ORIGINAL ARTICLE

CERVICAL CANCER INCIDENCE AND PATIENT SURVIVAL IN MANIZALES, COLOMBIA, 2008-2012

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ABSTRACT

Objective: To estimate the cervical cancer incidence and survival rates by histological subtype and stage in Manizales, Colombia during 2008-2012; and to compare the survival rate to the one from the previous five years. **Materials and methods:** Using population-based data, incidence rates by age were standardized for each histological subtype. Active and passive follow-up was performed to determine vital status and cause of death at 60 months. The Kaplan-Meier method and Cox models were adjusted to estimate overall survival by each covariant. **Results:** A total of 217 new cases were observed; with a mean incidence of 17.8 per 100,000 woman-years. Stages III-IV were more frequently observed in patients of medium and low socioeconomic status. At 5 years, the survival rate was 68.9%; ages over 70 years were associated with lower survival rates (p<0.001). Risk of death was 90% higher in patients with undifferentiated or unknown histological samples, when compared with those with squamous cell carcinoma (HR 1.9, 95% CI: 1.1-3.3). Likewise, the risk of death was 1.7 times higher for patients aged over 70 years (HR 2.7, 95% CI 1.6-4.8); and it was also found to be 3 times higher for stage III (HR 4.3, 95% CI: 1.8-10.2) and 7 times higher for stage IV (HR 8.7, 95% CI: 3.6-20.1), when compared with stage I. **Conclusion:** The incidence rate of cervical cancer in Manizales was found to be similar to the global and continental rates and lower than those from other Colombian cities with similar characteristics. Advanced stages were more frequent in women of low socioeconomic status. Survival was associated with age, histological subtype and staging.

Keywords: Uterine Cervical Neoplasms; Incidence; Survival; Colombia (source: MeSH NLM).

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INTRODUCTION

Cervical cancer is the second most common cancer in women, after breast cancer and followed by endometrial and ovarian cancers; it influences the global incidence of cancer, especially in Latin American, Southeast Asian, and African countries [1]. Despite scientific advances in surgery, chemotherapy and radiotherapy, global survival has had discrete improvements in the last two decades, even at the early stages of the disease [2]. GLOBOCAN 2018 showed a worldwide incidence of 14 cases per 100,000 women. In South America the cumulative incidence of cervical cancer is 2.5% with respect to world population [2].

The CONCORD 3 study, which evaluated five-year survival for the 18 most common cancers on five continents, showed a 50-70% cervical cancer survival in Central and South America, Asia, and Europe; 70% or more in Japan, Korea, Taiwan, Denmark, Norway, Switzerland, and

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Cuba; 60-69% in 29 other countries; and 50-59% in Argentina, Ecuador, Martinique, Peru, Uruguay, India, Kuwait, Latvia, Lithuania, Bulgaria, Poland, Russia, and Malta [1].

Manizales is a medium-sized city located on the central mountain range of the Colombian Andes, with a population of nearly 400,000 inhabitants mostly concentrated in urban areas (93% urbanization). During the period 2003-2007, the city reported an age-adjusted incidence rate of 19.9 per 100,000 women per year [3]. Other Colombian cities, such as Bucaramanga and Cali reported incidence rates of about 20 per 100,000 women per year, and Pasto with 27 cases per 100,000 [4]. During 2008-2012, the highest incidence was found in Barranquilla with 26.6 [5], followed by Pasto with 18 new cases per 100,000 women-year [6]; a lowest incidence in Cali with 15.3 [7] and in Bucaramanga with 13 new cases per 100,000 women-year [8].

A previous study about cervical cancer survival in Manizales during 2003-2007 found that overall survival at five years was 51.4%, with a higher probability of survival in women from the contributory social security regime, compared to those in the subsidized regime and special or exception regimes. By correlating survival with socioeconomic position, differences found could be explained by associated comorbidities, delays in diagnosis and barriers to accessing timely treatment [9].

These results increased the need to analyze a new period to monitor the behavior of incidence and survival, to obtain population-based epidemiological information with international standards that would allow us to know the performance of the health system as a whole and to explore the improvements or setbacks regarding survival. To this end, the present study aimed to estimate the incidence of cervical cancer and survival of patients, according to histological subtype and stages in Manizales, Colombia, during 2008-2012, and to compare changes in survival compared to survival in the previous five-year period.

KEY MESSAGES

Motivation for the study: For developing countries, it is important to evaluate the behavior over time of cervical cancer incidence and patient survival based on population data.

Main findings: The population from Manizales has an intermediate risk of developing cervical cancer of 18 new cases per 100,000 women in one year. At 5 years, 7 out of 10 patients were alive, compared to 5 out of 10 in a group of patients from previous years.

Implications: It is possible to improve early cervical cancer diagnosis to increase survival in women with this disease.

METHODS

Population and sample

This is an observational, retrospective, longitudinal and analytical study conducted, based on population data to estimate incidence and survival. According to official projections, data from 200,000 women living in the urban and rural jurisdictions of Manizales, department of Caldas, Colombia, were analyzed. The city has a population-based cancer registry indexed by the International Association of Cancer Registries and the International Agency for Research on Cancer (IARC) and meets international quality standards [10,11].

Procedure

Incidence estimates

The incidence count included all new cases diagnosed between January 1, 2008 and December 31, 2012, which topographic codes corresponded to those defined in the CONCORD 3 study (C53.0-C53.9 of the ICD-10). The histological typing (tumor morphology) was coded from the clinical history or from the biopsy reports and pathological anatomy studies, following the rules of the International Classification of Diseases for Oncology, third edition, first revision (ICD-O 3.1), the histological groupings of the CONCORD 3 study, and the rules of the National Comprehensive Cancer Network 2019 (NCCN) [12].

Initially the histological types were grouped in eight categories and later reduced to three, called "large groups", distributed in squamous cell carcinoma, adenocarcinoma, and a category that grouped other histological types and undifferentiated or unspecified tumors. The clinical staging was done according to the classification of the International Federation of Gynecology and Obstetrics (FIGO) [13].

The incidence rate denominator includes the official data from the projections of the total women population by five-year groups from 0 to 85 years and older [14]. Direct method standardization was applied as per Segi's world population [15]. Incidence rates by histological type were calculated for the period 2008-2012 and for each single calendar year.

Survival estimates

All new cases from the studied period were included, except those which only source of information was the death certificate, since these cases have no follow-up time and would underestimate survival. Passive monitoring was done taking

into account the date of the last medical care or the last social security payment report, and on the vital status in administrative and civil databases in the country (the Unique Database of Affiliates of the General System of Social Security in Health, the Master Database of Compensated Affiliates of the Health Resources Administrator, the voter registry of the National Registry of Civil Status, and the database of the Attorney General's Office). The date of death and cause of death were verified, case by case, in the module of the Unique Registry of Affiliates of the division of Vital Statistics of the Territorial Health Directorate of Caldas. In patients whose complete information about their vital status was not obtained from administrative databases, an active follow-up was carried out by consulting clinical records in oncological centers. The follow-up was carried out until December 2018, truncated at 60 months; the patients who died from causes other than cervical cancer were considered as censored.

Study variables

Age, histological type, social security regime, socioeconomic level and clinical stage at diagnosis were analyzed as independent explanatory variables of survival. The variables age, histological type and staging at diagnosis have been used as predictors in other survival studies and are considered necessary adjustment variables in oncological studies [16]. The cut-off point for age was set based on previous studies that have used ages between 65 and 75 years in comparison with younger groups of patients [17,18].

The socioeconomic stratum of the place of residence at the time of diagnosis was the indicator of socioeconomic position. In Colombia, this indicator is defined in categories from 1 to 6 according to the external and internal physical characteristics of the homes, ranging from the purely functional and indispensable to the aesthetic, ornamental and sumptuous characteristics. In this regard, 1 and 2 correspond to the "low" socioeconomic stratum; 3 and 4, "medium"; and 5 and 6, "high" [9]. In the analysis, the categories "medium" and "high" were regrouped in order to have enough observations in each group, because in the richest strata the proportion of the population is lower, and the frequency of cervical cancer is very low.

In Colombia, health insurance financed by contributions from workers and employers (contributory system) is mandatory for dependent employees and partially voluntary for independent workers. A small proportion (<5%) of the population working in certain public sectors, such as defense and education, has exceptional or special health insurance plans (special or exceptional regime). Poor population is covered by a subsidized system founded through taxes (subsidized regime) [19]. In theory, the special and contributory regimes offer the best access to healthcare, but in practice the special/exceptional regimes have shown some problems that could worsen the conditions of their affiliates compared to those of the contributory regime [20,21]. Recent laws from 2011 [22] and 2015 [23] have advocated for universal healthcare access without socioeconomic differences. However, these legislative changes have not been fully implemented, and patients diagnosed before 2010 may have experienced different survival rates depending on their health insurance regime and their socioeconomic position.

Statistical analysis

The analyses were carried out using Microsoft Excel and Stata 14.2 (Stata Corporation, College Station, Texas, USA). Central and dispersion measures and relative frequencies for categorical variables were used in the univariate analysis. Incident case distributions by histological type and clinical staging are presented. In the bivariate analysis, the Kruskal-Wallis test was used to compare the distribution of the clinical stage according to health insurance and socioeconomic level. Survival results are presented using Kaplan-Meier curves. The Mantel-Haenzel log-rank test was used to compare survival estimates according to independent variables.

In addition, three multivariate Cox regression models were adjusted for both the health insurance regimen and socioeconomic level: i) a univariate (null) model; ii) a multivariate A model with age, histological subtype and clinical stage as covariates; and iii) a B model containing all the variables of model A plus an additional term to adjust the effect of the health insurance regimen according to socioeconomic level and, vice versa, the effect of socioeconomic level according to health insurance regimen for survival.

Ethical aspects

Confidentiality policies were respected to protect the sensitive information of the Population Cancer Registry of Manizales. The research has been authorized by the Research Ethics Committee of the Faculty of Health Sciences of the University of Caldas, and was classified as a minimum risk study according to Colombian legislation in force (Resolution 8430 of 1993 of the Ministry of Health).

RESULTS

Incidence

We found 217 incident cases in the study period. The mean age at diagnosis was 53.2 years (min.: 24 years; max.: 98

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years). The percentage of cases with microscopic verification (alteration in the cytological smear + biopsy specimen histology) was 79.0%, a figure adjusted to the recommendations of the IARC [10,24]. The predominant histological type was squamous cell carcinoma (Figure 1).

Regarding clinical stage at the time of diagnosis, stages I and II were observed in 46.1% of the population; stages III and IV in 53.9%; no stage information was found in 25% of the cases due to the lack of clinical records on tumor size, nodal involvement, and metastasis. From the total of patients, 95% had health insurance at the time of diagnosis; and the middle socioeconomic stratum predominated. The distribution of cases by health insurance scheme and socioeconomic level is presented in Table 1. The clinical stage at the time of diagnosis was analyzed according to the categories of socioeconomic level and a significant difference was found between the low and medium-high socioeconomic level. No differences were found in clinical stage according to health insurance regimen.

The average incidence rate for the 5-year period of 2008-2012 was 17.8 new cases per 100,000 women-years; 2.4% lower than that observed for the period of 2003-2007 and equivalent to an annual percentage change of -2.2%. By calendar year, there was a decrease in annual incidence (age-adjusted rate, all histological types) from 17.0 to 13.2 new cases per 100,000 woman-years between 2008 and 2012. Figure 2 shows the behavior of the annual incidence by histological type.

Survival

At the end of follow-up, 129 patients were alive and 88 were deceased, 63 died from cervical cancer before 60 months. There were 15 deaths from causes other than cervical cancer and 7 of those were found in death certificates; the percentage of follow-up losses was 3.2% (n = 7 cases). Survival estimates at 1, 3 and 5 years are presented in Table 1. Adenocarcinoma (histological type), early stage diagnosis and age under 70 years were variables associated with higher survival (Table 1).

In the multivariate analysis (Table 2), the risk of dying from cervical cancer up to 60 months after diagnosis was 90% higher in patients with undifferentiated or unspecified histological type compared to squamous cell carcinoma. Depending on the clinical stage, the risk increases three times for stage III and seven times for stage IV in contrast to stage I (Figure 3).

DISCUSSION

The mean age at the time of diagnosis found in this study is slightly lower than the one reported in Europe (53 vs. 56 years, respectively) and higher than the one reported in the Caribbean countries (48 years) [1,2,25].

The distribution by histological type was similar to that documented in the literature, in descending order of fre-

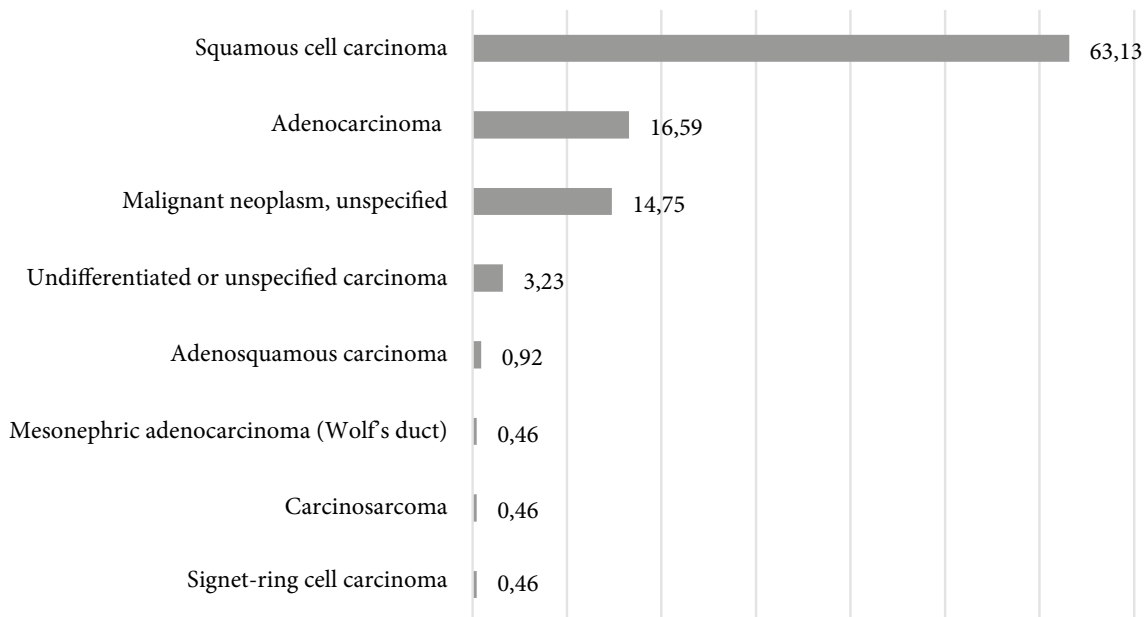

Figure 1. Histological classification (large groups) of cervical tumors (n = 217). Manizales, 2008-2012.

Table 1. Survival estimates in patients with cervical cancer according to health insurance, socioeconomic level, and prognostic factors. Manizales, 2008-2012.

Variables	Cases (n)	Deaths (n)	Percentage of Survivors			Log-rank	Follow-up average (months)
			12 months	36 months	60 months		
All cases	214	63	88.6	74.7	68.9		47.6
Health insurance							
Contributory - Special/Exempt	134	37	88.7	76.1	70.2	$X^2 = 0.68$	48.3
Subsidized	75	25	87.8	70.7	64.7	p = 0.409	45.6
Socioeconomic stratum							
Low	65	23	87.5	67.3	61.8	$X^2 = 6.07$	44.0
Medium-High	116	36	86.8	74.2	67.5	p = 0.048	47.2
Unknown	33	4	96.9	90.4	87.1		55.5
Histological subtype							
Squamous Cell	137	38	91.1	76.5	70.7	$X^2 = 7.37$	48.6
Adenocarcinoma	36	7	91.3	82.5	79.4	p = 0.020	52.1
Others or not specified	41	18	77.4	61.5	53.3		40.1
Clinical stage							
Stage I	61	9	95.1	88.4	85.0	$X^2 = 77.37$	54.5
Stage II	39	5	94.7	86.8	86.8	p < 0.001	54.0
Stage III	37	19	77.4	53.2	42.9		36.1
Stage IV	22	18	67.0	28.7	11.5		23.1
Unknown	55	12	92.6	82.4	76.1		51.9
Age at diagnosis (years)							
20 to 69	181	46	89.4	78.5	73.6	$X^2 = 13.74$	49.2
70 or more	33	17	83.8	50.8	38.1	p < 0.001	37.3

quency: squamous cell, adenocarcinoma, and others. According to the World Health Organization, the most frequent histological type worldwide is the squamous cell, which represents 70-80% of cases, followed by adenocarcinoma, and other histological types with 10-15% each [12]. In accordance with world literature, undifferentiated, poorly differentiated, or rare histological subtypes have a worse prognosis and are generally observed in patients over 70 years old, while common histological variants present in younger patients with better survival [12].

From the total cases, 53.9% were diagnosed in advanced stages (III and IV). Globally, advanced stages continue to

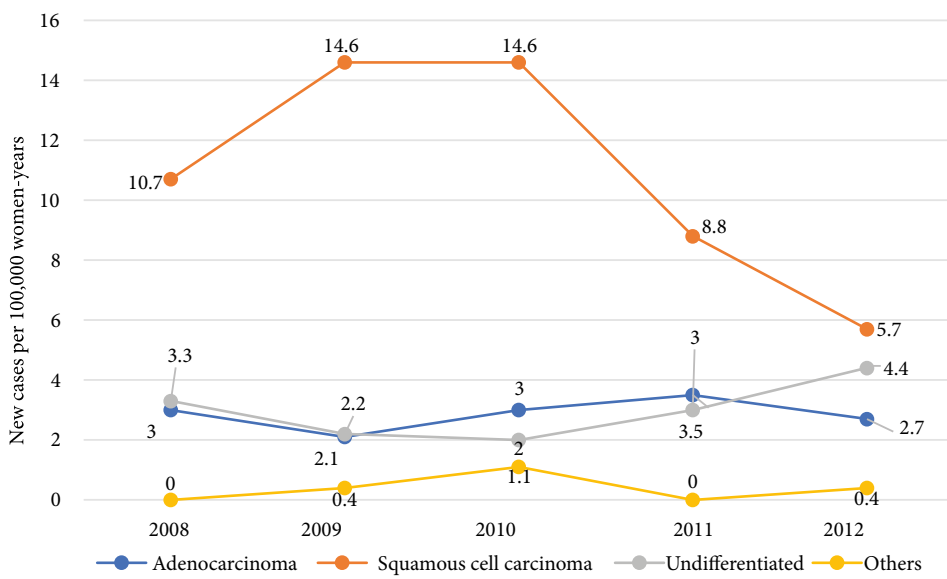

Figure 2. Age-adjusted incidence by histological type and year.

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Table 2. Survival analysis using proportional risk models (Cox) according to covariates

Variables	Univariate analysis		Multivariate analysis					
			Model A			Model B		
	HR	95% CI	HR	95% CI	p value	HR	95% CI	p value
Health insurance								
Contributory - Special/Exempt	Ref.		Ref.			Ref.		
Subsidized	1.2	0.7-2.0	1.1	0.6-2.0	0.802	1.0	0.6-1.9	0.892
Socioeconomic stratum								
Low	Ref.		Ref.			Ref.		
Medium-High	0.8	0.5-1.3	0.9	0.5-1.7	0.843	0.9	0.5-1.7	0.841
Unknown	0.3	0.1-0.8	0.7	0.2-2.2	0.524	0.7	0.2-2.3	0.571
Histological subtype								
Squamous cell	Ref.		Ref.			Ref.		
Adenocarcinoma	0.7	0,3-1,5	1.2	0.5-3.0	0.695	1.2	0.5-3.0	0.615
Others, or not specified	1.9	1,1-3,3	1.7	0.9-3.3	0.111	1.7	0.9-3.3	0.119
Clinical stage								
Stage I	Ref.		Ref.			Ref.		
Stage II	0.9	0.3-2.7	0.8	0.3-2.5	0.855	0.9	0.3-2.6	0.788
Stage III	5.2	2.4-11.7	4.4	1.9-10.3	<0.001	4.3	1.8-10.2	0.001
Stage IV	11.2	5.0-25.2	8.7	3.6-20.8	<0.001	8.7	3.6-20.1	<0.001
Age at diagnosis (years)								
20 to 69	Ref.		Ref.			Ref.		
70 or more	2.7	1.6-4.8	1.7	0.8-3.3	0.123	1.7	0.8-3.4	0.141

HR: hazard ratio; 95% CI: 95% confidence.
Ref: Reference

be very high, especially in third world countries such as sub-Saharan Africa with 64% of new cases in stage III-IV. In the Americas, except for North America, Cuba, Chile and Uruguay, advanced stages represent 48% [1,2]. In a previous study in Manizales, it was reported that 54.7% of the new cases of cervical cancer corresponded to stages I and II [9], results similar to the ones presented now. The difference in the clinical stage distribution according to the socioeconomic level denotes the known close relationship between poverty and the possibility of finding advanced disease, which indirectly influences the survival in this subset of patients [16].

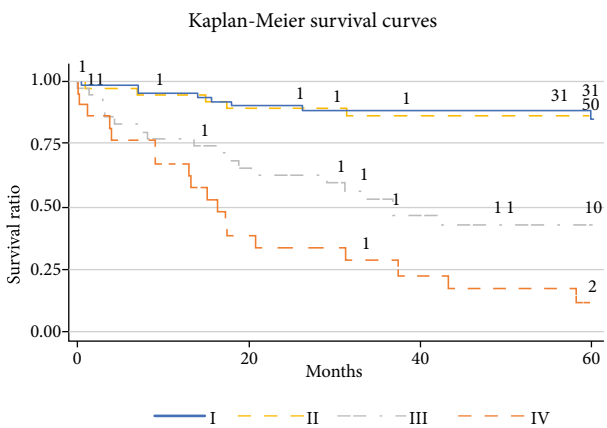

Figure 3. Specific survival to cervical cancer according to clinical stage at the time of diagnosis

The age-adjusted incidence rates for histological types showed stable behavior, with minimal variations, with no statistically significant differences from previous periods [7,11]. Compared to the global scenario (GLOBOCAN 2018), the incidence rate in Manizales (17.8 per 100,000) is slightly higher than the world average of 14.0 per 100,000 inhabitants [2], but lower than that reported by the African continent. In the Colombian scenario, the incidence in Manizales is higher than that reported in cities such as Bucaramanga (13.0 per 100,000) [8] and Cali (15.3 per 100,000) [7], similar to that observed in Pasto (18.0 per 100,000) [6], and lower than that of Barranquilla (26.6 per 100,000) [5].

The global 5-year survival rate reported in this research (68.9%) corresponds to the group of countries with intermediate-high performance in the CONCORD 3 study, which includes several developed countries in Europe and Asia.

According to the mentioned study, the survival of patients with cervical cancer ranges from 50 to 70% in Central and South America and in several countries of Asia and Europe, while it is 70% or more in Japan, Korea, Taiwan, Denmark, Norway, Switzerland and Cuba. Countries such as Canada, United States, Brazil, Puerto Rico, China, Hong Kong, Singapore, Israel, Turkey, Australia, New Zealand and 18 countries in Europe, have survival rates between 60 and 69% [1].

In the Colombian context, data from the National Institute of Cancerology (INC), a national referral hospital, indicate that the probability of global survival at 2 years for this cancer was 62.3% [26]. This figure is lower than the 74% survival at 36 months reported in this study, a difference that could be explained by the complexity of cases that attend the INC as a national reference entity.

Survival was 51.4% in a previous (2003-2007) cohort of incident cases in Manizales, with a higher probability of survival in women in the contributory social security regime, compared to women in the subsidized regime and special or exceptional regimes [9]. Results in this new cohort indicate an increase of more than 15% in survival and that could be due to improvements in the quality of care or better access to timely treatment for women living in the city.

In this study, the most influential factor for survival was the clinical stage at the time of diagnosis, with a significant proportion of cases in advanced stages, which indicates that, despite the improvement in overall survival, there are clear possibilities for progress in early detection that will continue to improve health outcomes. Other factors such as tumor histological type and age of diagnosis were adjusted to what is described in the international literature [12].

One of the strengths of this study is that it was carried out from data of the Population Cancer Registry of the city of Manizales, which complies with the data quality standards of the international agencies specialized in the matter.

This study achieves important progress by providing a complete data report for clinical staging in comparison with the previous study, which ratifies the importance of data use from the country's population cancer registries. The greater the magnitude of data used, the greater the efforts invested in improving its quality. Punctually, progress was made from 42% to 75% of cases with valid and complete information for this variable [9]. In addition, a decade of incident cases (2003-2012) has been followed up, allowing the system performance to be evaluated based on the baseline defined in the first 5-year period. These results can also be extrapolated to other intermediate Andean cities in Colombia, with which Manizales shares some sociodemographic and healthcare system characteristics.

There were some limitations to the study such as the fact that it was not possible to complete the follow-up of all patients, although the percentage of losses was less than 10%, which is usually accepted in this type of study. In addition, there were difficulties to find complete data for some variables such as those related to socioeconomic position. Nevertheless, in the descriptive analyses, the categories "unknown" or "no data" were preserved, in order not to lose the intended exhaustiveness in the studies with population data. Thus, in the case of staging, for example, the category "unknown" is informative of the proportion of cases that did not reach the staging, which can be due to barriers regarding healthcare access and the quality of the clinical records. For some variables, the number of cases and the number of events was insufficient to obtain stable estimates, which forced the regrouping of categories with the consequent loss of information.

In conclusion, the incidence of cervical cancer in Manizales is similar to global rates and places the city close to the global average; in Latin America, Manizales is in the group with the best rates. In the national scenario, the incidence is intermediate compared with other cities where there is a population-based register. The favorable change in the survival of cervical cancer in Manizales could be evidenced, going from 52% to 69%. Likewise, in the multivariate analysis no significant differences were observed in the survival according to socioeconomic level, but advanced stages were observed in women of medium and low socioeconomic levels.

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Contributions of the authors: CCBR, NEAO and WAAR participated in the conception, design, data collection, analysis and interpretation of the results, as well as in the critical review and final approval of the article. They assume responsibility for its content.

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