban residence modified the effect of age, type of health insurance, region, and education on having had a Pap test. Other authors have reported that younger women have reduced probabilities of having Pap test (14, 16, 25, 31, 32), especially if residing in rural areas (14). Although better coverage of subsidised health insurance in rural areas has been reported in Colombia (21), people with subsidised health insurance receive 40% less health care compared to those with contributory health insurance (21). In this regard, our results also show that women in rural areas with subsidised insurance have a lower probability of having had a Pap test. This finding supports that having health insurance does not ensure accessing health care services in Colombia (24). Not having health insurance is also a critical factor for not having a Pap test (15, 25), especially in rural areas (15). Barriers for enrolling, co-payments established by health insurance companies, or lack of specialists are difficulties faced by rural people with no insurance in Colombia (39). Additionally, Pap screening in the Atlantic and Amazon-Orinoquía regions is particularly poor (40), especially in rural areas, as we identified.

Our study demonstrates the remarkable role of education at the individual and neighbourhood levels. Limited access to education decreases the Pap test uptake, particularly in rural locations. Education is critical to access information about CC screening programmes (15, 32, 34), know the role of the human papillomavirus infection (41) and other risk factors (30), and decrease myths about the Pap test (42). Moreover, lack of awareness of Colombian citizen health care rights makes Colombians more vulnerable by limiting their capacity to access health services and perpetuating the ineffectiveness of bureaucracy (24). This highlights the importance of education in access to health care in Colombia, including Pap testing. Coughlin et al. (43) have suggested that the context has a supplementary role in the uptake of Pap tests. We found that the differences among women with different educational backgrounds were greater in areas that had a higher prevalence of no education, suggesting that the impact of education on Pap testing goes beyond individual educational achievement. Additionally, negative opinions of neighbours or peers about Pap screening influence the willingness of women to have the test (44, 45). Certain attitudes of partners could make participating in CC screening programmes difficult (44); machismo and jealously of partners are obstacles women experience when seeking a Pap test, especially if the health care provider is male (45, 46). In contrast, support from partners, children, and family members increases women's likelihood of having a Pap test (44). Furthermore, feeling ownership of one's body is described as a critical factor for Pap test uptake (45, 46), explaining why women who made their own health care decisions were more likely to have had a Pap test.

Unemployment has been also associated with lack of autonomy and decreased access to information about the Pap test (25), explaining why not working was associated with lower reports of Pap test uptake. Notwithstanding, having a job in Colombia does not necessarily mean having health insurance (47) despite affiliation with a health insurance provider is mandatory for employees and self-employed individuals (17). Another obstacle for having Pap testing is that women are implicitly acknowledging to family and peers that they are or have been sexually active (44, 48); fear of negative reactions from parents or others in authority could be a barrier for Pap screening by young and single women (44). On the other hand, having children has been associated with increased uptake of Pap tests (15, 25, 48) because women want to be healthy so they can look after their families (44), and also because maternity often exposes women to health care services.

One of the limitations of the present study is that self-reported information might not represent the actual Pap test coverage in Colombia. Test uptake could be overestimated or underestimated because of social desirability and lead to misclassification bias (31). Using objective measures about CC screening has been recommended to overcome this problem (49). Because this was a cross-sectional study, caution is necessary in assuming cause-effect relationships between risk factors and Pap test uptake, particularly for factors where risk changes over time.

In conclusion, 13% of the women who participated in this study and were eligible for CC screening in Colombia never had a Pap test. This nationwide study demonstrates the continued presence of inequities and a social gradient for the uptake of Pap tests which need to be considered when planning and evaluating CC programmes. The likelihood of having had a Pap test was lowest among poor, unemployed, and women whose health care decisions depended on others. Furthermore, having a rural residence decreased the probability of Pap testing among younger women, those with no health insurance, living in isolated regions, and those with limited-to-no education. A context of high prevalence of no education in the neighbourhood decreased Pap test uptake, particularly among women living in rural areas. Specific strategies should be developed to consider individual and contextual factors when designing new approaches to increase participation of women in CC screening programmes. Efforts to improve access to CC screening should focus on disadvantaged populations, especially among those living in rural/isolated areas.

3.5. References

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CHAPTER 4 – SPATIAL VARIATIONS IN CERVICAL CANCER PREVENTION IN COLOMBIA: GEOGRAPHICAL DIFFERENCES AND ASSOCIATED SOCIO-DEMOGRAPHIC FACTORS

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Chapter 4 builds on the individual and local factors associated with primary and secondary cervical cancer (CC) prevention presented in the previous chapters. Chapter 4 presents the results of spatial clustering analysis and risk ratio maps that identified an increased risk of a lack of HPV vaccination awareness and Pap testing among socially deprived departments and those adjacent to the Colombian border. This study provides evidence of similar spatial patterns in access to primary and secondary CC prevention by Colombian departments, after accounting for area-based socio-demographic factors, such as percentages of women with lack of education, subsidised insurance, and rural residence. The study further identifies departments where the low rates of primary and secondary CC prevention are not completely explained by the individual risk factors identified in previous chapters, suggesting the need for further study. The study results could guide decision makers and health care practitioners to target high-risk areas in Colombia for CC prevention programmes.

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4.1. Introduction

Worldwide, 528,000 women were diagnosed with cervical cancer (CC) and 266,000 CC related deaths were reported in 2012 (1). Cervical cancer is a preventable disease (2) that inequitably impacts less developed regions of the world (1). Thousands of young women in developing nations continue to be diagnosed and die due to CC (3). In Latin America, nearly 69,000 new CC cases were estimated in 2012. The 2012 age-standardised incidence rate of CC in Colombia was 18.7 per 100,000, which is higher than the rates for Costa Rica, Chile, and Brazil, but lower than those for Bolivia, Nicaragua, and Paraguay (1). Limited access by women to CC prevention programmes (4), socio-cultural and economic barriers, and organisational challenges to CC prevention programmes have been described as obstacles to decreasing the burden of CC in Latin America (5).

A combination of primary and secondary strategies is recommended for preventing CC (5, 6). While primary prevention aims to reduce the occurrence of disease among susceptible individuals (e.g. through disease education, vaccination, health promotion), secondary prevention seeks to reduce the burden of illness and improve outcomes by case-finding early in the disease process (e.g. through screening) (7). Although education has been described as a key factor for the success of CC prevention programmes (8), Colombian studies have shown limited knowledge and awareness of the human papillomavirus (HPV) and its role in the development of CC (9), as well as the importance of HPV vaccination (10, 11). While in one study 77% of Colombian women reported participating in CC screening programmes (i.e., Pap testing) in the previous three years, there are still many women with limited access to Pap testing in Colombia (4).

Among Colombian women, different factors have been associated with the lack of Pap testing and not having heard of HPV vaccination. Having a limited education (9), living in rural areas (11), and having subsidised health insurance (11) have been associated with limited access to CC prevention programmes. Population density might also be an indicator of whether women participate in CC prevention initiatives, because of the association between population density and access to health care (12).

While spatial variations in CC mortality have been described (13) across the 33 Colombian administrative divisions, called departments (32 departments and the Capital District, Bogotá, D.C.), spatial analyses of primary and secondary CC prevention have not been reported to date. The spatial analysis of primary and secondary CC prevention data could improve our understanding of geographical variations in risk (14) and identify any spatial patterns and disease clusters (15).

The overall goal of this study was to identify spatial variations in both the department frequencies of young women who have never heard of HPV vaccination and the department frequencies of young women in Colombia who have never had Pap testing. The first objective of this study was to use global and local tests for clustering to describe spatial patterns in the department frequencies of women aged 13-49 years who had not heard of HPV vaccination (NHrd-Vac) and the department frequencies of women aged 18-49 years who had not had Pap testing (NHd-Pap). The second objective was to examine whether the identified spatial patterns could be explained by department-level differences in socio-demographic attributes among women, including a lack of formal education, having subsidised health insurance, and living in rural areas, as well as differences in department population density.

4.2. Methods

4.2.1. Data Sources

Data aggregated by Colombian departments (Appendix D) were used for this ecological study. The data were obtained from the 2010 Colombian National Demographic and Health Survey (NDHS) and the Colombian National Administrative Department of Statistics (*Departamento Administrativo Nacional de Estadística*–DANE). The 2010 NDHS was a representative nationwide survey comprising health information reported by 53,521 women aged 13-49 years (16). The 2010 department total population estimates used in this study were made available by DANE (17).

Two CC prevention outcomes were summarised for each department from the 2010 NDHS: 1) the relative frequency of NHrd-Vac in women aged 13-49 years; and 2) the relative frequency of

NHd-Pap in women aged 18-49 years. To compute the relative frequency of NHrd-Vac women in a given department, the numerator was the department number of women aged 13-49 who never heard of HPV vaccination (those who had not heard of HPV and a vaccine to prevent CC), and the denominator was the total department number of women aged 13-49 years surveyed in the 2010 NDHS. To compute the relative frequency of NHd-Pap women by department, the numerator was the department number of women aged 18-49 years who reported never having had Pap testing, and the denominator was the department total number of eligible women aged 18-49 years surveyed about CC prevention in the 2010 NDHS. According to the NDHS, women eligible to answer CC questions were those 18 years or older, who had experienced intercourse, and did not have a hysterectomy (16).

To describe socio-demographic risk factors, department percentages of women with no education (hereinafter called no education), having subsidised health insurance (hereinafter called subsidised insurance), and living in rural areas (hereinafter called rurality) were calculated for women aged 13-49 and 18-49 years. These percentages were used as potential risk factors for NHrd-Vac and NHd-Pap. Furthermore, the 2010 population density (hereinafter called density) was calculated per department as the total department population divided by the area of the department (in km^2). The five geographic regions established in the 2010 NDHS were used to summarise results across departments (Appendix D).

4.2.2. Spatial Clustering

For both outcome variables (frequencies of NHrd-Vac and NHd-Pap women), global and local clustering tests were used to identify aggregations of cases (18). To determine if global clustering was present, a global Moran's I for each study outcome was calculated using the empirical Bayes index proposed by Assunção and Reis (19, 20) via Monte Carlo simulation through the *spdep* package in the R software (21). This index used either the age-specific number of NHrd-Vac women or the number of NHd-Pap women as the numerator and the total department age-specific number of women as the denominator to account for the underlying population at risk (19). Neighbouring departments were defined using a first-order Queen argument, accounting for the spatial relationships of departments sharing borders and corners (20).

Kulldorff's spatial scan statistics (SaTScan software, version 9.4.1) were used to identify the local clusters for each study outcome (22). The null hypothesis for the underlying test assumed that the risk of NHrd-Vac women and then NHd-Pap women was equally likely inside and outside a circular window that summarised the observed and expected outcomes for each department (22). This test was computed using a purely spatial Poisson probability model via Monte Carlo simulation (23) with the maximum spatial cluster size of the population at risk set to 50% of population at risk.

4.2.3. Model Building

4.2.3.1.Expected number of cases

The expected numbers of NHrd-Vac and NHd-Pap women were estimated for each of the Colombian departments. These estimates were determined assuming a constant risk across all departments in the country (24) using the formula (25): $e_i = (\Sigma_i y_i / \Sigma_i y_i^P) \cdot y_i^P$, where, for department i, e_i was the expected number of cases for an outcome in the department, y_i was the observed number of cases in the department, and y_i^P was the number of women surveyed in the NDHS in the department. To estimate the expected number of NHrd-Vac women, y_i was the number of surveyed women aged 13-49 years in department *i* who never heard of HPV vaccination, and y_i^P was the number of surveyed women aged 13-49 years in department i. To estimate the expected number of NHd-Pap women, y_i was the number of surveyed women aged 18-49 years in department i who reported never having had Pap testing, and y_i^P was the number of at-risk women aged 18-49 years surveyed in department i.

4.2.3.2.Modelling department risk of NHrd-Vac and NHd-Pap

Two multilevel Poisson models were created in STATA 12 (StataCorp LP, College Station, TX, USA) using generalised linear mixed models (GLMM) with department number as a random intercept. These models were used to assess how the socio-demographic factors of interest were associated with the department relative frequencies of NHrd-Vac and the department relative frequencies of NHd-Pap women.

Due to unmet linearity assumptions between no education and density and the dependent variables, no education and density were recoded as binary variables. The resulting categories of no education were created based on the national prevalence of no education for women aged 13-49 and for women aged 18-49. Departments were classified for each age group as "1=at or above the national prevalence of no education" or "0=below the national prevalence of no education." For the NHrd-Vac model, the categories of population density were created based on the 2010 Colombian population density. Departments were classified as "1=below the national population density" or "0=at or above the national population density."

Unconditional analyses were completed, using $p<0.2$ to identify variables to be considered in subsequent model building (26). A manual forward strategy was followed, using likelihood ratio tests to compare full and reduced models.

Confounding factors were identified and retained in the model if including the factor resulted in a >10% change in a coefficient estimate for another study variable. Then, for each of the two resulting multivariable models, all possible two-way interactions were assessed between significant risk factors and confounders and were retained and reported if $p<0.05$.

To confirm the variables included in the two STATA-built models, the models were re-examined in WinBUGS version 1.4.3 (27). In each model, two zero mean Gaussian random effects were incorporated to account for the spatially structured (μ) and unstructured (v) heterogeneity (28). The resulting model for department *i* had the form: $\ln y_i = \ln e_i + \alpha + \beta_1 X_1 + \beta_2 X_2 + \ldots + \beta_m X_m + \mu_i + \upsilon_i$, where the expected numbers of cases (e_i) computed for each department were used as the offset variables (28); and α and the betas (i.e. β_1, β_2, …, β_m) respectively represented the intercept and the coefficients of the independent variables $X_1, X_2, \ldots, X_m$ in the fixed-effects model. Additionally, μ_i and υ_i respectively represented the spatially structured and unstructured heterogeneity for department i. The exponentiated value of $(\ln(y_i) - \ln(e_i))$ or (y_i/e_i) represented the predicted risk of the outcome in each department relative to the expected value based on the national average risk or the predicted risk ratio for the department.

To represent the magnitude of the spatially structured and unstructured heterogeneity on a scale comparable to the fixed effects in the two models, median risk ratio ratios (RRR_M) were calculated for each random effect using an adaptation of the formula for the median incidence rate ratio (29): $RRR_M(\sigma_g) = \exp(0.954 \cdot \sigma_g)$, where σ_g was the standard deviation of either the spatially structured (g=μ) or unstructured (g=v) random effects in each of the models.

4.2.3.3.Bayesian analyses

The WinBUGS models used Bayesian applications to estimate the parameters and random effects in our models. Non-informative priors (i.e. priors with a normal distribution, a mean of 0, and a large variance or small precision equal to 0.00005) were used for all regression coefficients in both models (30).

The structured spatial heterogeneity (μ_i) incorporated a Gaussian conditional autoregressive (CAR) prior distribution as the spatial correlation structure (28, 31). The unstructured heterogeneity (υ_i) was assigned a gamma distribution for the precision (or inverse variance) with a mean of 0.5 and a variance of 0.0005 (28).

Estimates of differences among predicted values associated with fixed effects of the socio-demographic factors were reported from the Bayesian analyses as risk ratio ratios (RRR) along with 95% credible intervals (Cr. I) (32). Risk ratio (RR) maps (28) were created in ArcGIS version 10.1 (ESRI, Redlands, California, USA) to visually depict quartiles of the differences observed among departments.

The burn-in period (T=100,000 time steps) was selected for the two models based on characteristics of the Brook-Gelman-Rubin diagnostic plots (33). The time between independent samples was estimated to be 10,000 (burn-in period/10) (34). In order to have sufficient power for the analysis, based on the number of variables in the analysis, the number of independent data points required for the analysis was estimated to be 100 (35). Combining these two estimates, the simulation for each Markov chain needed to be run for a minimum of 1,000,000 time steps after the burn-in period. To ensure that any data generated from the non-stationary distribution of the Markov chain minimally biases the parameter estimates, the burn-in period should be less than 5% of the length of the simulation (34); following this, each Markov chain was simulated for T=2,100,000 time steps. We sampled every 100th observation after the burn-in period to decrease the correlation between successive sample points (36). To decrease the errors associated with the estimates for the models, four Markov chains were employed for each model (36).

To confirm the Markov chains were sampling from their stationary distributions, we used the convergence diagnosis and output analysis (CODA) for Markov chain Monte Carlo (37) calculated using the R software package (21). Specifically, the Gelman and Rubin (33), Geweke (38), Raftery-Lewis (39), and Heidelberger-Welch (40) diagnostic tests were computed on data sampled at every time step (32). The Raftery-Lewis diagnostic was calculated on the data generated via sampling every 100 time-steps (41).

4.3. Results

Of the 53,521 women aged 13-49 years who participated in the 2010 NDHS, 39,158 (73.2%) reported NHrd-Vac. Of the 40,392 women aged 18-49 years who answered CC prevention questions, 5128 (12.7%) reported NHd-Pap. The percentage of NHrd-Vac women ranged from 52.2% in Bogotá, D.C to 90.6% in Vaupés and the percentage of NHd-Pap women ranged from 7.6% in Antioquia to 34.4% in Guaviare (Table 4-1). By region, Amazon-Orinoquía had the highest percentage (85.5%) of women NHrd-Vac, while for NHd-Pap, the Atlantic and Amazon-Orinoquía regions had the highest percentages (16.4% and 16.3%, respectively) compared to the other regions.

Table 4-1. Frequency distributions of women aged 13-49 years who never heard of HPV vaccination (N=53,521) and women aged 18-49 years who reported ever having had Pap testing (N=40,392) by Colombian departments, 2010.

Region	**Department**	**Women aged 13-49 years who had not heard of HPV vaccination (%)**	**Women aged 18-49 years who had not had Pap testing (%)**
	National	39,158 (73.2)	5128 (12.7)
Eastern	Bogotá D.C	1926 (52.2)	269 (9.2)
	Boyacá	1142 (74.7)	112 (9.9)
	Cundinamarca	1103 (69.2)	143 (11.8)
	Meta	1054 (77.4)	96 (9.1)
	Norte de Santander	1458 (75.4)	215 (14.7)
	Santander	1479 (74.4)	192 (13.0)
Atlantic	Atlántico	1360 (72.8)	216 (16.0)
	Bolívar	1106 (74.9)	188 (17.4)
	Cesar	935 (74.9)	138 (14.8)
	Córdoba	1119 (70.8)	144 (12.8)
	La Guajira	926 (78.7)	166 (19.6)
	Magdalena	965 (73.2)	139 (14.3)
	San Andrés y Providencia	716 (57.0)	208 (19.4)
	Sucre	1195 (77.2)	194 (17.2)
Central	Antioquia	2370 (68.5)	201 (7.6)
	Caldas	1207 (65.2)	118 (8.3)
	Caquetá	951 (81.1)	126 (14.4)
	Huila	938 (74.3)	103 (10.8)
	Quindío	1342 (68.8)	118 (8.0)
	Risaralda	1341 (68.3)	131 (8.7)
	Tolima	1048 (72.9)	117 (10.8)
Pacific	Cauca	1020 (77.3)	113 (11.4)
	Chocó	1047 (85.5)	175 (18.7)
	Nariño	1245 (83.8)	116 (10.4)
	Valle del Cauca	2339 (63.1)	279 (9.8)
Amazon-Orinoquía	Amazonas	1239 (86.8)	194 (25.7)
	Arauca	912 (84.4)	99 (12.2)
	Casanare	978 (83.5)	86 (9.6)
	Guainía	870 (85.5)	85 (10.0)
	Guaviare	916 (82.7)	296 (34.4)
	Putumayo	994 (84.2)	88 (9.5)
	Vaupés	1055 (90.6)	167 (22.3)
	Vichada	862 (89.0)	96 (10.1)

The national prevalence of no education was 2.1% and 2.5%, respectively, for women aged 13-49 and 18-49 years. The percentage of women aged 13-49 years with subsidised insurance varied from 22.6% in Bogotá, D.C to 73.4% in Vaupés. For women aged 18-49, the percentage with subsidised insurance ranged from 21.9% in Bogotá, D.C to 73.8% in Chocó. The percentages of Colombian women aged 13-49 and 18-49 years living in rural areas were 27.3% and 26.6%, respectively. Women aged 13-49 and 18-49 years in the Amazonas department were most likely to live in rural areas (60.1% and 57.8%, respectively). The national population density was 40.4 per km^2 and ranged from 0.64 per km^2 in Vichada to 4588 per km^2 in Bogotá, D.C.

4.3.1. Spatial Clustering

There were significant global spatial autocorrelations among the relative department frequencies of NHrd-Vac (Moran's I=0.49, p=0.0003) and NHd-Pap (Moran's I=0.34, p=0.004) women. Via Kulldorff's spatial scan statistic, three significant clusters for both outcome variables were identified (Fig. 4-1). Fig. 4-1(A) illustrates the clusters for NHrd-Vac women. The first cluster (RR=1.18, p<0.0001) in dark grey includes ten departments. The second cluster (RR=1.13, p<0.0001) in medium grey includes three departments. The third cluster (RR=1.17, p<0.0001) in light grey consists only of the department of Chocó. Fig. 4-1(B) illustrates the clusters for NHd-Pap women. The first cluster (RR=2.36, p<0.001) in dark grey encompasses three departments. The second cluster (RR=1.36, p<0.001) depicted in medium grey includes six departments. Finally, the third cluster (RR=1.49, p<0.001) in light grey consists solely of the department of Chocó.

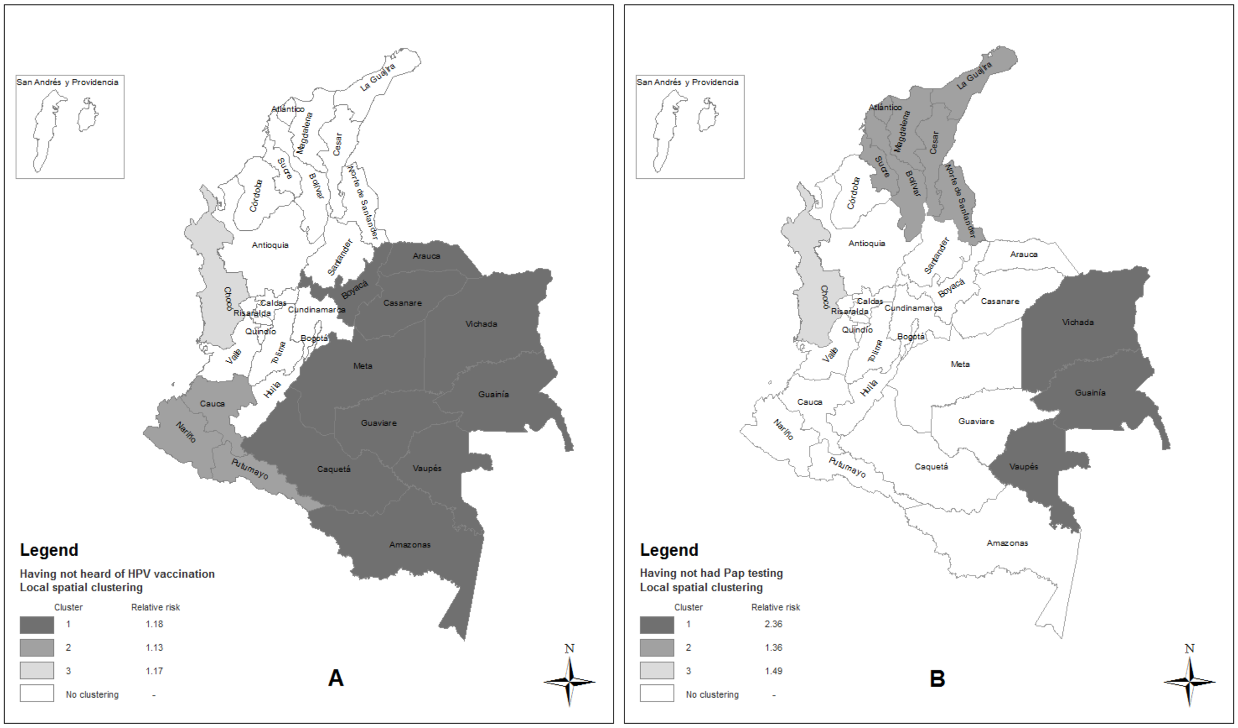

Fig. 4-1. Kulldorff's spatial scan statistic identified three clusters with their respective risk ratios for each CC prevention outcome. (A) Department clusters based on the relative frequency of women who had not heard of HPV vaccination. (B) Department clusters based on the relative frequency of women who had not had Pap testing.

4.3.2. Model Building and Results of Bayesian Analyses

For the models of NHrd-Vac and NHd-Pap, the informal and formal diagnostic assessments for the Bayesian models suggested that the Markov chains reached their stationary distributions and that sufficient samples were collected from these distributions. For example, the results of the Gelman and Rubin diagnostic illustrated that the potential scale reductions estimated for the models were approaching 1, suggesting that the simulated values were drawn from the stationary distribution. For our choice of burn-in period and simulation run length for both the NHrd-Vac and NHd-Pap models, the Raftery-Lewis diagnostic computed dependence factor values that were lower than 5. The *p*-values in the Geweke and the Heidelberger-Welch diagnostics were greater than 0.05 for both models.

4.3.2.1.Department risk of women not having heard of HPV vaccination

The unconditional analysis of potential predictors for the department risk of NHrd-Vac relative to the national average, identified no education (*p*=0.002), subsidised insurance (*p*<0.0001), rurality (*p*<0.0001), and density (*p*<0.0001) as possible predictors for the risk of NHrd-Vac. In the final Bayesian model accounting for spatially structured and unstructured heterogeneity by department, only subsidised insurance and density were retained. No confounders or significant interactions were identified. The Bayesian spatial analysis identified the same fixed effects structure as the frequentist GLMM model including a random intercept for department.

In a given department, for every 10% increase in the percentage of women with subsidised insurance, the RR of NHrd-Vac increased by 1.08 times (95%Cr. I=1.06-1.09) (Table 4-2). Additionally, the department RR of NHrd-Vac increased by 1.07 (95%Cr. I=1.02-1.12) times if the population density was below the national average population density. Furthermore, the RRR_M was 1.02 (95%Cr. I=1.01-1.04) for the spatially structured heterogeneity (μ) and 1.03 (95%Cr. I=1.02-1.05) for the unstructured heterogeneity (v). These results suggest that the relative difference in the risk of NHrd-Vac between two randomly selected departments with the same covariate pattern relative to the national average was 1.02 times higher for departments that were neighbours (μ) than for departments that were not, and differed by 1.03 times due to heterogeneity associated with other unmeasured department factors not explained by neighbourhood relationships (v).

Table 4-2. The final multivariable model showing the association between socio-demographic factors and the department risk of having not heard of HPV vaccination among women aged 13-49 years relative to the national average for Colombia, 2010.

Variables	RRR	95%Cr.I
Subsidised insurance[a]	1.08[b]	(1.06-1.09)
Population density		
Below the national average population density	1.07	(1.02-1.12)
At or above the national average population density	Ref.	

[a] Department percentage of women with subsidised insurance
[b] Relative change associated with a 10% increase in subsidised insurance

4.3.2.2.Department risk of women not having had Pap testing

The unconditional analysis for the department risk of NHd-Pap relative to the national average, identified no education ($p<0.0001$), subsidised insurance ($p=0.001$), and rurality ($p=0.006$) as significant risk factors. Density was not a significant predictor ($p=0.2$) and was excluded from the model. In the final multivariable model, no education, rurality, and subsidised insurance were retained. Subsidised insurance was identified as a confounder for the association between no education and the department risk for NHd-Pap. The relative effect of the percentage of women living in rural areas varied depending on whether the percentage of women with no education was above or below the national average ($p=0.009$). The final fixed effects included in the NHd-Pap model formed using Bayesian spatial analysis were the same the frequentist random intercept GLMM.

For each 10% increase in the percentage of women living in rural areas in departments at or above the national prevalence of no education, the RR of having more observed than expected cases of NHd-Pap women increased by 15% (RRR=1.15; 95%Cr. I=1.02-1.30) (Table 4-3). However, no significant differences in the RR of NHd-Pap were observed with an increasing percentage of women living in rural areas in departments below the national prevalence of no education (RRR=0.97; 95%Cr. I=0.86-1.10).

Table 4-3. The final multivariable model showing the association between socio-demographic factors and the department risk of having not had Pap testing among women aged 18-49 years relative to the national average for Colombia, 2010.

Variables	RRR	95%Cr.I
Subsidised insurance[a]	1.06[f]	(0.94-1.19)
Rurality[b] **in departments at or above the national prevalence of no education**[c,d]	1.15[f]	(1.02-1.30)
Rurality[b] **in departments below the national prevalence of no education**[c,d]	0.97[f]	(0.86-1.10)
Prevalence of no education (in an area with 26.6%[e] **of rurality)**		
At or above the national average	1.32	(1.03-1.66)
Below the national average	Ref.	

[a] Department percentage of women with subsidised insurance
[b] Department percentage of women living in rural areas
[c] National prevalence of no education among women 18-49 years= 2.54%
[d] Interaction between percentage of women living in rural areas and whether the department was below the national prevalence of no education (p=0.009)
[e] National percentage of women aged 18-49 years living in rural areas= 26.6%
[f] Relative change associated with a 10% increase

In a model centred at the national percentage of women living in rural areas (26.6%), departments where the percentage of women with no education was at or above the national prevalence of 2.54% were at 1.32 (95%Cr. I=1.03-1.66) times higher risk of NHd-Pap than those departments below the national prevalence. Similarly, in a model centred at the 75th percentile of women living in rural areas (39.3%), departments with a percentage of women with no education at or above the national prevalence of no education were at greater risk (RRR=1.63; 95%Cr. I=1.27-2.07) of NHd-Pap than departments below the national prevalence of no education. In contrast, in a model centred at the 25th percentile of women living in rural areas (21.4%), this difference was smaller and not significant (RRR=1.21; 95%Cr. I=0.92-1.58).

Additionally, the median RRR of NHd-Pap comparing two randomly selected departments with the same covariate patterns was 1.09 (95%Cr. I=1.01-1.28) for departments that were neighbours (μ), and 1.19 (95%Cr. I=1.02-1.29) associated with heterogeneity due to unmeasured department factors not explained by location (v).

4.3.2.3.Risk ratio maps of NHrd-Vac and NHd-Pap

The predicted department RRs for NHrd-Vac and NHd-Pap including covariates and the spatially structured (μ) and unstructured heterogeneity (v) were summarised in Fig. 4-2.

Chocó, in the Pacific region, and the departments located in the Amazon-Orinoquía region, with the exception of Casanare, were in the highest risk range of NHrd-Vac relative to the national average, Fig. 4-2(A). The highest risk range of NHd-Pap, Fig. 4-2(B), was identified in three departments in the Atlantic region (La Guajira, Sucre, and Bolívar), the department of Chocó (Pacific region), and four departments of the Amazon-Orinoquía region (Vichada, Guainía, Vaupés, and Amazonas).

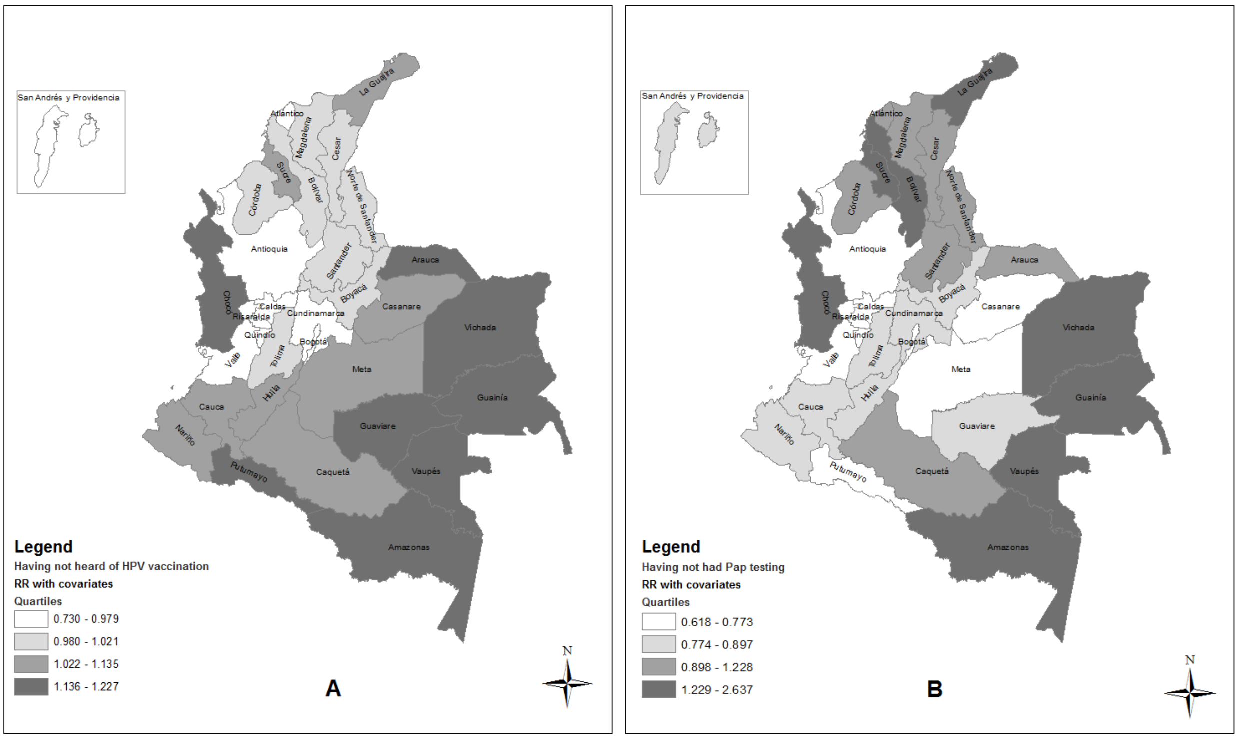

Fig. 4-2. Risk of not having heard of HPV vaccination (A) and not having had Pap testing (B) relative to the national average after accounting for the fixed effects, as well as the spatially structured and unstructured heterogeneity included in the final multivariable models for Colombia, 2010. The darker the shade of grey the higher the risk ratio in the department.

Fig. 4-3(A) depicts the differences in the department RR for NHrd-Vac relative to the national average associated with measured risk factors included as fixed effects in the final model. The departments coloured in dark grey (i.e. Chocó, Arauca, Vichada, Guainía, Guaviare, Vaupés, Amazonas, and Putumayo; which are located in the Pacific and Amazon-Orinoquía regions) had the greatest component of their RR of NHrd-Vac explained by department differences in subsidised insurance and population density.

Fig. 4-3(B) shows the component of the RR explained by the location of each department and the relationship among neighbours (μ). The departments of Cesar, Magdalena, Atlántico, and Bolívar (Atlantic region), as well as departments located in the Eastern (i.e. Norte de Santander, Santander, and Boyacá) and Central regions (Antioquia) were in the highest RR range associated with spatial clustering of NHrd-Vac in women not explained by the fixed effects in the model.

Fig. 4-3(C) depicts the differences in RR associated with the residual unstructured heterogeneity among departments (v). The departments of Atlántico (Atlantic region), Antioquia and Tolima (Central region), Santander and Norte de Santander (Eastern region), Nariño (Pacific region), Meta (Eastern region), and Vichada (Amazon-Orinoquía region) were in the highest RR range not explained by either the fixed effects in the final model or the heterogeneity associated with the spatial location.

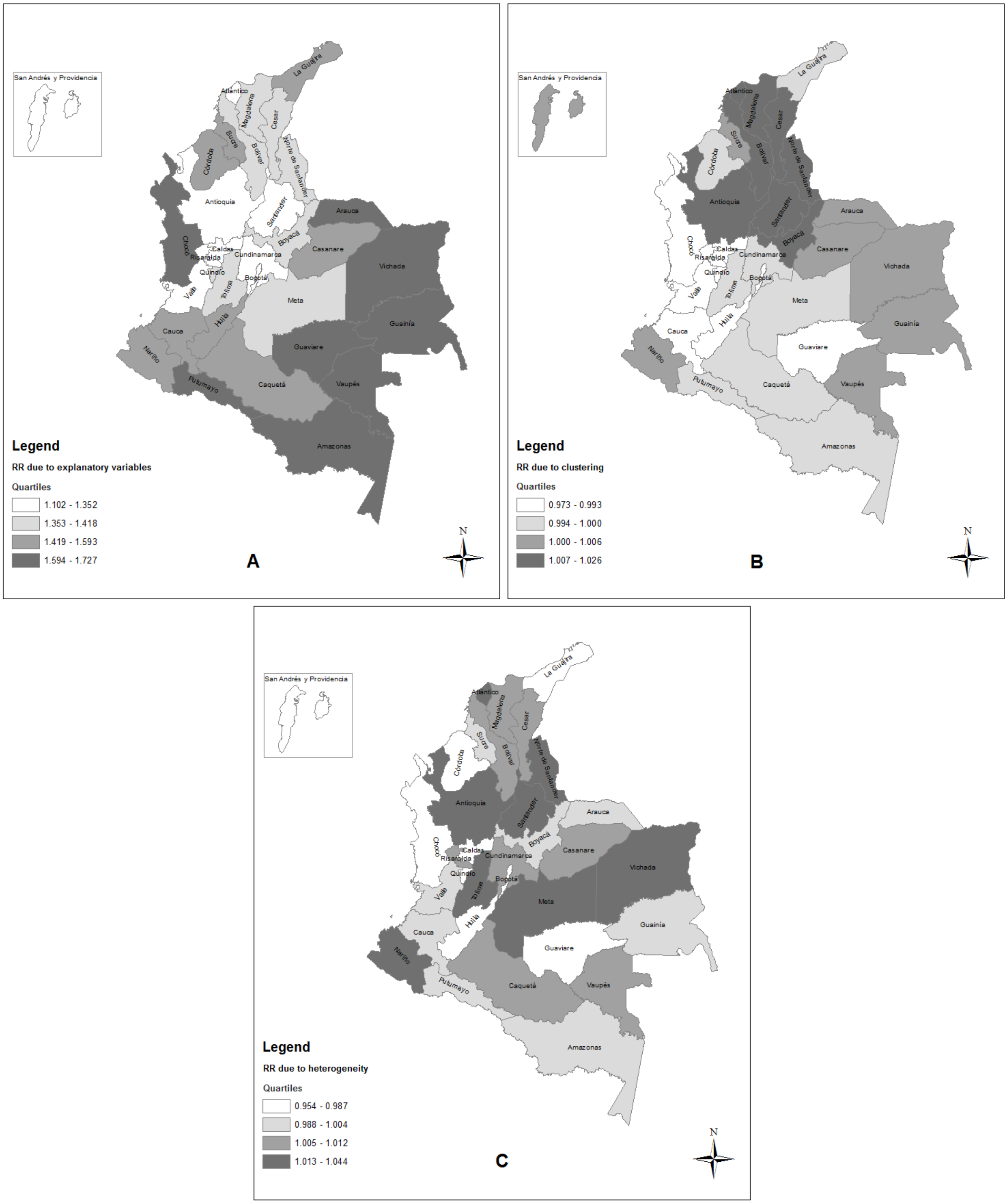

Fig. 4-3. Maps of the department risk ratios (RR) for not having heard of HPV vaccination in Colombia, 2010. (A) RR explained by fixed effects in the final multivariable model. (B) RR explained by the spatial structured heterogeneity (μ) or clustering. (C) RR explained by the unstructured heterogeneity (v) in the model. The darker the shade of grey the higher the risk ratio in the department attributed to the model component.

Fig. 4-4(A) represents the department variation in the RR for NHd-Pap explained by the fixed effects in the final multivariable model. Departments located in the Amazon-Orinoquía (i.e. Vichada, Guainía, Guaviare, Vaupés, and Amazonas), Pacific (i.e. Chocó), and Atlantic (i.e. La Guajira and Córdoba) regions had the greatest component of their RR of NHd-Pap attributed to department differences in no education and women living in rural areas, adjusted for the percentage with subsidised insurance.

Differences in the RR associated with spatial clustering (μ) are shown in Fig. 4-4(B). Departments located in the Atlantic (i.e. La Guajira, Atlántico, Cesar, and Bolívar), Eastern (i.e. Santander and Norte de Santander), and Amazon-Orinoquía (i.e. Guainía and Vaupés) regions had the highest RR range associated with their location.

Fig. 4-4(C) shows the component of the RR explained by the residual unstructured heterogeneity (v). Departments located in the Atlantic (i.e. Atlántico and Bolívar), Eastern (i.e. Norte de Santander and Santander), and Amazon-Orinoquía (i.e. Vichada, Guainía, and Vaupés) regions were in the highest RR range attributed to unmeasured risk factors that were not spatially correlated.

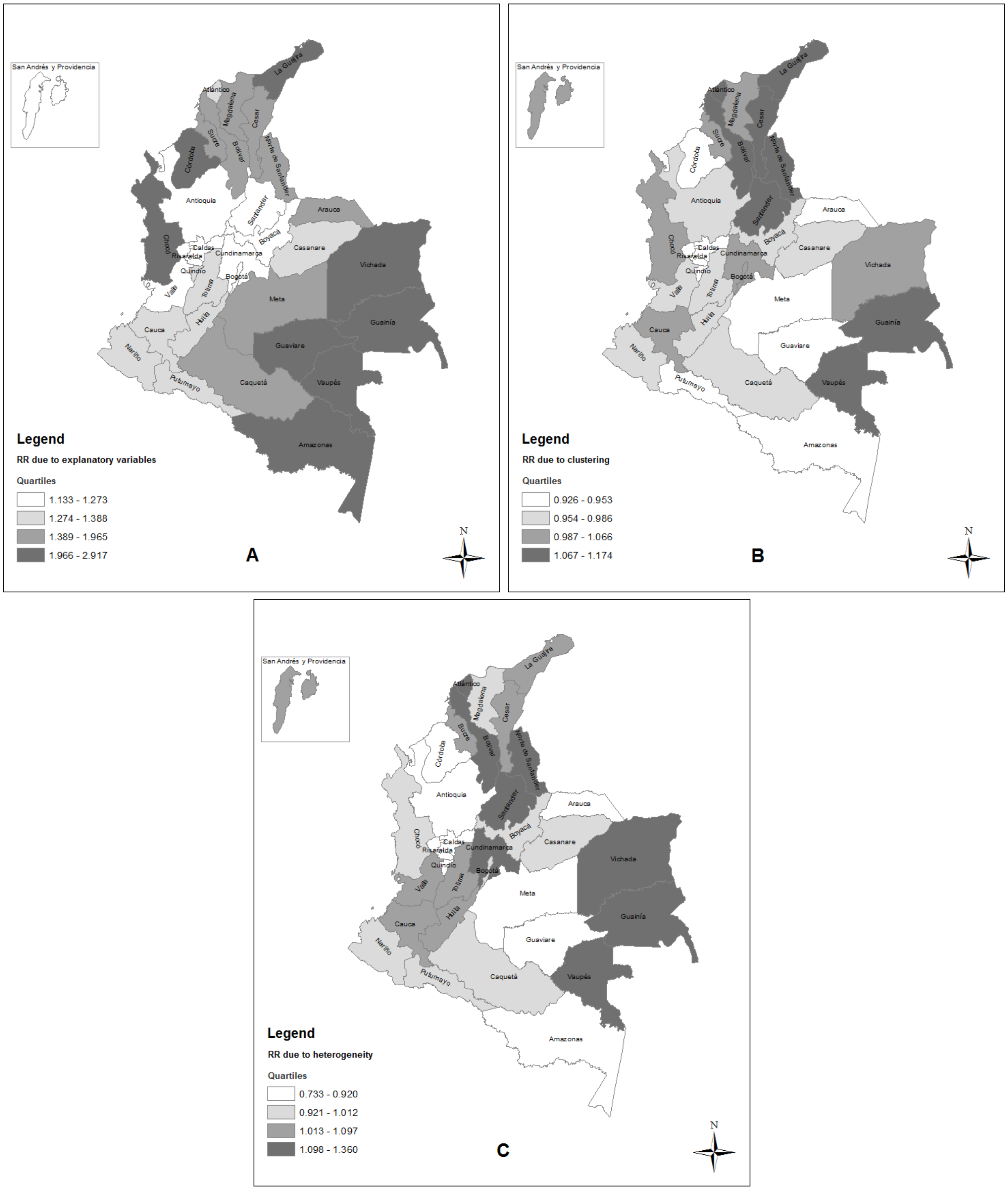

Fig. 4-4. Maps of the department risk ratios (RR) for having not had Pap testing in Colombia, 2010. (A) RR explained by fixed effects in the final multivariable model. (B) RR explained by the spatial structured heterogeneity (μ) or clustering. (C) RR explained by the unstructured heterogeneity (v) in the model. The darker the shade of grey the higher the risk ratio in the department attributed to the model component.

4.4. Discussion

The methodological approach used in this study provides valuable information about the spatial distribution of Colombian women having limited awareness of, or access to, primary and secondary strategies for CC prevention. Although other local and nationwide studies in Colombia have measured individual factors affecting knowledge or awareness of the HPV vaccination and access to Pap testing (4, 10, 11, 42), we are unaware of studies assessing the spatial variations in CC prevention in the country. Our results identified spatial patterns of NHrd-Vac and NHd-Pap in departments adjacent to the Colombian border. These results could be used to target interventions in high-risk departments and improve the awareness or participation of Colombian women in primary and secondary CC prevention programmes.

The specific spatial patterns of NHrd-Vac and NHd-Pap cases identified via tests for local clustering are critical findings because they reveal departments in which the current CC prevention programmes are resulting in a lower than average awareness and uptake by local women. By using Bayesian spatial analysis, we also recognised and controlled for area-based socio-demographic factors associated with increased risk of women reporting NHrd-Vac or NHd-Pap. Finally, the use of spatial modelling identified residual variation due to unmeasured factors, suggesting that additional factors could be influencing CC prevention programmes in Colombia and providing a focal point for further studies.

Women living in departments with a high prevalence of no education, subsidised health insurance, rurality, and low population density were more likely to report NHrd-Vac or NHd-Pap. For example, each 10% increase in the department percentage of women with subsidised insurance had an 8% increase in the risk of NHrd-Vac. This finding is particularly important given that about 50% of Colombians are affiliated with subsidised health insurance (43), especially those with a low socioeconomic status and living in rural areas (44). Subsidised insurance has been previously associated with subscribers having limited information on HPV vaccination in Colombia (9-11).

The results of our analysis demonstrated that population density was associated with NHrd-Vac, with an increased risk when the department population density was below the national average. Although previous reports have recognised that people living in departments with accessibility issues due to geographic location experience challenges to obtain health care services (e.g. Chocó, Vaupés, Vichada, Guainía, and Amazonas) (45, 46), population density has not previously been reported as a factor affecting the awareness of a preventive health service in Colombia, such as having heard of HPV vaccination. This finding might be linked to the shortage of health care providers described in departments located in the Pacific and Amazon-Orinoquía regions (47), limited health care services being offered in low-populated regions, or an increased reticence in these areas to discuss issues related to sexuality.

After considering the importance of department subsidised insurance, rurality, and no education among women, we found that the NHd-Pap risk was higher for women in the departments of La Guajira, Sucre, Bolívar, Chocó, Vichada, Guainía, Guaviare, Vaupés, and Amazonas. For departments with high rurality (e.g. above 26.6% of women living in rural areas), the NHd-Pap risk was higher in departments with a high percentage of non-educated women compared to those with a lower prevalence of no education. Also, the risk of NHd-Pap increased with the percentage of women living in rural areas, but only for departments with high levels of women with no formal education. While the interaction between education and rurality has previously been described at the individual level (48), the interaction between rurality and low education in their respective effects on the risk of NHd-Pap at the department level had not previously been identified in Colombia. Having a high department prevalence of no education and rurality would suggest a high risk of lack of Pap testing and an apparent target for intervention. The development of CC screening programmes must consider the differing impacts of rurality between departments with high and low levels of no-formally-educated women, and the role of high levels of no education in departments with high percentages of women living in rural areas.

The results of the present study illustrate the role that department socio-demographic factors have in determining the risks of NHrd-Vac and NHd-Pap. Our findings support the hypothesised social differences between departments located in the central and peripheral areas of Colombia (49). Several departments in these areas of the country have poor educational, social, and health indicators. For example, Guainía has the lowest schooling rates, while Chocó has the highest infant mortality and the lowest life expectancy in Colombia (49). Poverty and other socioeconomic conditions associated with ethnic diversity could account for some of the spatial or unstructured heterogeneity associated with the risk of NHrd-Vac or NHd-Pap observed in our results. Statistics from Colombia have identified the distribution of poverty by departments, excluding those located in the Amazon-Orinoquía region (50). The departments with a high percentage of population living in poverty are Cauca, La Guajira, Chocó, Sucre, and Córdoba. From these departments, La Guajira, Cauca, and Chocó have the highest levels of extreme poverty (50). Furthermore, people living in several departments of the Amazon-Orinoquía, Atlantic, and Pacific regions struggle to face difficulties related to inappropriate dwellings (43), a lack of access to basic services (43), inadequate road conditions or absence of roads (51), and internally displaced people (49, 52).

To our knowledge, this is the first study conducted in Colombia that identifies spatial variations in accessing primary and secondary CC preventing strategies among young women. We described clusters where departments show a higher risk of having more cases of NHrd-Vac and NHd-Pap than expected and used Bayesian modelling to examine different department socio-demographic factors associated with these risks. Most of the socio-demographic variables identified by our spatial analysis have been previously recognised in Colombia as factors associated with individuals having not heard of HPV vaccination or having not had Pap testing (4, 9-11, 42, 48, 53). However, these studies did not explore department socio-demographic factors to explain spatial differences in CC prevention in Colombia.

In addition to providing evidence of spatial variations in CC prevention in Colombia, the methods used in our study could guide the evaluation of geographical variations in cancer prevention programmes in different settings. Studies in other countries have explored geographical variations in primary and secondary CC prevention; although, these studies have not incorporated Bayesian analysis to estimate the importance of spatial and unstructured correlation among geographic regions. For example, a Canadian study identified the appropriateness of breast, colorectal, and CC screening in Ontario using the Local Indicator of Spatial Association (54). The results of this study showed low levels of screening and areas with low screening despite the presence of community centres or physicians' offices nearby. A

German study, that used least square regressions and spatial lag models, found that cancer screening was better in areas with more access to health care (55). This study also identified that higher voter turnout was related to higher CC screening and that a longer travel time to a specialist's office was negatively associated with CC screening. However, this approach modelled the screening rate data as a normally distributed continuous outcome and did not result in estimates of spatially correlated and uncorrelated errors. Our study focused on CC prevention awareness and access in Colombia, considering the underlying population at risk, associated socio-demographic factors, and the structured spatial and unstructured variations.

While previous studies examining variations in CC incidence have incorporated a Bayesian spatial approach, the studies report limited diagnostics validating the simulated data used in their analysis. The study of Vicens et al (56) found variations in cervical and prostate cancer incidence in the Girona Health Region not associated with deprivation index. The authors reported the use of the deviance information criterion and conditional predictive ordinate to assess model fit in this analysis. Another study evaluated the geographic incidence of breast and cervical cancer in Cuba (57). The results of this study showed differences in the risk of CC in some municipalities and the presence of CC clusters in the municipalities located in the eastern area of Cuba. The authors used the deviance information criterion to assess model fit and trace and autocorrelation plots to check convergence of the models. The approach used in our study not only examined the spatial variations in NHrd-Vac and NHd-Pap by Colombian departments using Bayesian spatial analysis, but also included a thorough validation of the simulated data used in the analysis using informal and formal diagnostics.

The results of our formal diagnostics of the simulated data used to study the Bayesian models support the data were sampled from a stationary distribution. Sampling from a stationary distribution is essential for accurately estimating parameters and random effects in a model. Previous studies of other health conditions, different than CC, have reported the use of some of the formal diagnostics included in our study. For example, a study about disparities in mortality due to heart attack and stroke in Tennessee (58) identified convergence based on the Brooks-Gelman-Rubin, Geweke, and Heidelberger-Welch diagnostics. The study about the incidence of suicide in England and Wales used the Gelman and Rubin statistic to assess convergence of chains (59). The model diagnostics that we completed included visual diagnostics, as well as the Gelman and Rubin, Geweke, Raftery-Lewis, and Heidelberger-Welch diagnostic tests.

Limitations to this study include the source of the primary data. The dependent and independent variables extracted from the 2010 NDHS were based on self-reported information. These data might not be representative of the actual department prevalence of lack of HPV vaccination awareness (in which having not heard of HPV vaccination was used as a proxy for the lack of knowledge of primary prevention options for HPV), lack of Pap testing, no education, rurality, and affiliation to subsidised health insurance. Additionally, social desirability could be a factor leading to misclassification bias (60). Ecological fallacy must also be considered, although we did see consistency between our fixed effects results and results from previous individual-level and multi-level studies (4, 9-11, 42, 48, 53). We also expect higher levels of collinearity among risk factors measured at the group level rather than at the individual level, particularly for socio-demographic measures (61).

Given that CAR models could be a source of spatial confounding (62), we corroborated the results of the NHrd-Vac and NHd-Pap models using restricted spatial regressions (RSR) in the R software (63). The largest relative difference between the fixed effect estimates from RSR approach and the Bayesian CAR model among all of the factors contained in the final models was less than 5%. These results show that the use of CAR models for the analyses did not show substantial evidence of confounding in our results. Additionally, we confirmed the results of our estimates using one chain, no burn-in period, and no thinning, taking into account the controversial practice of burn-in, multiple chain use, and thinning (64). The relative estimates obtained using this approach were identical to those presented in our results.

In conclusion, our study proposes a structured methodology to analyse spatial variations in the access of primary and secondary CC prevention programmes available to women in Colombia. Our results are relevant given the scarcity of Bayesian spatial studies about CC prevention and could be used to shape policies and focus resources at the department level in Colombia. We identified that departments adjacent to the Colombian border had a higher risk of NHrd-Vac and NHd-Pap. We observed that the department prevalence of subsidised insurance and population density were factors related to the risk of NHrd-Vac. The risk of NHd-Pap was associated with the department prevalence of women with no education and rurality, accounting for the prevalence of subsidised insurance. Our results could be used to focus available resources in areas in greater need of CC prevention programmes in the country. Finally, the methodological approach used in this study could be successfully replicated in other settings.

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CHAPTER 5 – THE ROLE OF SOCIO-DEMOGRAPHIC FACTORS IN PREMATURE CERVICAL CANCER MORTALITY IN COLOMBIA

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After identifying inequities in primary and secondary cervical cancer (CC) prevention in the previous studies, this chapter contributes with evidence on inequities in CC mortality among women aged 20-49 years in Colombia. This is the first study in Colombia specifically focused on socio-demographic factors associated with CC among young women. Differences in CC mortality were identified by educational level, type of health insurance, region of residence, and by whether women lived in urban or rural areas. Also, this is the first study in Colombia reporting that the inequities in CC mortality between women who were highly educated compared to those with no-to-limited education were relatively larger among the youngest compared to the oldest group. The findings of this work underline the need to plan, implement, and evaluate access of Colombian women to CC prevention strategies, timely diagnosis, and early treatment.

5.1. Introduction

Cervical cancer (CC) imposes a high burden of disease worldwide, being the third most important cause of cancer-related deaths among women in 2012 (1). Developing countries account for almost 90% of total CC deaths (1). Developing countries are further inequitably impacted by premature CC deaths in young women (2), including mothers and caregivers (3) and, in many cases, important contributors to family income (4). In Latin American countries, CC caused more than 28,000 female deaths in 2012 (1). Compared to Canada and the United States, Latin American countries have greater age-standardised mortality rates due to CC, especially in Central America and countries located in the Andean region (5). In Colombia, a country part of the Andean region, CC has been ranked as the second most common cause of cancer deaths in women after breast cancer (6).

While mortality rates from CC in Colombia have been decreasing in recent years (7), the burden of this disease continues to be an important concern (6), in spite of having effective tools for prevention (2). Measured as total avoidable years of life lost in Colombia, CC ranks above other causes of mortality, such as hypertensive heart disease or liver cancer (8). Because cancer in Colombia is often diagnosed in late stages, the effectiveness of potential treatment options can be limited (9). Additionally, many people in Colombia do not have health insurance, even though they can be affiliated with the contributory or subsidised system depending on their capacity to pay (10). Public teachers, university workers, police or military forces, and employees of the Colombian Oil Company have special health insurance plans (10).

Previous studies in Colombia have described associations between one or two socio-demographic factors and CC mortality focused on wider age ranges, including all women more than 15 years of age (11, 12) and women aged 25 to 64 years (13). Differences in CC mortality have been explored among departments, or Colombian administrative divisions (11, 14), rural or urban residence (11), educational level (12, 13), and lack of health insurance (14). However, there is no evidence regarding how these socio-demographic variables impact premature mortality associated with CC in young women (i.e. women aged 20-49 years) in Colombia, or how these risk factors might differentially impact younger as compared to older women under 50 years of age. The need for studies centred on young women to better understand specific risk factors for premature deaths from CC has previously been identified (2).

Nationwide studies are needed to understand the specific roles of education and type of health insurance in CC mortality among young women in Colombia, while accounting for differences between urban and rural residences and variation across geographic regions. Moreover, variations in CC mortality between limited-to-no-educated and highly educated women by age group need to be explored, given that Colombian women 25 years or more tend to make more use of their rights to access health care (15) and that young women have low quality of reproductive and sexual health (16). The ability of women to act on the information they gain from their education might vary based on age.

Similarly, age-specific differences in the effect of type of health insurance as a risk factor for CC mortality should be considered because most Colombians who use the *tutela* action (i.e. a legal constitutional mechanism to protect fundamental human rights (17)) to access health services had contributory health insurance (15) and older age is related to an increased utilisation of health care (18). As for education, the capacity of women to access the services available under their health insurance might vary based on their age.

The resulting information from nationwide studies considering these variations could be used to identify targets for intervention in the diagnosis and treatment of young women with CC, taking into consideration the effect of CC on young women (2), as well as the existence of marked regional (19), health care system-related (20), and educational disparities in the Colombian population (19).

The study described here examined differences associated with socio-demographic factors in CC mortality among young women in Colombia between 2005 and 2013. The objectives of this study were to: 1) describe socio-demographic characteristics of women aged 20-49 years who died from CC, 2) identify differences in CC mortality rates by educational level, type of health insurance, urban or rural residence, and geographic region of residence among women aged 20-

49 years, and 3) evaluate if there were age-specific differences in the importance of education or type of insurance as risk factors for CC mortality.

5.2. Methods

5.2.1. Source of Cervical Cancer Mortality Data Stratified by Potential Risk Factors

Official mortality records of all individuals who died in Colombia between January 2005 and December 2013 were obtained from the National Administrative Department of Statistics (*Departamento Administrativo Nacional de Estadística*—DANE). The causes of death in these records were coded according to the International Classification of Diseases—10th revision. The code C53 (malignant neoplasm of cervix uteri), along with applicable sub-codes (C530, malignant neoplasm of the endocervix; C531, malignant neoplasm of the exocervix; C538, overlapping lesion of cervix uteri; C539, cervix uteri, unspecified) were used to extract all female deaths attributed to CC by year of death. Additionally, unspecified malignant neoplasms of the uterus (code C55) were reallocated according to the proportion of deaths due to cervical (code C53) and corpus uterine cancer (code C54) by age group and year of death, as recommended by Loos et al (21).

All female deaths from CC were consolidated in one data set. The socio-demographic characteristics of each woman, including age, educational level, type of health insurance, rural or urban residence, and geographic region of residence, were then extracted from the mortality records to be considered as potential risk factors in the analysis. From this data set, the subset of women aged 20-49 years was selected for analysis. The total numbers of observed CC deaths were stratified by age: 20-24 years, 25-29 years, 30-34 years, 35-39 years, 40-44 years, and 45-49 years. The resulting outcome for the analysis was the age-group specific count of deaths due to CC further stratified by one or more of the following variables: educational level, type of health insurance, urban or rural residence, and department of residence. Department CC counts per age group were summarised for each of the five geographic regions described in the 2010 National Demographic and Health Survey (NDHS) (22). The NDHS evaluated different factors associated with reproductive and sexual health in a sample of more than 53,000 women between 13 and 49 years.

Mortality data used for this analysis were publicly available upon request to DANE and, therefore, this study was exempted from ethics review by the University of Saskatchewan Ethics Board.

5.2.2. Source of Population at Risk Data Stratified by Potential Risk Factors

The numbers of women at risk of dying due to CC for the risk factor-specific strata were extracted from population projections by DANE (23) and the NDHS data sets.

In the first step, 2009 national population projections based on the 2005 census (23) were used to determine the population at risk categorised by the same five-year age groups used for CC cases. The population at risk was based on 2009 information as this was the mid-point of the 2005 to 2013 study period. Total department counts of women at risk per age group were classified in one of the five geographic regions used in the NDHS.

In the second step, women at risk were stratified based on the other socio-demographic variables of interest. The proportions of women between 20 and 49 years of age for each level of education, type of health insurance, and for urban or rural residence were calculated from the NDHS data set for each 5-year age group and region of residence. The appropriate proportions were then applied to the 2009 population projections for each age group and region of residence to generate the necessary strata-specific numbers of at-risk women for subsequent analyses.

5.2.3. Statistical Analysis

The total numbers and proportions of CC deaths were described for each category of the risk factors of interest using all available data. The same descriptors were calculated for the subset of cases with complete information for all potential risk factors of interest. The subsequent analysis was completed using two different analytical approaches to evaluate the importance of missing risk factor information in the DANE mortality records. The first approach excluded women who had unavailable or missing information in any of the variables of interest (complete case analysis). The second approach recognised the potential for selection bias by excluding cases with missing data and applied multiple imputation methods with the choice of technique informed by the missing data patterns (24). All the analyses were completed in STATA version 13 (StataCorp LP, College Station, TX, USA).

5.2.3.1.Complete case analysis

The first analysis considered only women aged 20-49 years with complete information for all of the variables of interest. Associations between each potential risk factor and CC mortality stratified by age group were individually evaluated using negative binomial models. The natural log of the population at risk stratified by age group and each risk factor was used as the offset in these regression models. Risk factors with *p*-values<0.2 were considered for inclusion in the multivariable analysis (25). A Wald test was used to estimate the overall *p*-value for multi-category variables. A likelihood ratio test was used to compare the negative binomial to the Poisson model (26). Preliminary analysis suggested that a negative binomial distribution fit the data better than that a Poisson distribution.

Multivariable negative binomial regression models were then used to identify differences in CC mortality, first by educational level (Model 1) and then by type of health insurance (Model 2). The decision was made to create two separate models because of the potential for type of health insurance to be an intervening variable on the causal pathway between educational level and CC mortality. Better education could lead to better insurance which then results in lower CC mortality. Correcting for insurance could result in biased underestimates of the direct impact of education on CC mortality (25).

Both models were analysed using the same set of variables (i.e. age group, region of residence, and urban or rural residence) to control for potential confounders. Interactions between age and educational level, as well as age and type of health insurance were evaluated. Pairwise comparisons were used to examine differences in CC mortality among categories of education for each age group and across categories of insurance for each age group.

A third model simultaneously evaluating all independent variables of interest intended to measure the joint effect of the education and health insurance did not converge, given that stratification of the population at risk resulted in denominators with zero counts. When the cells with zero denominators were eliminated, the model did converge, but 15% of the outcome observations were lost introducing a risk for selection bias. Interactions were not examined in this model. The results of this model were compared to main effects only models with education and then with insurance.

5.2.3.2.Imputed data analysis

The second approach to the analysis applied multiple imputations to minimise potential biases and loss of power and precision associated with missing risk factor data in the DANE mortality files. The patterns of missingness were visually assessed using the *misstable* command in STATA to determine an appropriate method for imputation (24). The result was a table showing the percentage of data with various patterns of missingness according to each of the variables. Variables were marked as missing or not missing for a given pattern. Multiple imputation by chained equations was chosen to optimise the analysis of the socio-demographic factors of interest (27), based on the percentage of all women, including those with incomplete data (28), who died from CC.

The method recommended by van Buuren et al (29) was followed to specify the multiple imputation model. This model incorporated data from all females who died from CC between 2005 and 2013 to account for those with missing age and included the socio-demographic variables of interest, as well as auxiliary variables. The auxiliary variables considered included urban or rural area where the death occurred, facility or place of death (e.g. home, health centre, hospital, etc.), marital status, person who certified the death, and year and region of death.

Using the mean frequency of the imputed data, women aged 20-49 years stratified by age groups were again cross-classified according to the risk factors of interest to obtain the number of strata-specific CC deaths. Negative binomial models were used to evaluate relationships between each socio-demographic factor and CC mortality stratified by age, with the corresponding population at risk used to determine the offset as previously described. Risk factors with *p*-values <0.2 were considered for inclusion in the multivariable analysis (25).

Two multivariable negative binomial regression models were used to identify differences in CC mortality by educational level (Model 1) and type of health insurance (Model 2), as described for the complete case analysis. The multiple imputation models also accounted for age group, region of residence, and urban or rural residence. As described for the complete case analysis, the interactions between age and education and age and type of insurance were evaluated.

Results were reported as incidence rate ratios (IRR) and 95% confidence intervals (95%CI). Differences were considered statistically significant if $p<0.05$. Comparisons between models were done used the Akaike's information criterion (AIC) (25).

5.3. Results

From 2005 to 2013, 1,768,273 deaths were reported in Colombia; 756,636 were women of any age. During this period, 14,355 women died from CC (code C53 and applicable sub-codes) and 2,535 were classified as unspecified malignant neoplasms of the uterus (code C55). From the unspecified category, 2,296 (90.6%) cases were reallocated to CC and 239 (9.4%) to corpus uterine. Therefore, the number of females of all ages who died from CC was 16,651, which corresponded to 2.2% of all deaths in females of all ages during the study period. Seventeen women in this group were eliminated from the data set because they resided out of the country, resulting in 16,634 women who died due to CC and resided in Colombia in 2005-2013.

From the 16,634 CC cases (excluding 18 cases with missing age), 5,093 women were aged 20-49 years, representing 30.6% of all deaths due to CC. The mean age of this group was 40.5 years (SD=6.4). Most women had primary education and subsidised health insurance (Table 5-1). A third of women lived in the Eastern region and most resided in urban areas of Colombia.

Table 5-1. Socio-demographic characteristics of women who died from cervical cancer and cases with complete data

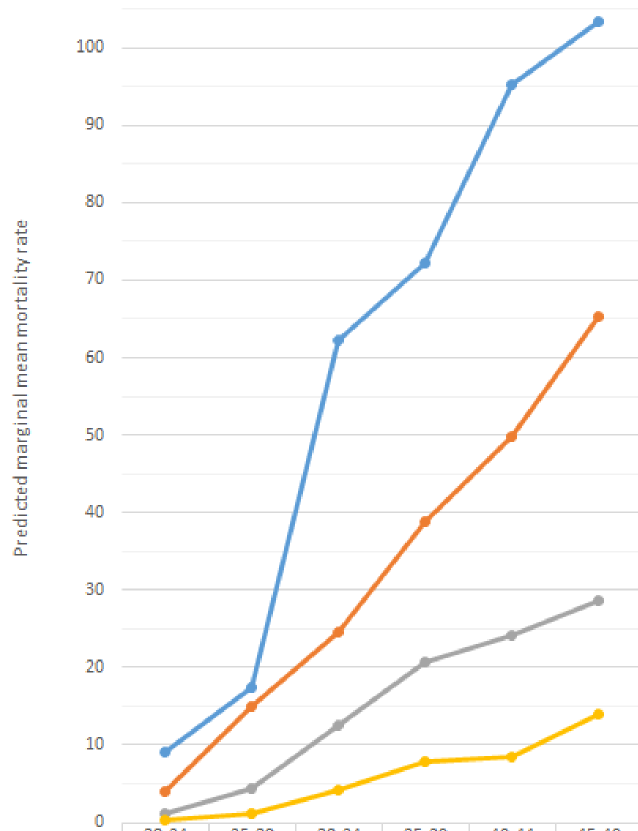
Socio-demographic characteristics	Women 20-49 years			
	Total cervical cancer mortality (n=5093)		Cervical cancer mortality with complete data (n=4247)	
	n	(%)*	n	(%)*
Educational level				
No education	346	(6.8)	334	(7.9)
Primary	2194	(43.1)	2136	(50.3)
Secondary	1506	(29.6)	1486	(35.0)
Higher	294	(5.8)	291	(6.9)
Missing information	753	(14.8)	-	-
Type of health insurance				
Non-affiliated	620	(12.2)	497	(11.7)
Subsidised	2863	(56.2)	2359	(55.5)
Special	86	(1.7)	77	(1.8)
Contributory	1435	(28.2)	1314	(30.9)
Missing information	89	(1.7)	-	-
Urban or rural residence				
Rural	829	(16.3)	687	(16.2)
Urban	4204	(82.5)	3560	(83.8)
Missing information	60	(1.2)	-	-
Region of residence				
Atlantic	1053	(20.7)	831	(19.6)
Central	1353	(26.6)	1164	(27.4)
Pacific	959	(18.8)	826	(19.4)
Amazon-Orinoquía	167	(3.3)	130	(3.1)
Eastern	1553	(30.5)	1296	(30.5)
Missing information	8	(0.2)	-	-
Age groups				
20-24 years	64	(1.3)	56	(1.3)
25-29 years	273	(5.4)	227	(5.3)
30-34 years	630	(12.4)	541	(12.7)
35-39 years	1040	(20.4)	872	(20.5)
40-44 years	1391	(27.3)	1154	(27.2)
45-49 years	1695	(33.3)	1397	(32.9)

Women aged 20-49 years who died due to cervical cancer in Colombia between 2005 and 2013. The table summarises all available data for women who died from cervical cancer and data for women with complete data for age, region of residence, educational level, type of health insurance, and rural or urban residence.
*Percentage of total cases in each category.

5.3.1. Complete Case Analysis

Of the 5,093 women who died from CC, 4,247 (83.4 %) had complete data for all risk factors of interest (Table 5-1). The negative binomial models, stratified by 5-year age category, identified significant differences in CC mortality among educational levels (Wald test, $p<0.0001$), types of health insurance (Wald test, $p<0.0001$), urban or rural residence ($p<0.0001$), and region of residence (Wald test, $p<0.0001$). Age by itself was also significantly associated with CC mortality (Wald test, $p<0.0001$).

The final model describing the association between education and CC mortality included rural or urban residence, region of residence, and age is presented in Tables 5-2, 5-3, 5-4 and Appendix E-1. A significant interaction was detected between educational levels and age groups (Wald test, $p<0.0001$) (Fig. 5-1, Table 5-2 [Model 1], and Table 5-3). Differences in CC mortality were observed among women with limited or no education compared to women with higher education across all age groups. However, the relative size of these differences tended to be larger among younger women than for those in the oldest age group (Table 5-2 [Model 1]). For example, when comparing women with primary education to those with higher education, the IRR for women aged 25-29 was significantly higher than the IRR for women aged 45-49 years based on non-overlapping confidence intervals. Larger differences in education also tended to be associated with higher IRR for all age groups than smaller differences in education.



	20-24	25-29	30-34	35-39	40-44	45-49
No Education	9.1	17.3	62.3	72.2	95.2	103.5
Primary	4.0	15.0	24.5	38.8	49.9	65.4
Secondary	1.1	4.4	12.6	20.6	24.2	28.7
Higher	0.3	1.2	4.2	7.8	8.4	14.0

Age group

Fig. 5-1. Marginal mean mortality rates due to cervical cancer according to age groups and educational level of women. Mortality rates presented here are adjusted by rural or urban residence and region of residence.

Table 5-2. Effect estimates for interacting variables in the cervical cancer models limited to complete data (n=4247).

	Associations between educational level or type of health insurance and cervical cancer mortality for each age group (years)											
	20-24		**25-29**		**30-34**		**35-39**		**40-44**		**45-49**	
	IRR	**(95%CI)**	**IRR**	**(95%CI)**	**IRR**	**(95%CI)**	**IRR**	**(95%CI)**	**IRR**	**(95%CI)**	**IRR**	**(95%CI)**
Model 1												
Educational level												
No education vs. higher education	32.5	(7.70-137)	14.3	(6.14-33.5)	14.7	(9.30-23.2)	9.27	(6.30-13.6)	11.4	(7.96-16.3)	7.42	(5.42-10.1)
Primary vs. higher education	14.1	(5.27-38.0)	12.4	(7.34-21.0)	5.77	(4.08-8.14)	4.98	(3.69-6.73)	5.96	(4.37-8.13)	4.69	(3.58-6.13)
Secondary vs. higher education	3.87	(1.47-10.2)	3.62	(2.13-6.14)	2.97	(2.10-4.21)	2.65	(1.94-3.60)	2.89	(2.10-3.97)	2.06	(1.54-2.75)
No education vs. primary education	2.30	(0.68-7.77)	1.15	(0.56-2.40)	2.55	(1.75-3.71)	1.86	(1.37-2.53)	1.91	(1.49-2.45)	1.58	(1.26-1.99)
Model 2												
Type of health insurance												
No insurance vs. contributory insurance	1.50	(0.60-3.72)	2.18	(1.43-3.35)	1.54	(1.12-2.13)	1.48	(1.12-1.94)	1.57	(1.21-2.03)	2.21	(1.73-2.81)
Subsidised vs. contributory insurance	1.96	(0.99-3.85)	1.79	(1.27-2.51)	1.74	(1.36-2.21)	1.55	(1.25-1.91)	1.96	(1.61-2.39)	1.96	(1.63-2.37)
Special vs. contributory insurance	2.91	(0.64-13.1)	0.29	(0.04-2.10)	0.64	(0.30-1.39)	0.59	(0.32-1.10)	0.93	(0.61-1.42)	0.79	(0.52-1.19)
Subsidised vs. special insurance	0.67	(0.16-2.82)	6.17	(0.86-44.4)	2.71	(1.26-5.81)	2.61	(1.41-4.83)	2.10	(1.40-3.16)	2.49	(1.6-3.74)
No insurance vs. special insurance	0.51	(0.11-2.44)	7.54	(1.03-55.2)	2.40	(1.09-5.31)	2.49	(1.31-4.73)	1.68	(1.08-2.61)	2.80	(1.82-4.32)
No insurance vs. subsidised insurance	0.77	(0.35-1.68)	1.22	(0.83-1.80)	0.89	(0.66-1.20)	0.95	(0.74-1.23)	0.80	(0.63-1.02)	1.12	(0.90-1.40)

IRR: Incidence rate ratios; 95%CI: 95% confidence intervals.
Model 1 assessed differences in cervical cancer mortality rates by educational level and Model 2 evaluated differences in mortality rates by type of health insurance. Both multivariable models included fixed effects for age group, urban or rural residence, and region of residence, as well as interactions with age. Only women with complete data for the risk factors of interest were included in these analyses.

Furthermore, across all education levels, women in older age groups tended to have higher mortality rates than those in the youngest age group (Fig. 5-1 and Table 5-3). The relative size of differences in risk associated with increasing age also tended to be smaller for women with less education compared to women with more education.

Table 5-3. Effect estimates for the interaction between age and education from complete and imputed data models.

	Associations between age group and cervical cancer mortality for each level of education							
	No education		**Primary education**		**Secondary education**		**Higher education**	
Age groups (years)	**IRR**	**(95%CI)**	**IRR**	**(95%CI)**	**IRR**	**(95%CI)**	**IRR**	**(95%CI)**
Complete data analysis (n=4247)								
25-29 vs. 20-24	1.90	(0.50-7.21)	3.78	(2.32-6.16)	4.03	(2.56-6.34)	4.31	(1.58-11.8)
30-34 vs. 20-24	6.83	(2.09-22.3)	6.16	(3.86-9.82)	11.6	(7.57-17.8)	15.1	(5.93-38.5)
35-39 vs. 20-24	7.90	(2.46-25.4)	9.77	(6.18-15.4)	19.0	(12.4-28.9)	27.7	(11.0-69.9)
40-44 vs. 20-24	10.4	(3.28-33.1)	12.6	(7.97-19.8)	22.2	(14.6-33.8)	29.8	(11.8-75.5)
45-49 vs. 20-24	11.3	(3.58-35.9)	16.5	(10.5-25.9)	26.4	(17.3-40.4)	49.7	(19.9-124)
Imputed data analysis (n=5098)								
25-29 vs. 20-24	2.61	(0.72-9.40)	3.85	(2.47-6.02)	4.46	(2.90-6.87)	4.19	(1.67-10.5)
30-34 vs. 20-24	7.55	(2.32-24.6)	6.28	(4.09-9.63)	12.5	(8.33-18.9)	13.8	(5.85-32.6)
35-39 vs. 20-24	10.0	(3.14-32.0)	10.1	(6.65-15.4)	20.6	(13.7-30.8)	25.4	(10.9-59.2)
40-44 vs. 20-24	13.3	(4.21-42.1)	12.9	(8.52-19.6)	24.1	(16.1-36.0)	28.9	(12.4-67.6)
45-49 vs. 20-24	15.0	(4.76-47.3)	16.8	(11.1-25.4)	29.4	(19.6-44.0)	47.4	(20.5-110)

IRR: Incidence rate ratios; 95%CI: 95% confidence intervals.
Results summarise both the analysis of data for cases with complete information on all risk factors of interest and the imputed data analysis for models examining the association between educational level and cervical cancer mortality (Model 1). Both multivariable models included fixed effects for age group, urban or rural residence, and region of residence, as well as interactions between educational level and age.

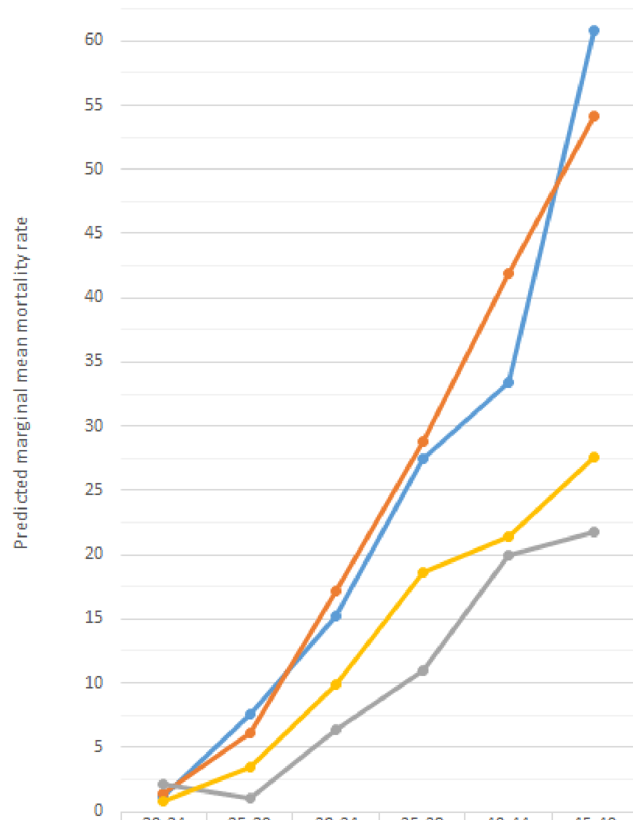
Table 5-4 shows the effect estimates for variables that were not included in the interaction between age and educational level in the multivariable model (Model 1). After adjusting for age group, region of residence, and urban or rural residence, CC mortality rates were lower among women from rural compared to those from urban areas. Mortality rates for women who resided in the Atlantic, Central, Pacific, and Amazon-Orinoquía regions were higher than those for women from the Eastern region.

Table 5-4. Effect estimates for non-interacting variables from of cervical cancer mortality models with complete data (n=4247).

	Associations with cervical cancer mortality			
	Model 1 Educational level		**Model 2 Type of health insurance**	
	IRR	**(95%CI)**	**IRR**	**(95%CI)**
Urban or Rural residence				
Rural	0.39	(0.35-0.43)	0.52	(0.47-0.57)
Urban	Ref.		Ref.	
Region of residence				
Atlantic	1.13	(1.00-1.28)	1.04	(0.92-1.18)
Central	1.30	(1.15-1.47)	1.28	(1.14-1.44)
Pacific	1.39	(1.23-1.57)	1.34	(1.18-1.51)
Amazon-Orinoquía	1.61	(1.32-1.97)	1.64	(1.34-2.01)
Eastern	Ref.		Ref.	

IRR: Incidence rate ratios; 95%CI: 95% confidence intervals.
Model 1 assessed differences in cervical cancer mortality rates by educational level and Model 2 evaluated differences in mortality rates by type of health insurance. Both multivariable models included fixed effects for age group, urban or rural residence, and region of residence, as well as interactions with age. Only women with complete data for the risk factors of interest were included in these analyses.

The second multivariable model evaluating the effect of type of insurance showed similar results for rural and urban differences and region of residence to Model 1 (Table 5-4 [Model 2] and Appendix E-2). However, in this model, there were no differences in CC mortality rates between women from the Atlantic and the Eastern regions.



	20-24	25-29	30-34	35-39	40-44	45-49
No Insurance	1.1	7.5	15.2	27.5	33.4	60.9
Subsidised	1.4	6.2	17.1	28.8	41.9	54.2
Special	2.1	1.0	6.3	11.0	19.9	21.7
Contributory	0.7	3.4	9.9	18.6	21.4	27.6

Age group

Fig. 5-2. Marginal mean mortality rates due to cervical cancer according to age groups and type of health insurance of women. Mortality rates presented here are adjusted by rural or urban residence and region of residence.

The second multivariable model also included a significant interaction between the type of health insurance and age group (Wald test, $p<0.0001$) (Table 5-2 [Model 2] and Appendix E-2). Mortality rates from CC were higher among women with no insurance and subsidised insurance compared to women with contributory insurance, except for women aged 20-24 years (Fig. 5-2 and Table 5-2 [Model 2]). Also, differences in CC mortality rates were observed between women with subsidised and special insurance among women aged 30+ years. Furthermore, mortality rates for women with no insurance were higher than women with special insurance, except for those aged 20-24 years. There were no significant differences between women with no insurance and subsidised insurance in any age group, nor between special and contributory insurance in any age group.

The model including type of health insurance (Model 2 and Appendix E-2) explained a larger portion of the total variance in CC mortality (AIC=1099) than the model including level of education (Model 1) (AIC=1136) (Appendix E-1).

In a subset model (n=4,234) examining the simultaneous associations of educational level and type of health insurance adjusted for region of residence and rural or urban residence, both education (Wald test, $p<0.0001$) and type of health insurance (Wald test, $p=0.02$) were associated with mortality due to CC. For example, the mortality rate for women with no education was higher than that for women with higher education (IRR=9.25; 95%CI=7.56-11.31) after adjusting for type of insurance and other risk factors. This was similar to the effect resulting from a separate model with educational level (IRR=10.5; 95%CI=8.68-12.70) adjusted for all other risk factors except type of insurance but with no interaction term. Also, the mortality rate for women with no health insurance was higher than for women with contributory insurance (IRR=1.16; 95%CI=1.02-1.33) in the model adjusted for education and other risk factors. This result was similar to that obtained using a separate model for type of health insurance (IRR=1.74; 95%CI=1.53-1.99) adjusted for all other risk factors except education but with no interaction term.

5.3.2. Missing Data, Multiple Imputation Process, and Imputed Data Analysis

Most women of all ages who died from CC (n=16,634) had complete information in the socio-demographic factors of interest and auxiliary variables (80.3%). Among the variables of interest, there were missing values for age (0.1%), educational level (16.3%), type of health insurance (1.8%), rural or urban residence (1.0%), and region of residence (0.2%). On the other hand, among the auxiliary variables, there were missing values for urban or rural area of death (0.2%), facility or place of death (0.2%), and marital status (7.0%). The visual assessment of the missing data in the variables of interest, showed a random missing or non-systematic pattern, in which the missing values had no special order or distribution. Taking into consideration that 19.7% of the women of all ages had one or more missing values, 20 imputations by chained equations were computed.

Using the imputed data for all women who died from CC, 5,098 cases were between 20 and 49 years. This number included five women whose age was missing in the original data and was then imputed within the age range of study. The two final multivariable models for CC mortality using the imputed data included fixed effects for age, rural or urban area of residence, region of residence, and an interaction with age in addition to either level of education or type of insurance (Tables 5-5 and 5-6, Appendices E-3 and E-4). The effect estimates for the variables of interest that were not interacting for the two models shown in Table 5-5 had the same direction and similar effect sizes of the estimates resulting from the complete case analysis (Table 5-4).

Table 5-5. Effect estimates for non-interacting variables resulting from the models with imputed data (n=5098).

	Associations with cervical cancer mortality			
	Model 1 Educational level		**Model 2 Type of health insurance**	
	IRR	**(95%CI)**	**IRR**	**(95%CI)**
Urban or Rural residence				
Rural	0.39	(0.36-0.43)	0.52	(0.47-0.57)
Urban	Ref.		Ref.	
Region of residence				
Atlantic	1.20	(1.08-1.34)	1.10	(0.98-1.23)
Central	1.25	(1.12-1.40)	1.24	(1.11-1.39)
Pacific	1.34	(1.19-1.49)	1.28	(1.14-1.43)
Amazon-Orinoquía	1.68	(1.41-2.01)	1.74	(1.45-2.09)
Eastern	Ref.		Ref.	

IRR: Incidence rate ratios; 95%CI: 95% confidence intervals.
Model 1 assessed differences in cervical cancer mortality rates by educational level and Model 2 evaluated differences in mortality rates by type of health insurance. Both multivariable models included fixed effects for age group, urban or rural residence, and region of residence, as well as interactions with age. Data sets including values from the multiple imputations for missing risk factor data were included in these analyses.

Similarly, the pairwise comparisons describing the IRR for CC mortality among educational levels and insurance types for each age group using the imputed data (Table 5-6) had the same direction and similar effect sizes to the estimates resulting from the complete case analysis (Table 5-2). Additionally, differences in mortality rates observed in the imputed data analysis between younger and older women for each level of education were similar using the complete case data analysis (Table 5-3). The model based on imputed data including the type of health insurance (Model 2) also explained a larger portion of the total variance in CC mortality (AIC=1138) than the model including the level of education (Model 1) (AIC=1178).

Table 5-6. Effect estimates for interacting variables in the cervical cancer models with imputed missing data (n=5098).

	Associations between educational level or type of health insurance and cervical cancer mortality for each age group (years)											
	20-24		25-29		30-34		35-39		40-44		45-49	
	IRR	**(95%CI)**	**IRR**	**(95%CI)**	**IRR**	**(95%CI)**	**IRR**	**(95%CI)**	**IRR**	**(95%CI)**	**IRR**	**(95%CI)**
Model 1												
Educational level												
No education vs. higher education	26.8	(6.65-108)	16.7	(7.93-35.1)	14.7	(9.50-22.6)	10.6	(7.42-15.1)	12.3	(8.90-17.1)	8.49	(6.38-11.3)
Primary vs. higher education	14.0	(5.69-34.6)	12.9	(7.96-21.0)	6.38	(4.61-8.83)	5.60	(4.22-7.43)	6.28	(4.72-8.36)	4.98	(3.87-6.39)
Secondary vs. higher education	3.46	(1.42-8.45)	3.69	(2.26-6.02)	3.15	(2.27-4.36)	2.81	(2.10-3.75)	2.88	(2.15-3.88)	2.15	(1.64-2.81)
No education vs. primary education	1.91	(0.57-6.36)	1.29	(0.69-2.42)	2.30	(1.61-3.27)	1.89	(1.43-2.49)	1.96	(1.57-2.45)	1.71	(1.39-2.09)
Model 2												
Type of health insurance												
No insurance vs. contributory insurance	1.55	(0.65-3.67)	2.54	(1.71-3.77)	1.67	(1.24-2.27)	1.71	(1.33-2.21)	1.90	(1.50-2.41)	2.51	(2.01-3.15)
Subsidised vs. contributory insurance	2.06	(1.08-3.94)	2.04	(1.48-2.81)	1.90	(1.51-2.40)	1.79	(1.46-2.19)	2.14	(1.77-2.58)	2.18	(1.82-2.60)
Special vs. contributory insurance	4.01	(1.13-14.3)	0.26	(0.04-1.91)	0.58	(0.27-1.26)	0.55	(0.29-1.02)	0.86	(0.57-1.29)	0.88	(0.60-1.28)
Subsidised vs. special insurance	0.51	(0.16-1.68)	7.76	(1.08-55.8)	3.26	(1.52-6.99)	3.28	(1.78-6.05)	2.49	(1.67-3.70)	2.47	(1.71-3.57)
No insurance vs. special insurance	0.38	(0.10-1.44)	9.66	(1.33-70.4)	2.87	(1.31-6.30)	3.14	(1.67-5.92)	2.21	(1.45-3.38)	2.86	(1.93-4.23)
No insurance vs. subsidised insurance	0.75	(0.36-1.57)	1.24	(0.88-1.76)	0.88	(0.67-1.16)	0.96	(0.76-1.21)	0.89	(0.72-1.11)	1.16	(0.94-1.42)

IRR: Incidence rate ratios; 95%CI: 95% confidence intervals.
Model 1 assessed differences in cervical cancer mortality rates by educational level and Model 2 evaluated differences in mortality rates by type of health insurance. Both multivariable models included fixed effects for age group, urban or rural residence, and region of residence, as well as an interaction with age. Data sets including values from the multiple imputations for missing risk factor data were included in these analyses.

5.4. Discussion

Cervical cancer is a preventable and, if diagnosed early, a treatable disease for many women (2). Despite this, the results of the present study reveal that a third of the women who died from CC in Colombia during the period of study were between 20 and 49 years. The loss of these women has a considerable consequence to young families and an economic impact on the Colombian society. Deaths in women of reproductive age could reflect limitations in strategies and resources to prevent and treat CC, such as challenges in accessing CC screening previously reported in Colombia (30). Screening can have an important impact on reducing CC deaths (31); however, to make a meaningful improvement in CC survival, screening needs to be accompanied by adequate access to follow-up and treatment options (14, 32). The results of our study suggest inequitable access to either or both CC diagnosis and treatment among young women in Colombia.

The present study considered differences in CC mortality for women between 20 and 49 years associated with educational level and type of health insurance. The direction and strength of these associations were robust regardless of whether complete case or multiple imputation analysis was used. This suggests that missing data did not result in meaningful selection bias or a substantial loss of precision in the results. The visual assessment of the pattern of missing data informed the choice of imputation method and suggested that the data were most likely missing at random (33).

We found differences in CC mortality according to educational level, where a relative gap in CC mortality was observed among women with limited or no education compared to women with higher education, especially in the youngest groups. Lack of education has been described as a factor that perpetuates a vicious circle by limiting access of individuals to crucial information to prevent diseases (30), access to health care (34), and the practice of individuals' health care rights (30, 34). Also, low levels of education have been associated with increased frequency of riskier behaviours (35). Other studies in Colombia have evaluated the relationship between education and mortality from other causes (12, 13, 35). Notwithstanding, the age groups considered in these studies differ from the target age groups used in our analysis and women with no education were not included as a category in the previous analyses. Moreover, an interaction effect between age and educational level has not been previously explored. Our results provide evidence for a social gradient in CC mortality based on educational level which has the greatest impact among the youngest women. This finding suggests that improving education in young women or developing specific programmes to improve access for women with no education or primary education could potentially decrease CC mortality.

We also observed differences in mortality rates according to health insurance with some variations among age groups. In addition to the differences in mortality among women with no insurance and those with contributory or special insurance, the observation that having subsidised insurance does not decrease CC mortality compared to not having insurance suggests the existence of potential limitations in CC diagnosis and cancer care for those with subsidised insurance, which could be a result of differences in benefits available as compared to contributory insurance (10, 20). Although not demonstrated, late diagnosis and limited access to cancer treatment options (9) are potential explanations for the differences in CC mortality rates observed according to type of health insurance.

Additionally, simply having health insurance does not guarantee access to health services (34, 36). Others have reported that patients face multiple barriers to access health care in Colombia, such as distance to health care centres, lack of cultural appropriateness of the services provided, political inefficiency, lack of knowledge about patients' health care rights, and administrative barriers imposed by health insurance companies (36). Sanchez et al (34) wrote that, in spite of being insured, patients need to pay out-of-pocket for health services or deal with unknown and complex administrative formalities imposed by health insurance companies, which delay the provision of diagnosis or treatment. Our finding that the models with insurance explained more variability in CC mortality than the models with education status, based on their AICs, suggest insurance programmes should be also a priority target for interventions to decrease CC mortality in Colombia for women between 20 and 49 years of age.

We also found that mortality rates in urban areas were higher than in rural areas after accounting for the effects of age, region of residence, and type of insurance or educational level. This result differs from studies conducted in other countries, in which CC mortality rates are high in rural areas (37, 38). However, our results coincide with a previous Colombian study that suggests high CC mortality rates in urban areas (11). The authors of the earlier study indicated that urban and rural differences in mortality rates could be affected by under-recording of CC deaths in areas with high levels of rurality (11). However, others have specified that under-registration is low in Colombia and should not greatly bias mortality results (13).

Another plausible explanation for the rural-urban differences found in our study could be that, once diagnosed with CC, women living in rural areas often move to urban regions to seek cancer treatment and follow-up in better equipped health care centres. Oncologic services are mainly concentrated in big Colombian cities (39), forcing many women to leave their homes. Furthermore, a qualitative study in Colombia indicated the use persuasive strategies by some health insurance companies to convince women to change their address for expediting their referral to oncologic centres located in bigger cities (34). If changing addresses is a common practice, then, it could be difficult to obtain accurate variations in CC mortality between rural and urban areas or even among Colombian regions.

Furthermore, mortality rates were higher among women living in the Atlantic, Central, Pacific, and Amazon-Orinoquía compared to the Eastern region after accounting for other risk factors. This finding could be related to social problems reported in departments of these regions including poverty or inadequate living conditions (19, 40), lack of access to primary and secondary CC prevention (30, 41), or unequal distribution of health care providers (42). This might be a further indicator of geographical and socioeconomic difficulties in accessing oncologic centres in Colombia. A study from the Colombian National Cancer Institute (9), the main cancer centre in the country, showed that 47% of patients seen in the Institute reside outside the capital of Colombia.

Our study is the first assessing CC mortality in Colombia among women aged 20-49 years using multivariable regressions to control for confounding by multiple socio-demographic variables and for missing values. We identified that CC mortality varied by both level of education and type of health insurance according to age groups, incorporating for the first time women who had special health insurance and women who did not have education. We made use of multiple databases to obtain the population at risk stratified for the risk factors of interest in our analysis. To obtain more complete estimates of CC mortality, cases classified as unspecified malignant neoplasms of the uterus were reallocated as CC cases. Additionally, to decrease loss of information and prevent potential bias due to missing data, we computed our results using multiple imputations in addition to complete case analysis. There was no evidence of substantial bias in the estimates from the complete case analysis in this data set.

The source of denominator data was the most substantial limitation of this study. To examine the effect of education, type of health insurance, and urban or rural residence, we made use of the best data available to estimate the population at risk for each age group. The distributions of 20-to-49-years women surveyed in the 2010 NDHS data set were applied to 2009 population projections in Colombia. Given that the 2010 NDHS was self-reported data, the distribution of the socio-demographic variables used to obtain the population at risk in our study would be limited by the quality of the survey results. Challenges with estimating risk factor group-specific denominator data for less populated regions also limited our ability to look at the joint effect of education and insurance in these data.

5.4.1. Conclusions

Gaps in CC mortality between women with limited-to-no-education and highly educated women were identified with the greatest disparity in the youngest age groups. We also identified that mortality rates were higher among older women. Women with contributory and special health insurance had lower mortality due to CC than women with subsidised or no health insurance. However, women with subsidised health insurance did not have significantly lower CC mortality rates than those with no insurance. This suggests the need to critically review access to diagnostic and treatment services for women served by the subsidised insurance plan. Information on type of insurance described more variation in CC mortality in the overall study population than education status after accounting for other risk factors such as age, rural and urban differences, and region of residence. However, education appeared to be a stronger individual risk factor when comparing mortality rates among the most and least educated women. The detection of inequitable risk ratios for CC mortality in young women associated with a number of socio-demographic risk factors represents an opportunity to target efforts to evaluate and improve CC prevention, diagnosis, treatment, and follow-up. Additionally, our results can be used to develop and implement interventions to optimise the impact of both existing and new resources to prevent premature mortality due to CC in Colombia.

5.5. References

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CHAPTER 6 – CONCLUSIONS

Understanding the role socio-demographic factors have in primary and secondary cervical cancer (CC) prevention (1-3) and CC mortality (4) in young Colombian women is key for both recognising inequities in the distribution of the social determinants of health (SDOH) and developing public policies to ensure resources are allocated to decrease the impact of CC in Colombian society.

This thesis identified socio-demographic characteristics associated with awareness of a primary prevention strategy and access to secondary prevention for CC. The objectives of this thesis also included determining if there were geographic areas with high risk of limited awareness of primary prevention or access to secondary CC prevention after accounting for previously identified socio-demographic factors. The final objective was to understand the socio-demographic factors associated with CC mortality among young women in Colombia. The purpose of this conclusions chapter is to highlight the most important findings from this work, discuss the relevance of the findings, examine strengths and weaknesses of the research, and suggest areas for future investigation.

6.1. Summary of Findings

This thesis describes inequities in the distribution of the SDOH in relation to CC prevention and CC mortality in Colombia. These inequities were expressed as limitations in the awareness of the human papillomavirus (HPV) vaccination (1, 3) and restrictions in accessing Pap testing (2, 3) faced by young women in Colombia. The mortality rates from CC also varied based on the socio-demographic attributes reported in official mortality records (4). The following paragraphs present the relevant findings of each of the chapters.

Chapter 2 reports on differences in the probability of having heard about HPV vaccination associated with socio-demographic attributes for women aged 13-49 years (1). This study was the first nationwide effort to measure whether women in Colombia were aware of the HPV vaccine and how this awareness varied based on their age, educational level, socioeconomic and working status, type of health insurance, urban or rural residence, and region of residence, among other factors. The results of this study show a low prevalence of women aware of the HPV vaccine and that women in socially disadvantaged conditions were less likely to have heard of the vaccine. The results also present significant interactions that show variations in the effects of age and region of residence based on the educational level of women, as well as differences in the effects of region of residence on having heard about the vaccine by rural or urban area of residence.

The work presented in Chapter 3 goes beyond previous Colombian reports that have used classical methodological approaches to evaluate factors associated with Pap testing. National data were explored using multilevel multivariable logistic regression to identify whether age, educational level, socioeconomic and working status, type of health insurance, living in a rural or urban area, region of residence, having children, and whether or not a woman reported making her own health care decisions were factors associated with having ever had a Pap test in a group of women aged 18-49 years. This analysis was unique in that it also took into consideration the role of contextual factors (2). The results of the analysis show that women with better socioeconomic conditions, those living in certain geographical regions and living in urban areas, as well as women with children were more likely to have had Pap testing. Women whose decisions were made by somebody else were less likely to have had Pap testing compared to those who made decisions for themselves. The educational level for each woman was an important factor to consider in this analysis, as well as the prevalence of no education in the neighbourhood where the women lived. The results showed a lower probability of Pap testing when the prevalence of no education in women's neighbourhood increased. In addition, it was observed that the effect of education, type of health insurance, age group, and region of residence varied with whether women lived in rural or urban areas.

Chapter 4 extends the questions presented in Chapter 2 and 3 by specifically exploring variation in the frequencies of women 13-49 years who had not heard of HPV vaccination and women 18-49 years who had not had Pap testing among geographic regions or departments (3). This study makes use of a structured methodology never applied before in Colombia to investigate spatial variations in access to primary and secondary CC prevention, after accounting for area-based socio-demographic factors. This study reports on the risk ratios for lack of awareness of HPV vaccine and failure to have had a Pap smear for each department, after accounting for socio-demographic factors of interest from the previous analyses in Chapter 2 and 3. The spatial clustering and the risk ratio maps presented in Chapter 4 show that living mainly in socially deprived departments increased the risk of women being unaware of HPV vaccination and lacking Pap testing, especially in departments adjacent to the Colombian border. The effect of the percentage of women living in rural areas on the lack of Pap testing varied according to whether the percentage of women with no education at the department level was above or below the national average.

The analysis presented in Chapter 5 examined associations between mortality rates due to CC and socio-demographic factors of women aged 20-49 years (4). This is the first study in Colombia to evaluate how socio-demographic factors relate to CC mortality specifically among young women. The results of this study show that the mortality rates of women with no education or primary education, those with no health insurance or subsidised insurance, women from certain geographic regions (i.e. Amazon-Orinoquía, Pacific, and Atlantic regions) and those with a rural residence differed from the rates for women with more education, those with contributory or special health insurance plans, those who resided in the Eastern region, and women from urban areas of Colombia. Larger relative differences in the mortality rates among educational levels were observed in younger women compared to older individuals. Also, differences in the mortality rates observed among types of health insurance varied among some age groups.

The four studies presented in Chapters 2 through 5 of this thesis identified common risk factors associated with the CC prevention and outcome measures of interest. Level of education, type of health insurance, having a rural or urban residence, and region of residence were consistent socio-demographic drivers of inequities in CC prevention and mortality in Colombia.

Women with limited or no education had a reduced probability of both having heard of HPV vaccination and having had Pap smears. As shown in Chapter 3, having had Pap testing was further influenced by the level of education of the neighbourhood where each woman lived, with additional differences for women with rural as compared to urban residences. Women with a rural residence were less likely to have Pap testing than women living in urban areas, observing wider differences in the odds of Pap testing among women with limited-to-no education compared to those with higher levels of education. Additionally, a higher prevalence of no education in a neighbourhood resulted in lower odds of having a Pap test in both rural and urban areas, especially when comparing women with limited-to-no education to those with secondary or higher education. Similarly, the findings presented in Chapter 4 demonstrated that a high prevalence of no education at the department level was associated with a low department prevalence of Pap tests, specifically in departments classified as being at or above the national prevalence of women living in rural areas. Finally, Chapter 5 shows that CC mortality rates were higher among women with limited or no education compared to women with higher education, observing wider differences in younger age groups.

The type of health insurance was another factor associated with the inequities in CC prevention and mortality presented in this thesis. Compared to women with contributory health insurance, those having subsidised insurance and women with no insurance had a decreased awareness of HPV vaccination. The effect of health insurance on having had Pap testing varied by whether women lived in rural or urban areas. Higher prevalences of women with subsidised insurance at the department level were further associated with not having heard of HPV vaccination and not having Pap testing in Chapter 4. In the case of CC mortality, having subsidised insurance and not having insurance were associated with increased CC mortality rates, with differences in mortality rates among types of health insurance by age groups. Also, there was no a significant difference in CC mortality between women with subsidised insurance and those with no insurance, regardless of age.

All chapters in this thesis explored differences between rural and urban residence. Compared to living in urban areas, having a rural residence reduced the probability of awareness of HPV vaccination, especially in some regions of Colombia, as was observed in the significant interaction between urban or rural residence and region of residence. Rural residence was also associated with a decreased reporting of having had Pap testing, particularly in some regions of the country and among women with no insurance or subsidised health insurance. Additionally, among all levels of education, women living in rural areas had a lower odds of Pap testing compared to those in urban areas. Furthermore, the ecological analysis in Chapter 4 identified that increases in the percentages of rurality at the department level were associated with an increased risk ratio of having more observed than expected cases of women with no Pap, but only in departments classified as having a prevalence of no education at or above the national prevalence of no education. In contrast, living in rural areas was associated with lower CC mortality rates.

Finally, living in the Amazon-Orinoquía region was commonly associated with low awareness of HPV vaccination and Pap test uptake and high rates of CC mortality. The results of the spatial analyses presented in Chapter 4 confirmed that, after accounting for other risk factors, several departments located in the Amazon-Orinoquía and a few departments from the Pacific and Atlantic regions (e.g. Chocó, Sucre, and La Guajira) had a higher risk of women not having access to primary and secondary CC prevention initiatives relative to the national average.

6.2. Relevance of the Findings

The results presented in this thesis could inform governmental and non-governmental agencies, policy makers, and health care professionals to help improve initiatives currently in place to prevent CC in Colombia.

All the chapters comprising this body of work provide new evidence of the impact of socio-demographic factors on CC prevention and mortality, specifically among young Colombian women. The results presented in the previous pages made use of multivariable regression models to account for confounding and interactions effects of the risk factors of study, overcoming some of the limitations of other studies in the CC prevention and mortality fields reported by other Colombian researchers.

The article presented in Chapter 2 is the first nationwide study examining factors associated with a primary prevention strategy for CC in Colombia. The study population incorporated women aged 13-49 years, expanding the age of participants reported in previous local studies on awareness of HPV vaccination in Colombia. The methodology used in this study considered interaction effects to demonstrate that the probability of HPV awareness had a differential impact based on the educational level and urban or rural residence of women. This study highlights the need for strengthening efforts to educate women in relation to CC, the role of HPV on the development of CC, and the importance of HPV vaccination, especially among younger age groups, women living in precarious social conditions, those with limited or no education, those living in rural areas, and women who lived in socially deprived regions of Colombia. The limited awareness of the vaccine by the youngest age groups in this study was a concerning result because these are the women in the target groups to receive HPV vaccination.

The methodology used for the analysis of the factors associated with Pap testing presented in Chapter 3 considered the potential for clustering in outcome due to similarities in responses within neighbourhoods and municipalities by using a multilevel multivariable logistic regression. The analysis also considered the potential for contextual effects based on the reported responses of other women in the same neighbourhood. The resulting effect of lack of education at the neighbourhood level on the probability of Pap testing is a new finding that requires attention when planning secondary prevention programmes for CC in Colombia. This contextual effect is pointing out that both individual attributes of women and the level of education of the immediate area where women reside could limit access to Pap testing. Also, the likelihood of having had a Pap test in Colombia was affected by education, type of insurance, age, and region of residence, with variations based on whether women had a rural or urban residence.

Chapter 4 expands on the analysis of the individual risk factors presented in Chapters 2 and 3, providing an ecological depiction of limitations in access to primary and secondary CC prevention programmes in Colombia. This is the first study in the country using global and local test for clustering to detect spatial correlations in the department frequencies of having not heard of the HPV vaccine and having not had a Pap test. Also, this study provides novel results based on the spatial regression models to explain lack of access to primary and secondary CC prevention. The finding showing a high risk of lacking access to CC prevention in several departments of the Amazon-Orinoquía, Pacific, and Atlantic regions after accounting for other known socio-demographic risk factors is a concern that should help identify specific departments where the delivery of CC prevention programmes could be enhanced and guide decision makers and health care practitioners to target high-risk areas in Colombia for CC prevention programmes.

The analysis of CC mortality in Chapter 5 made use of CC mortality records from 2005 to 2013 and population projection data made available by the National Administrative Department of Statistics of Colombia to examine the importance of socio-demographic risk factors including educational level and type of health insurance. Because of preliminary concerns about missing data in the mortality records, we compared a complete case analysis to analysis using multiple imputation and were able to show that there were no substantial differences in the results of the two approaches for these data. Unlike other studies conducted in Colombia, the mortality analyses presented in Chapter 5 were specifically focused on young women. This is also the first study in Colombia reporting that the relative inequities in CC mortality between highly educated and no-to-limited educated women were larger among younger women compared to the older women. This finding suggests that improving health care access for women with no or limited education or increasing the level of education could hypothetically reduce deaths due to CC. An additional remarkable result was that having a subsidised health insurance did not have a statistically significant impact on reducing CC mortality compared to not having a health insurance. This result implies that women with subsidised insurance face similar barriers to access health care than women with no insurance. Based on this result, additional efforts are needed to offer women in Colombia the same quality and access to health care benefits, regardless of their type of health insurance. The results of this study could guide the evaluation of the access that Colombian women have to timely diagnosis and to prompt consideration of the potential differences in access to early CC treatment

The findings of this thesis provide an opportunity to improve and develop strategies for CC prevention and ensure a prompt access to diagnosis, treatment, and follow-up for young women in Colombia. Policy makers and clinicians should be aware of the relevance of individual and contextual factors in CC prevention. Health promotion and disease prevention programmes, along with increased efforts to improve access of women to formal education, are key components to advance in the awareness and knowledge of CC and empower women in taking care of their own health. This is especially relevant in rural areas and those Colombian regions in which the current impact of CC prevention programmes have been demonstrated as limited. To overcome, in part, the fragmented structure of the Colombian health care system, it is essential to create innovative strategies to reach high-risk groups and ensure that women have an equitable access to care. It is desirable that these approaches are designed and evaluated in partnership with governmental and non-governmental agencies, community organisations, health insurance companies, health care providers, and other stakeholders to tailor each approach to the characteristics of women living in socially deprived Colombian departments.

6.3. Limitations

The primary limitations to this thesis are associated with the types of data that were available for analysis. The results presented in Chapters 2 through 4 rely on self-reported information obtained from the 2010 National Demographic and Health Survey (NDHS). The use of self-reported data could be a source of information bias, including over-reporting of screening participation and recall bias (5). Self-reported data could also lead to an inaccurate prevalence of the risk factors under study compared to the real distribution of these factors in Colombian women, resulting in misclassification bias. For example, it has been identified that women living in socially disadvantaged conditions tend to over-report participation in CC screening programmes (6). Artificially inflated screening rates could have an impact on the perceived quality of screening programmes (6), giving a sense of confidence to governmental and non-governmental agencies and health insurance companies with regards to successful CC screening coverage rates. Similarly, these inaccuracies could be present when investigating the prevalence of women who had heard of the HPV vaccine. The use of self-reported data in the 2010 NDHS might have a further impact on the mortality rates presented in Chapter 5, given that the population at risk computed for the analysis was based on age-stratified distributions of education, type of insurance, and rural or urban residence obtained from women in the NDHS.

The presence of social desirability, a type of information bias, is another problem related to self-reported data in the risk factors used in this thesis. Social desirability was defined by Chung and Monroe (7) as “the tendency of individuals to underestimate (overestimate) the likelihood they would perform an undesirable (desirable) action.” Sensitive questions obtained from the 2010 NDHS could be a source of social desirability, such as those inquiring about sexual activity or use of contraceptive methods (see Chapter 2), as well as questions about who makes final decisions on women's own health (see Chapter 3).

One more limitation to this thesis could be related to the dependent variable used in Chapter 2. This variable resulted from the amalgamation of two questions included in the 2010 NDHS. Women were asked if they had heard about HPV. If yes, they were also asked if they had heard about a vaccine to prevent CC. Women who answered both questions as "yes" were classified as having heard about HPV vaccination. The resulting measure evaluates awareness of HPV vaccination, but certainly it does not measure women's level of knowledge about the vaccine. Furthermore, in this initial study, the presence of clustering in the data due to neighbourhood and municipality was not considered in the formal analysis. This could lead to underestimation of standard errors (8, 9) and overestimation of test statistics (9). The use of multilevel analysis is recommended to avoid bias due to clustering (8). However, the impact of the failure to account for clustering in this analysis should have been relatively small based on comparison to the later analysis of the Pap test data. After accounting for the fixed effects in the model presented in Chapter 3, the variance partitioning coefficient reflecting the unaccounted differences among neighbourhoods and municipalities was 6% and 4.8%, respectively.

Recall and interviewer bias are additional limitations to this thesis. Recall bias could be a possible threat to validity in the 2010 NDHS data and the mortality records. However, in the NDHS, women would be relatively unlikely to make an error in whether they had heard about the HPV and also if they had ever heard about a vaccine to prevent CC. Women would most likely have had even less difficulty remembering whether they had a Pap smear before. This should have had a relatively little impact on the reported prevalence of the dependent variables studied in Chapters 2, 3, and 4. In relation to the mortality data, inconsistencies in the personal information of deceased individuals included in the death certificates have been described for specific data in Colombia, such as educational attainment, type of health insurance, and urban or rural residence (10). The person who completes this information could take it from medical records, if available; otherwise, these data could be required to a family member or companion person of the deceased. This could be a source of recall bias or social desirability bias.

The official results of the 2010 NDHS reported compliance with high standards in regards to training people who collected the information from participants (11); however, interviewer bias could be introduced at any time during the interviewing time, leading to inaccuracy of the estimates measured (12). This kind of interviewer bias could affect the quality of data depending on how an interviewer asks questions and also based on how characteristics of the interviewer might influence answers given by the interviewee (12).

Selection bias could be present in the 2010 NDHS data set, despite the intent to collect the data using random sampling techniques (11), given that participation in the survey was voluntary. This could result in a sample that differs from the target population (13). Women who participated in the 2010 NDHS were those who were at home and those who chose to answer the questions.

Limitations associated with missing data and low response rate were not a substantial concern for the 2010 NDHS data. The reported overall response rate of the 2010 NDHS was high (92%) (11) and there were no missing values in the independent risk factors evaluated. In Chapter 3, only 18 women did not supply information about their Pap testing status, representing less than 1% of missingness in the dependent variable (2). This small percentage of missing values did not have an important impact on the estimates. In contrast, the mortality data used in Chapter 5 had close to 20% missingness in some of the risk factors of interest and the auxiliary variables, with more missing values for educational level, type of health insurance, rural or urban residence, region of residence, and age (4). Given that missing values could have an impact on accuracy of estimates and reduce statistical power (14), multiple imputation was used during the data analysis to prevent bias and loss of power and precision.

Other limitations of this thesis are related to variables that were not available in the data sets used for the analyses. For example, although many authors have recognised distance to primary and specialised care as a barrier faced by Colombians to access health services (15-19), this information was not available in the 2010 NDHS nor in the mortality records. The inclusion of distance to a health centre under contract with each woman's health insurance company could have provided further understanding of variations in geographical access to primary or secondary

CC prevention, as well as treatment for CC. Also, population density has been associated with access to health care, with better access to services when the population density is high (20, 21). Chapter 4 included population density as one of the variables in the analysis (3). Incorporating population density could have shown whether preventive programmes for CC are reaching women living in areas with limited health services or demonstrated a lack of offer of cancer care for women living in small cities.

Furthermore, although income is one of the most important SDOH (22) and that a positive change in household income has been associated with a better health status of individuals in Colombia (23), information about income was unavailable in both the 2010 NDHS and the mortality data sets. Including income in the analysis could provide a picture of its relationship with access to CC prevention and treatment in Colombia. Measuring the impact of income on CC prevention could help health care providers and government entities to reorient CC-related services based on the needs of the population. Also, new policies could be developed for direction of resources towards regions and areas of Colombia most in need.

6.4. Future Work

Further studies could build upon the results presented in this thesis to expand the understanding CC prevention and mortality among young women in Colombia. Incorporating the variables recommended in the previous discussion, such as distance to a health centre and income, could provide insights about their impact on access primary and secondary prevention and treatment services for CC.

Considering that having knowledge about HPV is central to improve uptake of HPV vaccination, further studies using validated and culturally-appropriate surveys could be useful to measure the level of knowledge of HPV and HPV vaccination among women by their socio-demographic characteristics. More complete measurements of knowledge about HPV could, at the same time, decrease any potential bias introduced by the dichotomous self-reported data. The findings from this study would be helpful for policy makers to modify health education plans to the local needs of specific regional populations and increase the uptake HPV vaccination in Colombia.

As presented in Chapter 3 of this thesis, 13% of Colombian women had never have had a Pap test (2). To better understand the socio-demographic risk factors related to compliance with the recommendations by the Colombian National Institute of Cancer for Pap testing (24), longitudinal studies could be done to evaluate access to Pap test in the last three years. Also, given that an adequate follow-up is needed for a meaningful impact of CC screening (25), a retrospective study assessing factors related to follow-up among women with abnormal Pap smears could reveal areas of improvement in the continuum of care for women with cervical lesions. The inclusion of contextual and environmental factors, such as distance to treatment, associated with both access to recent Pap testing and proper follow-up would enlighten the role of such factors in accessing CC prevention and treatment programmes. To avoid misclassification linked with the use of self-reported data, objective information about CC screening coverage could be obtained from insurance companies' records.

In relation to access of women to timely CC diagnosis, the use of the data available from the cancer registries in Colombia represents a unique opportunity to study socio-demographic factors associated with the stage of CC at the at the time of diagnosis, access to treatment for CC, and survival of women with CC. The results of these studies would identify the presence of inequities in opportunities to access to medical care by socio-demographic characteristics of women. These findings could be useful to further evaluate deficiencies in current primary and secondary CC prevention programmes, focusing the attention on possible factors that could be implemented to reduce CC mortality in specific groups.

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Silvia Bermedo-Carrasco

Candidata a PhD

Escuela de Salud Pública, Universidad de Saskatchewan

Saskatoon, SK

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Dear Editor,

We recently published in BMC Public Health the article entitled *"The role of socio-demographic factors in premature cervical cancer mortality in Colombia."* The complete reference of the article is available at the end of this e-mail.

I would like to kindly request the permission to reproduce this article for including it in my doctoral thesis.

Please do not hesitate to contact me if you have any questions.

Sincerely,

Silvia Bermedo-Carrasco

PhD Candidate

School of Public Heath, University of Saskatchewan

Saskatoon, SK, Canada

Bermedo-Carrasco S, Waldner CL. The role of socio-demographic factors in premature cervical cancer mortality in Colombia. BMC Public Health. 2016; 16:981. http://dx.doi.org/10.1186/s12889-016-3645-1

APPENDIX B
EXEMPTION FROM ETHICS REVIEW

UNIVERSITY OF SASKATCHEWAN

Research Ethics Office
NRC/PBI Building Box 5000 RPO University
1607 – 110 Gymnasium Place Saskatoon SK S7N 4J8 Canada
Telephone: (306) 966-2975 Facsimile: (306) 966-2069

To: Robert W. Buckingham, PhD
School of Public Health
University of Saskatchewan
Health Sciences Building
107 Wiggins Road
Saskatoon, SK S7N 5E5

Student: Silvia Bermedo

Date: June 3, 2013

Re: PROFAMILIA and Measure DHS data sets

Thank you for submitting your study for review. In the opinion of the Research Ethics Board (REB) this study is regarded as as exempt as per **Article 2.4 of The Tri-Council Policy Statement (TCPS): Ethical Conduct for Research Involving Humans, December 2010** which indicates the following:

"REB review is not required for research that relies exclusively on secondary use of anonymous information, or anonymous human biological materials, so long as the process of data linkage or recording or dissemination of results does not generate identifiable information."

It should be noted that though your project is exempt of ethics review, your project should be conducted in an ethical manner (i.e. in accordance with the information that you submitted). It should also be noted that any deviation from the original methodology and/or research question should be brought to the attention of the Behavioural Research Ethics Board for further review.

Sincerely,

Beth Bilson, Chair
Behavioural Research Ethics Board
University of Saskatchewan

Cc: Rein Lepnurm, PhD, School of Public Health

Assistance with Ethics approval

Radcliffe, Beryl <beryl.radcliffe@usask.ca> 3 June 2013 09:13
To: "Bermedo-Carrasco, Silvia" <srb650@mail.usask.ca>
Cc: "Buckingham, Robert" <b.buckingham@usask.ca>, "Lepnurm, Rein" <r.lepnurm@usask.ca>

Hi Silvia and thank you for your clarification. Based on your response below your project would be exempt from ethics review. If you would like a formal letter, please provide your supervisor's name and contact information for the letter to be sent.

Beryl Radcliffe
Ethics Facilitator (Behavioural)
Research Ethics Office
Phone: 306-966-2084
Fax: 306-966-2069

Hi Beryl,

Thank you very much for your answer and information. Based on your comments, I would like to clarify the following points:

In relation to the PROFAMILIA and Measure DHS data sets, the data collection was anonymous. My research will relay exclusively on the use of this anonymous information. The data provided by the DHS will be analysed aggregately, it is not possible to generate identifiable information. In fact, there is no risk of participants' identification, since the database does not have unique characteristics of the surveyed women, such as identification number, name, social insurance number, etc.

In relation to the cancer mortality database, this is public information. Access to the database is given after a formal request sent to the Colombian Department of Statistics. In addition, the analysis of this database will not include any data linking to other data.

Subsequently, is it required to apply for an ethics approval? I reviewed the form and the majority of the questions do not apply for me.

Thank you again for your support,

Silvia Bermedo-Carrasco

On 22 May 2013 09:44, Radcliffe, Beryl <beryl.radcliffe@usask.ca> wrote:
Hi Silvia, we will need clarification on the PROFAMILIA and Measure DHS data set. As indicated in [page 19 - 20 of attached] Article 2.4 REB review is not required for research that relies exclusively on secondary use of anonymous information, or anonymous human biological materials, so long as the process of data linkage or recording or dissemination of results does not generate identifiable information.
Application Secondary use refers to the use in research of information or human biological materials originally collected for a purpose other than the current research purpose. Anonymous information and human biological materials are distinct from those that have been coded, and also from those that have been anonymized (see Section A of Chapters 5 below).
Rapid technological advances facilitate identification of information and make it harder to achieve anonymity. These activities may heighten risks of identification and possible stigmatization where a dataset contains information about or human biological materials from a population in a small geographical area, or information about individuals with unique characteristics (e.g., uncommon field of occupational specialization, diagnosis with

a very rare disease). Where the researcher seeks data linkage of two or more anonymous sets of information or human biological materials and there is a reasonable prospect that this could generate identifiable information, then REB review is required.

Section A of Chapters 5 For the purposes of this Policy, researchers and REBs shall consider whether information proposed for use in research is identifiable. The following categories provide guidance for assessing the extent to which information could be used to identify an individual:
* Directly identifying information - the information identifies a specific individual through direct identifiers (e.g., name, social insurance number, personal health number).
* Indirectly identifying information - the information can reasonably be expected to identify an individual through a combination of indirect identifiers (e.g., date of birth, place of residence or unique personal characteristic).
* Coded information - direct identifiers are removed from the information and replaced with a code. Depending on access to the code, it may be possible to re-identify specific participants (e.g., the principal investigator retains a list that links the participants' code names with their actual name so data can be re-linked if necessary).
* Anonymized information - the information is irrevocably stripped of direct identifiers, a code is not kept to allow future re-linkage, and risk of re-identification of individuals from remaining indirect identifiers is low or very low. Since your data set likely falls in this category, REB review is required.
* Anonymous information - the information never had identifiers associated with it (e.g., anonymous surveys) and risk of identification of individuals is low or very low.

Cervical cancer in Colombia in 2010. This information was provided by the National Department of Statistics in Colombia:
[Page 17] Article 2.2 Research that relies exclusively on publicly available information does not require REB review when:
(a) the information is legally accessible to the public and appropriately protected by law; or
(b) the information is publicly accessible and there is no reasonable expectation of privacy.
Please confirm that this data is publically assessable and that there will be no data linking to other data sets that could heighten the risk or re-identification.

Beryl Radcliffe
Ethics Facilitator (Behavioural)
Research Ethics Office
Phone: 306-966-2084
Fax: 306-966-2069

-----Original Message-----
From: sbermedo@gmail.com [mailto:sbermedo@gmail.com] On Behalf Of Silvia Bermedo-Carrasco
Sent: Wednesday, May 22, 2013 9:25 AM
To: Radcliffe, Beryl
Cc: Buckingham, Robert; Lepnurm, Rein
Subject: Assistance with Ethics approval

Dear Ms. Radcliffe,

My name is Silvia Bermedo-Carrasco; I am a PhD student at the School of Public Health. As per discussed by phone, I have a question regarding the datasets that with my supervisors and advisory committee are considering to use for my thesis research.

The first one comprises information from a health survey conducted in Colombia in 2010, including 53,521 women. This study was conducted by PROFAMILIA and Measure DHS. The latter agency provided me the anonymized database; there is no information about participants' ID or name. Only a individual code was assigned by the agencies to participants. I do not have access to participants' identifiers. The second dataset contains information about mortality due to cervical cancer in Colombia in 2010. This information was provided by the National Department of Statistics in Colombia. As the previous dataset, the information is also anonymous; it does not have confidential information that could be potentially used for tracking identity of people. All the analyses will be aggregated. Therefore, I want to ask you if an ethics approval is required.

Thank you very much for your information,

Silvia Bermedo-Carrasco
PhD student, School of Public Health

APPENDIX C

FINAL MULTILEVEL MODEL OF LOG ODDS HAVING HAD A PAP TEST

$$\log\left(\frac{\pi}{1-\pi}\right) = \beta_0 + \beta_1 X_{wealth} + \beta_2 X_{final\_say} + \beta_3 X_{children} + \beta_4 X_{work} + \beta_5 X_{education} + \beta_6 X_{insurance} + \beta_7 X_{region} + \beta_8 X_{Rural/urban} + \beta_9 X_{age} + \beta_{10} X_{neighbourhood\_prev\_no\_Educ} + \beta_{11} X_{neighbourhood\_prev\_no\_Educ} X_{education} + \beta_{12} X_{Rural/urban} X_{education} + \beta_{13} X_{Rural/urban} X_{insurance} + \beta_{14} X_{Rural/urban} X_{age} + \beta_{15} X_{Rural/urban} X_{region} + \nu + \mu,$$

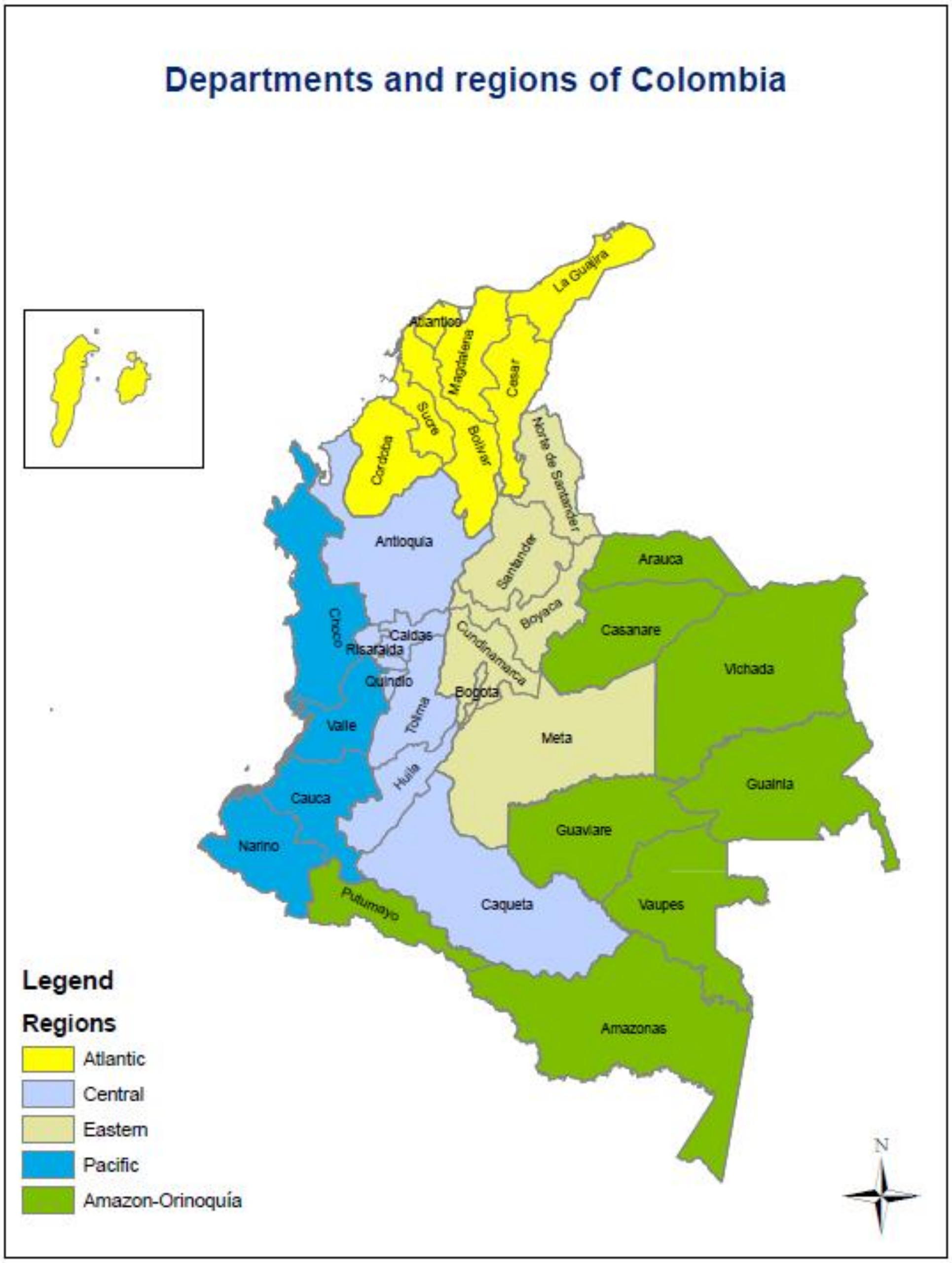
where the subscripted names represent:

- wealth: Wealth quintile; reference category=Highest
- final_say: Final say on health; reference category=Respondent alone
- children: Having had children or not; reference category= No
- work: Current working status; reference category= Yes
- education: Educational level; reference category= Higher
- insurance: Type of insurance; reference category= Contributory regimen
- region: Regions of the country; reference category= Eastern
- Rural/urban: rural/urban area of residence; reference category=Urban
- age: Group of age; reference category=18 to 24 years old
- neighbourhood_prev_no_Educ: Prevalence of no education within groups of houses
- ν error at the municipality level
- μ error at the neighbourhood level

APPENDIX D

DEPARTMENTS AND REGIONS OF COLOMBIA

The figure below shows the departments and regions established and used in the 2010 NDHS[1]



[1] Ojeda G, Ordóñez M, Ochoa LH. Encuesta Nacional de Demografía y Salud 2010. Bogotá; 2010

APPENDIX E

ADDITIONAL FILES CHAPTER 5

Table E-1 presents the estimates of the final model using complete data that assessed the association between educational level and CC mortality adjusting by rural or urban residence, region of residence, and age.

Table E-1. Results of the final model using complete data including the interaction between age and educational level (n=4247).

	IRR	(95%CI)	Wald test *p*-value
Educational level			<0.0001
No education	32.5	(7.70-137)	
Primary	14.1	(5.27-38.0)	
Secondary	3.87	(1.47-10.2)	
Higher	Ref.		
Rural or urban residence			<0.0001
Rural	0.39	(0.35-0.43)	
Urban	Ref.		
Region of residence			<0.0001
Atlantic	1.13	(1.00-1.28)	
Central	1.3	(1.15-1.47)	
Pacific	1.39	(1.23-1.57)	
Amazon-Orinoquía	1.61	(1.32-1.97)	
Eastern	Ref.		
Age groups			<0.0001
25-29 years	4.31	(1.58- 11.8)	
30-34 years	15.1	(5.93- 38.5)	
35-39 years	27.7	(11.0- 69.9)	
40-44 years	29.8	(11.8-75.5)	
45-49 years	49.7	(19.9-124)	
20-24 years	Ref.		
Age groups X educational level			<0.0001
25-29 years X no education	0.44	(0.08-2.34)	
25-29 years X primary education	0.88	(0.29-2.68)	
25-29 years X secondary education	0.93	(0.31-2.82)	
30-34 years X no education	0.45	(0.10-2.05)	
30-34 years X primary education	0.41	(0.14-1.16)	
30-34 years X secondary education	0.77	(0.27-2.15)	
35-39 years X no education	0.29	(0.06-1.27)	
35-39 years X primary education	0.35	(0.13-0.99)	
35-39 years X secondary education	0.68	(0.25-1.89)	
40-44 years X no education	0.35	(0.08-1.54)	
40-44 years X primary education	0.42	(0.15-1.19)	
40-44 years X secondary education	0.75	(0.27-2.07)	
45-49 years X no education	0.23	(0.05-1.00)	
45-49 years X primary education	0.33	(0.12-0.92)	
45-49 years X secondary education	0.53	(0.19-1.46)	

Table E-2 presents the estimates of the final model using complete data that assessed the association between with type of health insurance and CC mortality adjusting by rural or urban residence, region of residence, and age.

Table E-2. Results of the final model using complete data including the interaction between age and type of health insurance (n=4247).

	IRR	(95%CI)	Wald test *p*-value
Type of health insurance			0.07
Non-affiliated	1.5	(0.60-3.72)	
Subsidised insurance	1.96	(0.99-3.85)	
Special insurance	2.91	(0.64-13.1)	
Contributory insurance	Ref.		
Rural or urban residence			<0.0001
Rural	0.52	(0.47-0.57)	
Urban	Ref.		
Region of residence			<0.0001
Atlantic	1.04	(0.92-1.18)	
Central	1.28	(1.14-1.44)	
Pacific	1.34	(1.18-1.51)	
Amazon-Orinoquía	1.64	(1.34-2.01)	
Eastern	Ref.		
Age groups			<0.0001
25-29 years	4.69	(2.47-8.91)	
30-34 years	13.4	(7.30-24.8)	
35-39 years	25.4	(13.9-46.4)	
40-44 years	29.1	(15.9-53.1)	
45-49 years	37.6	(20.7-68.4)	
20-24 years	Ref.		
Age groups X type of health insurance			<0.0001
25-29 years X non-affiliated	1.46	(0.53-3.99)	
25-29 years X subsidised insurance	0.91	(0.43-1.95)	
25-29 years X special insurance	0.1	(0.01-1.20)	
30-34 years X non-affiliated	1.03	(0.39-2.70)	
30-34 years X subsidised insurance	0.89	(0.43-1.82)	
30-34 years X special insurance	0.22	(0.04-1.20)	
35-39 years X non-affiliated	0.99	(0.38-2.55)	
35-39 years X subsidised insurance	0.79	(0.39-1.61)	
35-39 years X special insurance	0.2	(0.04-1.04)	
40-44 years X non-affiliated	1.05	(0.41-2.69)	
40-44 years X subsidised insurance	1	(0.50-2.03)	
40-44 years X special insurance	0.32	(0.07-1.53)	
45-49 years X non-affiliated	1.47	(0.57-3.78)	
45-49 years X subsidised insurance	1	(0.50-2.02)	
45-49 years X special insurance	0.27	(0.06-1.29)	

Table E-3 presents the estimates of the final model using imputed data that assessed the association between with educational level and CC mortality adjusting by rural or urban residence, region of residence, and age.

Table E-3. Results of the final model using imputed data including the interaction between age and educational level (n=5098).

	IRR	(95%CI)	Wald test *p*-value
Educational level			<0.0001
No education	26.8	(6.65-108)	
Primary	14	(5.69-34.6)	
Secondary	3.46	(1.42-8.45)	
Higher	Ref.		
Rural or urban residence			<0.0001
Rural	0.39	(0.36-0.43)	
Urban	Ref.		
Region of residence			<0.0001
Atlantic	1.2	(1.08-1.34)	
Central	1.25	(1.12-1.40)	
Pacific	1.34	(1.19-1.49)	
Amazon-Orinoquía	1.68	(1.41-2.01)	
Eastern	Ref.		
Age groups			<0.0001
25-29 years	4.19	(1.67-10.5)	
30-34 years	13.8	(5.85-32.6)	
35-39 years	25.4	(10.9-59.2)	
40-44 years	28.9	(12.4-67.6)	
45-49 years	47.4	(20.5-109)	
20-24 years	Ref.		
Age groups X educational level			<0.0001
25-29 years X no education	0.62	(0.13-3.02)	
25-29 years X primary education	0.92	(0.33-2.56)	
25-29 years X secondary education	1.07	(0.39-2.95)	
30-34 years X no education	0.55	(0.13-2.35)	
30-34 years X primary education	0.45	(0.17-1.19)	
30-34 years X secondary education	0.91	(0.35-2.35)	
35-39 years X no education	0.39	(0.09-1.66)	
35-39 years X primary education	0.4	(0.16-1.03)	
35-39 years X secondary education	0.81	(0.32-2.07)	
40-44 years X no education	0.46	(0.11-1.93)	
40-44 years X primary education	0.45	(0.17-1.15)	
40-44 years X secondary education	0.83	(0.33-2.13)	
45-49 years X no education	0.32	(0.08-1.31)	
45-49 years X primary education	0.35	(0.14-0.90)	
45-49 years X secondary education	0.62	(0.24-1.57)	

Table E-4 presents the estimates of the final model using imputed data that assessed the association between with type of health insurance and CC mortality adjusting by rural or urban residence, region of residence, and age.

Table E-4. Results of the final model using imputed data including the interaction between age and type of health insurance (n=5098).

	IRR	**(95%CI)**	**Wald test *p*-value**
Type of health insurance			0.07
Non-affiliated	1.55	(0.65-3.67)	
Subsidised insurance	2.06	(1.08-3.94)	
Special insurance	4.01	(1.13-14.3)	
Contributory insurance	Ref.		
Rural or urban residence			<0.0001
Rural	0.52	(0.47-0.57)	
Urban	Ref.		
Region of residence			<0.0001
Atlantic	1.1	(0.98-1.23)	
Central	1.24	(1.11-1.39)	
Pacific	1.28	(1.14-1.43)	
Amazon-Orinoquía	1.74	(1.45-2.09)	
Eastern	Ref.		
Age groups			<0.0001
25-29 years	4.73	(2.55-8.75)	
30-34 years	13.5	(7.52-24.3)	
35-39 years	25.2	(14.1-44.9)	
40-44 years	30	(16.9-53.5)	
45-49 years	38.8	(21.8-68.9)	
20-24 years	Ref.		
Age groups X type of health insurance			<0.0001
25-29 years X non-affiliated	1.64	(0.64-4.25)	
25-29 years X subsidised insurance	0.99	(0.48-2.03)	
25-29 years X special insurance	0.07	(0.01-0.69)	
30-34 years X non-affiliated	1.08	(0.43-2.71)	
30-34 years X subsidised insurance	0.92	(0.46-1.83)	
30-34 years X special insurance	0.15	(0.03-0.64)	
35-39 years X non-affiliated	1.11	(0.45-2.74)	
35-39 years X subsidised insurance	0.87	(0.44-1.70)	
35-39 years X special insurance	0.14	(0.03-0.56)	
40-44 years X non-affiliated	1.23	(0.50-3.02)	
40-44 years X subsidised insurance	1.04	(0.53-2.03)	
40-44 years X special insurance	0.21	(0.06-0.81)	
45-49 years X non-affiliated	1.63	(0.67-3.98)	
45-49 years X subsidised insurance	1.05	(0.54-2.06)	
45-49 years X special insurance	0.22	(0.06-0.82)	