Retrospective Clinical Research Report

Journal of INTERNATIONAL MEDICAL RESEARCH

Journal of International Medical Research
50(6) 1–15

DOI: 10.1177/03000605221106706
journals.sagepub.com/home/imr
SAGE

Cutaneous melanoma incidence, mortality, and survival in Manizales, Colombia: a population-based study

Juan David Rodríguez-Betancourt[1,2,3] and Nelson Arias-Ortiz[2,3,4]

Abstract

Objective: We estimated the cutaneous melanoma (CM) incidence, mortality, and survival in Manizales, Colombia to establish predictors for survival.

Methods: This analytical cohort study used CM incident cases during 2006 to 2015 in the Manizales Cancer Registry (n = 132). Incidence and mortality rates were standardized using the direct method. Patients were followed up until 30 November 2020. Cause-specific survival was calculated using the Kaplan–Meier method for variables of interest, with the log-rank test for differences. Cox multivariate regression models were fitted.

Results: Incidence (per 100,000) increased from 1.6 to 3.0 in men and 2.6 to 2.8 in women during 2006–2010 to 2011–2015, respectively. Mortality was low and stable. Five-year survival was 68.7%, with significant differences according to age (hazard ratio [HR] >70 vs. ≤70 years: 3.37); histological subtype (HR for melanoma not otherwise specified and HR for nodular melanoma vs lentigo malignant melanoma and superficial spreading melanoma: 17.39 and 10.16, respectively); and clinical stage (HR stages III–IV vs. stages I–II: 5.94).

Conclusion: CM is characterized by increasing incidence and unfavorable prognosis, particularly in patients aged >70 years, with melanoma not otherwise specified and nodular melanoma, and advanced stages. Promoting photoprotection and early detection and management of suspicious skin lesions is crucial.

[1]Young Researchers Program, Ministerio de Ciencia, Tecnología e Innovación, Bogotá, Colombia
[2]Population-based Manizales Cancer Registry, Instituto de Investigaciones en Salud, Universidad de Caldas, Manizales, Colombia
[3]Departamento de Salud Pública, Universidad de Caldas, Manizales, Colombia
[4]Grupo de Investigación Promoción de la Salud y Prevención de la Enfermedad, Universidad de Caldas, Manizales, Colombia

Corresponding author:
Nelson Arias-Ortiz, Cra. 25 No. 48-57, Facultad de Ciencias para la Salud, Universidad de Caldas. Manizales, Caldas, Colombia, 170004.
Email: nelson.arias@ucaldas.edu.co

Keywords
Melanoma, incidence, mortality, survival, Colombia, cohort study

Date received: 13 December 2021; accepted: 23 May 2022

Introduction

In 2020, cutaneous melanoma (CM) accounted for 1.7% of the 19 million new cancer cases worldwide.[1] This cancer has shown an increase in incidence and in burden disease in recent decades around the world, mainly in developing countries.[2] In most nations, 5-year survival of CM ranges from 60% to 90%, with large differences between regions.[3]

In Latin America, research on the epidemiology of CM has been scarce. However, there is evidence suggesting that the epidemiological behavior of this cancer differs from that reported in other regions, mainly owing to higher proportions of acral lentiginous melanoma (ALM) in Latin American populations, which could have a negative impact on the prognosis.[4–9] Additionally, suggested risk factors for ALM (previous trauma, long-term physical stress, other mechanical factors)[10,11] differ from those traditionally identified for other histological types of CM, like ultraviolet (UV) radiation exposure and phenotypic and genetic susceptibility;[12] therefore, different preventive and therapeutic approaches at individual and population levels are required.

In Colombia, CM mortality has increased in recent years;[13] however, epidemiological research on this cancer has been insufficient.[14] Thus, it is important to investigate the epidemiological patterns of CM in Latin American populations. Understanding of these patterns is a fundamental to decision-making in clinical and public health settings, according to the local context. The objectives of this study were therefore to estimate the CM incidence, mortality, and survival rates and to establish predictors for survival among patients diagnosed with CM between 2006 and 2015 in Manizales, Colombia, using data from the population-based cancer registry (PBCR) of the city, the Manizales Cancer Registry (MCR), which meets international standards proposed by the International Agency for Research on Cancer (IARC).[15]

Methods

Study setting and participants

This analytical population-based cohort study was performed in Manizales, Colombia, an Andean city with 434,403 inhabitants, according to the National Household and Population Census in 2018.[16] The MCR has been in operation since 2002, monitoring urban and rural areas of Manizales and producing comparable, valid, and reliable data on the epidemiology of cancer in the city.[15] The MCR includes all primary malignant tumors in all locations identified through active collection of data on patient and tumor variables from health care providers and pathology laboratories, according to IARC rules. The topography and morphology coding of tumors complies with the rules of the International Classification of Diseases for Oncology, Third edition (ICD-O-3).[17]

All incident cases of CM and deaths owing to CM in Manizales between 1 January 2006 and 31 December 2015 were included in the present study. Passive follow-up was performed for 60 months or until 30 November 2020 to identify the event (death owing to melanoma) and the

time-to-event. First, using personal identification numbers, the vital status for each case was confirmed by consulting government databases (electoral census and health insurance registries). Then, the date and cause of death for patients identified as having died in the previous step were verified in the official death certificates via the National Administrative Department of Statistics (DANE, its acronym in Spanish) vital statistics platform. Patients who did not present the event at the end of follow-up, and those who died owing to other causes or whose cause of death could not be verified, were censored. One case registered as death certificate only (DCO) was excluded from the survival analysis as the survival time was zero by definition.

Variables and data sources

Quality indicators

In total, 99.2% (n = 131) of cases were microscopically verified; the remaining 0.8% of cases corresponded to the previously mentioned DCO case (n = 1). Annual incidence rates were unstable over time, ranging from 0.9 to 4.0 in men and from 1.1 to 5.3 in women, which is expected for a small PBCR and a rare cancer. The mortality-to-incidence (M:I) ratios in men were 0.62 and 0.33 during the periods 2006–2010 and 2011–2015, respectively. The M:I ratios in women were 0.30 and 0.17 in the same periods, which reflected improvement in the completeness of the MCR. Regarding histological subtype, 31.1% (n = 41) of cases were melanoma, not otherwise specified (NOS). In 7.6% (n = 10) of cases, the topography code was unspecified. In 3% (n = 4) of cases, the age was unknown.

Incident cases and deaths

For incidence estimates, we considered all new cases of melanoma that occurred in Manizales between 2006 and 2015 and that were captured in the MCR. Cases were identified in the MCR database using morphology codes 8720-8774 and topography codes 44.0–44.9, 51.0, 60.9, 63.2, and 80.9 of the ICD-O-3. For mortality calculations, we included all deaths owing to melanoma (ICD Tenth Revision code: C43) in Manizales during the aforementioned period, according to anonymized death statistics databases published by DANE.

Population data

To calculate the denominators (population at risk), the Manizales age- and sex-specific population per year were obtained from DANE population estimates according to the 2018 census mentioned above.[18]

Histology and topography

Histological subtypes of CM were defined according to morphology codes 8720-8774 of the ICD-O-3, divided into five categories: ALM; nodular melanoma (NM); superficial spreading melanoma (SSM); lentigo maligant melanoma (LMM); and melanoma, NOS. Topographic sites were grouped into six categories: head and neck, trunk, non-acral upper limb, non-acral lower limb, acral (palms, soles of the feet, and subungual), and unspecified site.

Cancer stage

To obtain the data necessary for cancer staging, we consulted patients' clinical files and pathological reports. We then applied the criteria of the 7th Edition of the American Joint Committee on Cancer,[19] the classification in use during the study period.

Health insurance

In Colombia, the health insurance system covers 97.7% of the population (cutoff

year: 2020). Individuals are assigned to different types of health insurance regime (HIR) depending on their income and employment status: contributory (workers and their families, 73.5% of the population in Manizales); subsidized (vulnerable populations, 18.2% in Manizales); and special and exception (workers in the education sector, police, and military, 2.4% in Manizales). There is a low proportion of uninsured individuals (5.9% in Manizales).[20] In this investigation, HIR information was obtained from the clinical records.

Regarding the control of bias, death certification coverage in Manizales is considered exhaustive (approximately 99%). All deaths are certified by a physician, and the rate of accurate certification is 96.4% for total deaths and 93.2% for cancer deaths.[21] Owing to the availability of information about the cause of death, the high quality of death certification, and low probability of misclassification, the authors chose to use cause-specific survival rather than relative survival to estimate CM survival.

As for study size, cases were not randomly selected but rather represent a census of all melanoma cases diagnosed in Manizales during the study period. No sampling was performed in this study.

Statistical methods

Incidence and mortality rates

Specific incidence and mortality rates were estimated by sex and age (18 quinquennial groups) and standardized using the direct method, with Segi's world standard population as reference. The age-standardized rates were corrected for cases with unknown age, according to the methods defined by IARC.[22] Rates were expressed per 100,000 person-years.

Survival analysis

Two- and five-year cause-specific survival probabilities by sex, age, HIR, topography, histological subtype, Breslow thickness, ulceration, and clinical stage were calculated using Kaplan–Meier survival functions; the log-rank test was used for comparisons.

Cox regression models were fitted using the forward method, to yield three models: i) a univariate model (null model); ii) "model A" including sex, age, topography, histological subtype, Breslow thickness, ulceration, and clinical stage; and iii) "model B" including only sex, age, histological subtype, and clinical stage. In model B, statistically significant variables were retained, as was sex because latter variable is theoretically relevant even if it is not statistically significant. The proportional hazards assumption was evaluated with the Schoenfeld residuals test. The final model equation was:

$$\begin{aligned} ln\ (HR) = {} & ln(\lambda_0(t)) + \beta_1 * sex + \beta_2 * age \\ & + \beta_3 * H_2 + \beta_4 * H_3 + \beta_5 * H_4 \\ & + \beta_6 * stage \end{aligned}$$

where $H_{2–4}$ were dummy variables for histological subtypes with SSM and LMM (grouped into a single category) as reference, considering their similar prognosis according to the literature[23] ($H_2 = \text{NOS}$, $H_3 = \text{NM}$, $H_4 = \text{ALM}$); clinical stage was dichotomized as stages I–II versus stages III–IV (early vs. late diagnosis, respectively). To obtain sufficient observations and improve precision of the estimations in model A, Breslow thickness was categorized as ≤ 4 mm or >4 mm. Statistical analysis was performed in Stata 14.2® (StataCorp LLC, College Station, TX, USA).

Ethical considerations

This investigation was approved as minimal-risk research (according to

Resolution 8430-1993 of the Ministry of Health of Colombia) by the Bioethics Committee of the Facultad de Ciencias para la Salud, Universidad de Caldas (consecutive number CBSS-044, act N° 010 of 2020).

In Colombia, reporting has been compulsory for some cancers since 2015, but not for melanoma. Data collection was done after the sources that voluntarily provide their data to the MCR gave institutional informed consent, guaranteeing the confidentiality of the information in accordance with the guiding principles of the International Association of Cancer Registries. The MCR adheres to the guidelines of this association in such a way that it ensures: a) the preservation of anonymity for individuals reported to the registry, and if necessary, for those making such notifications; b) that cancer registry data are of the best quality possible, and c) that the best possible use of cancer registry data is made for the benefit of the patient, cancer control, and medical research. The MCR applies rigorous procedures to ensure confidentiality; only the research team had access to private data and all patient details were de-identified.

The reporting of this study conforms to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[24]

Results

Sociodemographic, clinical, and histological characteristics of the included CM cases are shown in Table 1. A total of 132 incident cases of CM were observed, with most (59.1%) among women. Mean age at diagnosis was 60 years (standard deviation 17.8 years). For both sexes, the most frequent topographic site was lower limb (including skin of the hip), followed by head and neck, trunk, and upper limb. Acral tumors (palm, sole, and subungual) were observed in 22.1% of cases. NM was the most frequent histological subtype (25.8%) in both men and women. Breslow thickness was <1 mm in most patients, but significant differences were observed by sex, with greater thickness in men (Pearson's chi-square test = 12.645; $p = 0.013$). Advanced clinical stages were more frequent in men than in women (Fisher's exact test = 9.514). At 60 months of follow-up, 41 deaths owing to melanoma and 9 deaths owing to other causes (cardiovascular disease, infectious diseases, and kidney failure) were observed. There were no losses to follow-up.

CM incidence, mortality, and survival rates by sex and period are presented in Table 2. In women, the incidence was very similar between periods; in men, however, the rate nearly doubled from the period 2006–2010 to 2011–2015. Mortality was slightly higher in men during both periods; nonetheless, this rate was low and remained stable.

Survival probability was higher for women than for men, and it decreased in both sexes between periods. Cause-specific survival estimates according to sociodemographic, clinical, and histological variables are shown in Table 3. Five-year cause-specific survival was 68.7%. Patients aged 70 or more years had lower survival rates than younger patients. Differences were observed according to topography, with lower survival rates for patients with an unspecified site and acral lesions in comparison with other sites. Regarding histological subtypes, higher survival rates were observed for LMM and SSM than for other morphologies.

As expected, survival was lower with higher Breslow thickness. Survival was also lower in patients with ulcerated tumors. In summary, advanced clinical stages were associated with lower survival, with a 25-fold lower survival rate in stage IV compared with stage I. No differences according to HIR were observed.

Table 1. Sociodemographic, histological, and clinical characteristics of incident cases of cutaneous melanoma (Manizales, 2006–2015).

	Men		Women		Total	
	n	%	n	%	n	%
Total cases	54	40.9	78	59.1	132	100
Mean age, years (SD)*	61.4 (15.3)		58.9 (19.4)		59.9 (17.8)	
Age (years)						
<70	37	68.5	49	62.8	86	65.2
≥70	16	29.6	26	33.3	42	31.8
No information	1	1.8	3	3.9	4	3
Health insurance						
Contributive	39	72.2	51	65.4	90	68.2
Subsidized	11	20.4	18	23.1	29	22.0
Exception	3	5.6	6	7.7	9	6.8
Uninsured	0	0	2	2.6	2	1.5
Special	0	0	1	1.3	1	0.8
No information	1	1.8	0	0	1	0.7
Topography						
Lower limb and hip	16	29.6	38	42.3	49	37.2
Sole	9	16.7	11	14.1	20	15.2
Other parts	3	5.6	17	21.8	20	15.2
Subungual	1	1.9	4	5.1	5	3.8
Foot	3	5.6	1	1.3	4	3.0
Head and neck	14	25.9	23	28.2	36	27.2
Face	10	18.5	17	21.8	27	20.4
Scalp and neck	4	7.4	5	6.4	9	6.8
Trunk	10	18.5	13	16.7	23	17.4
Upper limb and shoulder	6	11.1	8	10.3	14	10.6
Other parts	4	7.4	6	7.7	10	7.6
Subungual	1	1.9	2	2.6	3	2.3
Palm	1	1.9	0	0.0	1	0.8
Unspecified site	8	14.8	2	2.6	10	7.6
Histological subtype						
Nodular	13	24.1	21	26.9	34	25.8
Acral lentiginous	9	16.7	15	19.2	24	18.2
Superficial spreading	5	9.3	18	23.1	23	17.4
Lentigo malignant	5	9.3	5	6.4	10	7.6
Not otherwise specified	22	40.7	19	24.4	41	31.1
Breslow thickness (mm)						
≤1.0	8	14.8	30	38.5	38	28.8
1.01–2.0	7	13.0	13	16.7	20	15.2
2.1–4.0	12	22.2	12	15.4	24	18.2
>4.0	8	14.8	11	14.1	19	14.4
No information	19	35.2	12	15.4	31	23.5
Ulceration						
Absent	19	35.2	48	61.5	67	50.8
Present	20	37.0	21	26.9	41	31.1
No information	15	27.8	9	11.5	24	18.2

(continued)

Table 1. Continued.

	Men		Women		Total	
	n	%	n	%	n	%
Regional lymph nodes (N)						
N0	22	40.7	33	42.3	55	41.7
N1	3	5.6	6	7.7	9	6.8
N2	2	3.7	3	3.9	5	3.8
N3	4	7.4	2	2.6	6	4.6
No information	23	42.6	34	43.6	57	43.2
Distant metastasis (M)						
M0	34	63.0	61	78.2	95	72.0
M1	16	29.6	10	12.8	26	19.7
No information	4	7.4	7	9.0	11	8.3
Clinical stage						
I	7	13.0	19	24.4	26	19.7
II	13	24.1	12	15.4	25	18.9
III	3	5.6	7	9.0	10	7.6
IV	16	29.6	10	12.8	26	19.7
No information	15	27.8	30	38.5	45	34.1

*Excluding four records with unknown age.

Table 2. Cutaneous melanoma incidence, mortality and survival rates by sex and period (Manizales, 2006–2015).

	Men		Women	
	2006–2010	2011–2015	2006–2010	2011–2015
Incidence* (95% CI)	1.6 (0.8–2.4)	3.0 (2.0–4.0)	2.6 (1.7–3.4)	2.8 (1.9–3.6)
Mortality* (95% CI)	1.0 (0.4–1.6)	1.0 (0.5–1.6)	0.8 (0.4–1.3)	0.5 (0.2–0.9)
Survival† (95% CI)	62.7 (35.1–81.2)	53.5 (36.3–68.0)	81.8 (63.9–91.3)	74.0 (58.0–84.7)

*Age-standardized rate per 100,000 person-years (Segi's population). †Five-year cause-specific survival (%).
CI, confidence interval (interpreted as a precision interval assuming that cases were not randomly selected but represent a census of all melanoma cases diagnosed in Manizales during the study period).

Overall survival (OS) of CM was 6 percentage points lower than cause-specific survival (62.6% vs. 68.7%); differences between OS and cause-specific survival were greater in men than in women (48.1% vs. 56.4% and 72.7% vs. 77.3%, respectively).

Table 4 shows the results of Cox regression models for predictors of survival. Although a greater hazard of death was observed in univariate analysis for all variables studied, these risks were attenuated or even disappeared in model A for sex, topography, histological subtype, and ulceration, mainly owing to Breslow thickness and clinical stage, which were the variables with stronger effects. Additionally, there was collinearity between the clinical stage and Breslow thickness; therefore, it was decided to preserve only clinical stage in the final model. In model B, statistically significant hazard ratios (HRs) were observed for age ($p = 0.005$), histological subtype (NOS, $p = 0.008$; NM, $p = 0.030$), and clinical

Table 3. Cause-specific survival estimates of cutaneous melanoma according to sociodemographic, histological, and clinical variables (Manizales, 2006–2015).

	n	Melanoma deaths	2-year survival (95% CI)	5-year survival (95% CI)	*p*-value†
Global*	131	40	75.9 (67.5–82.4)	68.7 (59.9–76.0)	
Sex					
Female	77	17	85.4 (75.2–91.6)	77.3 (66.1–85.2)	0.0049
Male	54	23	62.2 (47.8–73.8)	56.4 (42.0–68.5)	
Age (years)					
<70	86	22	80.0 (69.8–87.1)	72.9 (62.1–81.1)	0.0125
≥70	41	18	64.6 (47.6–77.3)	56.4 (39.4–70.3)	
Health insurance					
Contributive	89	27	74.9 (64.4–82.7)	69.0 (58.1–77.6)	0.7578
Subsidized	29	10	71.4 (50.9–84.5)	64.0 (43.5–78.8)	
Exception	9	2	88.8 (43.3–98.3)	77.7 (36.4–93.9)	
Special	1	0	100	100	
Uninsured	2	0	100	100	
No information	1	1	100	–	
Topography					
Head and neck	36	5	91.6 (76.3–97.2)	86.0 (69.6–93.9)	<0.001
Trunk	23	4	86.3 (63.4–95.3)	81.8 (58.5–92.7)	
Upper limb (non-acral)	10	2	80.0 (40.8–94.5)	80.0 (40.8–94.5)	
Lower limb (non-acral)	23	6	77.2 (53.7–89.8)	72.1 (48.0–86.4)	
Acral	29	13	68.2 (47.8–82.0)	53.6 (33.7–69.9)	
Unspecified site	10	10	10.0 (0.5–35.8)	–	
Histological subtype					
Lentigo malignant	10	0	100	100	0.0004
Superficial spreading	23	1	95.6 (72.9–99.3)	95.6 (72.9–99.3)	
Nodular	34	10	76.1 (57.9–87.3)	70.0 (51.4–82.6)	
Acral lentiginous	23	9	78.2 (55.4–90.3)	60.2 (37.4–77.0)	
NOS	41	20	56.5 (39.6–70.4)	48.4 (32.1–63.0)	
Breslow thickness (mm)					
≤1.0	38	0	100	100	<0.001
1.01–2.0	20	2	100	89.7 (64.7–97.3)	
2.1–4.0	24	9	75.0 (52.6–87.9)	62.5 (40.3–78.4)	
>4.0	19	12	45.6 (22.5–66.1)	34.2 (14.1–55.4)	
No information	30	17	48.5 (29.5–65.1)	41.0 (23.1–58.2)	
Ulceration					
Absent	67	6	93.9 (84.6–97.6)	90.9 (80.8–95.8)	<0.001
Present	41	21	62.8 (46.1–75.7)	47.6 (31.6–62.0)	
No information	23	13	45.5 (24.2–64.6)	40.4 (20.1–60.0)	
Clinical stage					
I	26	0	100	100	<0.001
II	25	6	84.0 (62.8–93.6)	76.0 (54.2–88.4)	
III	10	3	90.0 (47.3–98.5)	68.5 (30.4–88.7)	
IV	26	25	15.3 (4.8–31.4)	3.8 (0.28–16.4)	
No information	44	6	90.5 (76.7–96.3)	85.5 (70.6–93.2)	

*Excluding one case with death certificate only. †Log-rank test.

NOS, not otherwise specified; CI, confidence interval (interpreted as a precision interval assuming that cases were not randomly selected but represent a census of all melanoma cases diagnosed in Manizales during the study period).

Table 4. Cox regression results for predictors of melanoma survival (Manizales, 2006–2015).

	Univariate analysis	Multivariate analysis	
	HR (95% CI)	Model A* HR (95% CI)	Model B†Δ HR (95% CI)
Sex			
Male	Ref	Ref	Ref
Female	0.44 (0.24–0.79)	0.63 (0.17–2.28)	0.58 (0.27–1.23)
Age (years)			
<70	Ref	Ref	Ref
≥70	2.07 (1.15–3.71)	3.47 (1.01–11.95)	3.37 (1.43–7.95)
Topography			
Acral	Ref	Ref	–
Head and neck	0.23 (0.09–0.59)	0.15 (0.01–1.31)	
Lower limb (non-acral)	0.46 (0.18–1.18)	0.21 (0.02–1.66)	
Upper limb (non-acral)	0.30 (0.07–1.33)	1.17 (0.09–14.61)	
Trunk	0.41 (0.16–1.06)	1.08 (0.12–9.06)	
Histological subtype			
SSM/LMM	Ref	Ref	Ref
NOS	25.17 (3.38–187.33)	24.05 (1.81–319.11)	17.39 (2.09–144.65)
NM	14.97 (1.95–114.55)	7.16 (0.73–69.31)	10.16 (1.25–82.65)
ALM	18.67 (2.41–144.73)	2.26 (0.11–46.22)	7.50 (0.88–63.83)
Breslow thickness (mm)			
≤4.0	Ref	Ref	–
>4.0	7.43 (3.49–15.81)	12.80 (3.17–51.61)	
Ulceration			
Absent	Ref	Ref	–
Present	6.91 (3.08–15.48)	1.64 (0.46–5.77)	
Clinical stage			
I/II	Ref	Ref	Ref
III/IV	9.23 (4.30–19.80)	13.71 (3.55–52.86)	5.94 (2.72–12.97)

*Model A: Observations = 66, events = 23, LR = 55.34, $p < 0.001$.
†Model B: Observations = 87, events = 38, LR = 56.63, $p < 0.001$.
ΔGlobal test of proportional hazards assumption (Schoenfeld residuals): $\chi^2 = 10.65$; $p = 0.099$.
Ref, reference; HR, hazard ratio; CI, confidence interval; SSM, superficial spreading melanoma; LMM, lentigo malignant melanoma; NOS, not otherwise specified; NM, nodular melanoma; ALM, acral lentiginous melanoma; LR, likelihood ratio.

stage at diagnosis ($p < 0.001$), meaning independent effects on survival of these three variables. Model B had a greater likelihood ratio than model A, and its proportional hazards assumption was not violated (Schoenfeld residuals test: $\chi^2 = 10.65$).

Discussion

This was the second population-based study in Colombia to investigate the epidemiology of CM. Our findings represent a relevant contribution to the knowledge base regarding the epidemiological behavior of this cancer in the country. The increase in CM incidence in Manizales agrees with trends evidenced in developing countries;[2] rates were similar to those reported in other Latin American countries but lower than those among European, North American, and Australian populations.[22] Additionally, the low mortality

rate observed in this study matches patterns worldwide[1] but differs from ascending patterns reported at the national level.[13]

In accordance with reports in Latin American[5,6,25,26] and some European populations[7,28] but unlike observations among North Americans,[29] the diagnosis of CM is most frequent in women. However, survival is lower in men, which may be because, at diagnosis, men present a greater depth of tumor invasion, a greater frequency of ulceration, and a greater presence of distant metastases; consequently, men are diagnosed in advanced stages of disease. In this sense, it is noteworthy that the frequency of advanced stages in Manizales (27.3%) was found to be much higher than that of high-incidence countries (approximately 8%);[30,31] moreover, advanced stage at diagnosis has been identified as a distinctive feature of CM in Colombia.[32]

Health insurance has been reported to be a predictor of survival in patients with cancer (including CM) in Colombia[5,33,34] and the United States.[35] Nonetheless, in this study, we found no differences in survival according to HIR, which could be owing to the low frequency of cases in some categories, particularly for the special and exception HIR. However, this study was not designed to measure inequities and it is possible that socioeconomic variables other than the HIR can better explain the differences in survival.

Regarding histological subtype, NM and ALM were found to be predominant in Manizales, in contrast to reports in non-Latin American populations.[36,37] These subtypes tend to present particularly unfavorable histopathological and clinical characteristics at diagnosis,[10,38–40] which entail a worse prognosis than those of the SSM and LMM subtypes,[23,41] as we found in this study. These histological and clinical features, in addition to sociodemographic and genetic factors and barriers in access to health care, could explain why survival is lower in Latin American populations, like that in Manizales, than the rates reported in high-incidence countries.[3,42] Moreover, and in accordance with the high proportion of ALM mentioned above, the distribution by topography in this study was differed remarkably from that of high-incidence countries because of the high proportion of CM in non-photoexposed sites, which also has an impact on survival (acral site survival: 53.6%).

Relative survival has been the approach traditionally used in population-based cancer survival studies, in part owing to a lack of access to the cause of death for every cancer patient.[43] However, as Sarfati et al.[44] point out, cause-specific survival is also a valid approach in these studies, particularly in the context of availability of accurate information on cause of death and types of cancer with good survival; these two conditions, which are fulfilled in our study, can reduce the possible impact of misclassification. In this way, the CM cause-specific survival observed in this investigation was similar to that reported in other studies among Latin American populations, in which the predominance of ALM has been also confirmed.[5–7] Similar to reports in Peru,[8] Brazil,[9] and Mexico,[6] the histological subtype ALM presented the most unfavorable survival in this study (within subtypes with specified histology), which adds evidence confirming the consistent epidemiological pattern already known in Latin America.

Histological subtypes of CM that are related (SSM, LMM) and unrelated (ALM) to UV radiation coexist in Manizales (NM may derive from both pathways),[45] which requires combined preventive actions, as follows: 1) continuation of known interventions based on promotion of photoprotection; and 2) secondary prevention strategies based on early detection of suspicious skin lesions, mainly those located in acral sites, which is necessary to

improve diagnosis and treatment at early stages. For the above, early detection programs should include health education for the general population oriented toward promoting timely consultation, especially among men, as well as improved training for health professionals in primary care services.

Unlike the findings in European, North American, and Australian populations where the CM incidence is high and its survival is very favorable, in Manizales and other Latin American populations, CM is an infrequent cancer but its prognosis is relatively poor[1,3] owing to the particular clinical, histological, and social characteristics of the population.[4,46] Thus, it is necessary to continue surveillance for CM and improve prevention strategies, together with expanding research on this cancer, particularly ALM.

Important limitations in this study include a considerable amount of unknown information on histologic and clinical variables. On the one hand, this is related to recognized difficulties of quality and access to information sources specific to the PBCRs in developing countries;[47,48] on the other hand, in certain cases where we gained access to the information sources, the quality of the pathology reports was poor in terms of detailed descriptions of tumor characteristics. Such difficulties translate into shortcomings in the quality and completeness of our results, which has also been evidenced in Colombian population-based studies on stomach cancer[34] and melanoma.[5] In the latter study, the percentage of missing data for the histological variables Breslow thickness, ulceration, and histological subtype of melanoma was 58%, 55%, and 28%, respectively. Although the distribution by histologic type could change in a scenario with complete information, the findings of the present study in terms of histologic subtype and clinical stage are consistent with those reported in a case series carried out in the Department of Caldas,[25] of which Manizales is the capital city. An aspect to be studied in detail in further research is the high frequency of NM, which might correspond to SSM detected in advanced stages of vertical growth. Consequently, removing barriers to accessing sources of information in PBCRs and improving the training of pathologists in pigmented lesions and the quality of pathological reports of melanoma in the regional context must be given priority to provide more accurate data on melanoma in Colombia and Latin America.[14] However, challenges to attaining a sufficient level of expertise among pathologists in low-incidence countries must be taken into account.

We also recognize that the low number of cases in some subgroups did not allow us to perform multivariate analyses with sufficient power, so the results of these models should be interpreted with caution owing to the possibility of bias and low precision of the estimates derived from a small sample size in some categories. For instance, regarding the observed differences in survival by sex, and according to the tables in Castañeda et al.,[49] following 232 patients (116 men, 116 women) would result in finding statistically significant HRs in favor of women, independent of stage and age, as has been reported in high-incidence countries.[29]

Conclusions

In Manizales, CM was found to be more frequent among women and older people and is usually diagnosed at advanced stages, mainly among men. Mortality and incidence rates are low, but the latter rate is increasing. Survival probabilities are not favorable, similar to other Latin American regions. Age, histological subtype, and clinical stage are strong predictors of survival.

Histological subtypes that are related and unrelated to UV radiation exposure coexist in Manizales, similar to other Latin American populations. This suggests that preventive strategies should focus equally on primary prevention (photoprotection) and secondary prevention (early detection and specific management of suspicious lesions).

Acknowledgement

We thank the Vital Statistics Department, Dirección Territorial de Salud de Caldas.

Author contributions

Both authors contributed equally to the design of the study; acquisition, analysis, and interpretation of the data; and writing of the article.

Data availability statement

The research data are available on request.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the Universidad de Caldas (grant number 0340420, Project "Population-based Manizales Cancer Registry"); Instituto Nacional de Cancerología de Colombia (INC; grant number 0096-2021, Agreement between the UC and the INC); and Ministerio de Ciencia, Tecnología e Innovación de Colombia, Instituto Científico Pfizer Colombia, and Asociación Colombiana de Facultades de Medicina (grant number 887-2020, Announcement "Young Researchers and Innovators in Medicine").

ORCID iDs

Juan David Rodríguez-Betancourt https://orcid.org/0000-0003-2192-458X
Nelson Arias-Ortiz https://orcid.org/0000-0001-5093-3384

References

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2021; 0: 1–41. DOI:10.3322/caac.21660
2. Fitzmaurice C, Akinyemiju TF, Al Lami FH, et al. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 29 cancer groups, 1990 to 2016: a systematic analysis for the Global Burden of Disease Study. *JAMA Oncol* 2018; 4: 1553–1568. DOI:10.1001/jamaoncol.2018.2706.
3. Allemani C, Matsuda T, Di Carlo V, et al. Global surveillance of trends in cancer survival 2000–14 (CONCORD-3): analysis of individual records for 37.513.025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. *Lancet* 2018; 391: 1023–1075. DOI:10.1016/S0140-6736(17)33326-3.
4. De Vries E, Sierra M, Piñeros M, et al. The burden of cutaneous melanoma and status of preventive measures in Central and South America. *Cancer Epidemiol [Internet]*. 2016; 44: S100–S109. DOI:10.1016/j.canep.2016.02.005.
5. Reyes E, Uribe C and De Vries E. Population-based incidence and melanoma-specific survival of cutaneous malignant melanoma in a Colombian population 2000–2009. *Int J Dermatol* 2018; 57: 21–27. DOI:10.1111/ijd.13839.
6. Lino-Silva LS, Domínguez-Rodríguez JA, Aguilar-Romero JM, et al. Melanoma in Mexico: Clinicopathologic Features in a Population with Predominance of Acral Lentiginous Subtype. *Ann Surg Oncol* 2016; 23: 4189–4194. DOI:10.1245/s10434-016-5394-x.
7. Vazquez VDL, Silva TB, Vieira MDA, et al. Melanoma characteristics in Brazil: Demographics, treatment, and survival analysis. *BMC Res Notes* 2015; 8: 1–9. DOI:10.1186/s13104-015-0972-8.
8. Castaneda CA, Torres-Cabala C, Castillo M, et al. Tumor infiltrating lymphocytes in acral lentiginous melanoma: a study of

a large cohort of cases from Latin America. *Clin Transl Oncol* 2017; 19: 1478–1488. DOI:10.1007/s12094-017-1685-3.
9. Nunes LF, Quintella Mendes GL and Koifman RJ. Acral melanoma: A retrospective cohort from the Brazilian National Cancer Institute (INCA). *Melanoma Res* 2018; 28: 458–464. DOI:10.1097/CMR.0000000000000476.
10. Durbec F, Martin L, Derancourt C, et al. Melanoma of the hand and foot: Epidemiological, prognostic and genetic features. A systematic review. *Br J Dermatol* 2012; 166: 727–739. DOI:10.1111/j.1365-2133.2011.10772.x.
11. Jung HJ, Kweon SS, Lee JB, et al. A clinicopathologic analysis of 177 acral melanomas in Koreans: Relevance of spreading pattern and physical stress. *JAMA Dermatol* 2013; 149: 1281–1288. DOI:10.1001/jamadermatol.2013.5853.
12. Caini S, Gandini S, Sera F, et al. Meta-analysis of risk factors for cutaneous melanoma according to anatomical site and clinicopathological variant. *Eur J Cancer [Internet]* 2009; 45: 3054–3063. DOI:10.1016/j.ejca.2009.05.009.
13. García MA. Mortalidad por melanoma cutáneo en Colombia: estudio de tendencias. *Rev la Asoc Colomb Dermatología* 2017; 25: 8–15.
14. Schmerling RA, Loria D, Cinat G, et al. Cutaneous melanoma in Latin America: the need for more data. *Rev Panam Salud Publica [Internet]* 2011; 30: 431–438. DOI:10.1590/s1020-49892011001100005.
15. Arias-Ortiz NE and López-Guarnizo GA. Evaluación de calidad de los datos del Registro Poblacional de Cáncer de Manizales, Colombia. *Rev Colomb Cancerol* 2013; 17: 132–141.
16. DANE. Población ajustada por cobertura censal. Censo General de Población y Vivienda. 2018.
17. World Health Organization. *International Classification of Diseases for Oncology*, Third Edition. 3rd ed. Fritz A, Percy C, Jack A, Shanmugaratnam K, Sobin L, Parkin DM, et al., editors. Geneva; 2013. 242 p. DOI:10.32388/5xg1qe
18. DANE. Estadísticas por tema: Demografía y Población. https://www.dane.gov.co/index.php/estadisticas-por-tema/demografia-y-poblacion.
19. Balch CM, Gershenwald JE, Soong SJ, et al. Final version of 2009 AJCC melanoma staging and classification. *J Clin Oncol* 2009; 27: 6199–6206. DOI:10.1200/JCO.2009.23.4799.
20. Ministerio de Salud y Protección Social de Colombia . Cifras de aseguramiento en salud [Internet]. 2022 [cited 2022 Feb 16]. DOI: https://www.minsalud.gov.co/proteccionsocial/Paginas/cifras-aseguramiento-salud.aspx
21. Cendales R and Pardo C. Quality of death certification in Colombia. *Colomb Med* 2018; 49: 121–127. DOI:10.25100/cm.v49i1.3155.
22. International Agency for Research on Cancer. Cancer Incidence in Five Continents, Vol. XI [Internet]. Bray F, Colombet M, Mery L, Piñeros M, Znaor A, Zanetti R, et al., editors. *Lyon: World Health Organization*; 2021. 1558 p. DOI:10.1016/0959-8049(93)90227-7.
23. Lattanzi M, Lee Y, Simpson D, et al. Primary melanoma histologic subtype: Impact on survival and response to therapy. *J Natl Cancer Inst* 2019; 111: 186–188. DOI:10.1093/jnci/djy086.
24. Von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Ann Intern Med [Internet]* 2007 [cited 2022 Mar 16]; 147: 573–577. DOI:10.7326/0003-4819-147-8-200710160-00010.
25. Botello-Mojica HM, Insuasty-Moreno AP and Jaramillo-Ayerbe F. Caracterización del melanoma maligno en la Clínica de Tumores de Piel y Mucosas, Universidad de Caldas, 2005–2015. *Rev la Asoc Colomb Dermatología y Cirugía Dermatológica* 2017; 25: 276–283. DOI:10.29176/2590843x.301.
26. Pozzobon F, Fierro E, Acosta Á, et al. Características del melanoma cutáneo primario en el Instituto Nacional de Cancerología 2006-2010. *Rev Colomb Cancerol* 2013; 17: 111–118. DOI:10.1016/s0123-9015(13)70013-1.

27. Bay C, Kejs AMT, Storm HH, et al. Incidence and survival in patients with cutaneous melanoma by morphology, anatomical site and TNM stage: A Danish population-based register study 1989-2011. *Cancer Epidemiol [Internet]* 2015; 39: 1–7. DOI:10.1016/j.canep.2014.10.010.
28. De Vries E, Houterman S, Janssen-Heijnen MLG, et al. Up-to-date survival estimates and historical trends of cutaneous malignant melanoma in the south-east of The Netherlands. *Ann Oncol* 2007; 18: 1110–1116. DOI:10.1093/annonc/mdm087.
29. Smith AJ, Lambert PC and Rutherford MJ. Understanding the impact of sex and stage differences on melanoma cancer patient survival: a SEER-based study. *Br J Cancer [Internet]* 2021; 124: 671–677. DOI:10.1038/s41416-020-01144-5.
30. Prado G, D'Amore P, Tagliero A, et al. A cross-sectional study of trends in the stage of melanoma at diagnosis in the United States from 2001-2011. *J Am Acad Dermatol* 2016; 75: 1057–1059. DOI:10.1016/j.jaad.2016.07.030.
31. Koblinski JE, Maykowski P and Zeitouni NC. Disparities in melanoma stage at diagnosis in Arizona: A 10-year Arizona Cancer Registry study. *J Am Acad Dermatol* 2021; 84: 1776–1779. DOI:10.1016/j.jaad.2021.02.045.
32. Meijs M, Herrera A, Acosta A, et al. Burden of skin cancer in Colombia. *Int J Dermatol [Internet]* 2022 [cited 2022 Apr 19]; DOI:10.1111/IJD.16077.
33. Arias-Ortiz NE and De Vries E. Health inequities and cancer survival in Manizales, Colombia: A population-based study. *Colomb Med* 2018; 49: 63–72. DOI:10.25100/cm.v49i1.3629.
34. De Vries E, Uribe C, Pardo C, et al. Gastric cancer survival and affiliation to health insurance in a middle-income setting. *Cancer Epidemiol [Internet]* 2015; 39: 91–96. DOI:10.1016/j.canep.2014.10.012.
35. Amini A, Rusthoven CG, Waxweiler TV, et al. Association of health insurance with outcomes in adults ages 18 to 64 years with melanoma in the United States. *J Am Acad Dermatol [Internet]* 2016; 74: 309–316. DOI:10.1016/j.jaad.2015.09.054.
36. Singh P, Kim HJ and Schwartz RA. Superficial spreading melanoma: An analysis of 97 702 cases using the SEER database. *Melanoma Res* 2016; 26: 395–400. DOI:10.1097/CMR.0000000000000245.
37. Chopra A, Sharma R and Rao UNM. Pathology of Melanoma. *Surg Clin North Am [Internet]* 2020; 100: 43–59. DOI:10.1016/j.suc.2019.09.004.
38. Green AC, Viros A, Hughes MCB, et al. Nodular melanoma: A histopathologic entity? *Acta Derm Venereol* 2018; 98: 460–462. DOI:10.2340/00015555-2855.
39. Greenwald H, Friedman E and Osman I. Superficial spreading and nodular melanoma are distinct biological entities: a challenge to the linear progression model. *Melanoma Res* 2012; 22: 1–8. DOI:10.1097/CMR.0b013e32834e6aa0.Superficial.
40. Borkowska AM, Szumera-Ciećkiewicz A, Spałek MJ, et al. Clinicopathological Features and Prognostic Factors of Primary Acral Melanomas in Caucasians. *J Clin Med* 2020; 9: 2996. DOI:10.3390/jcm9092996.
41. Teramoto Y, Keim U, Gesierich A, et al. Acral lentiginous melanoma: a skin cancer with unfavourable prognostic features. A study of the German central malignant melanoma registry (CMMR) in 2050 patients. *Br J Dermatol* 2018; 178: 443–451. DOI:10.1111/bjd.15803.
42. Svedman FC, Pillas D, Taylor A, et al. Stage-specific survival and recurrence in patients with cutaneous malignant melanoma in Europe – A systematic review of the literature. *Clin Epidemiol* 2016; 8: 109–122. DOI:10.2147/CLEP.S99021.
43. Rachet B and Coleman MP. Commentary: Estimating cancer survival-which is the right approach? *Int J Epidemiol* 2010; 39: 611–612. DOI:10.1093/ije/dyq053.
44. Sarfati D, Blakely T and Pearce N. Measuring cancer survival in populations: relative survival vs cancer-specific survival. *Int J Epidemiol* 2010; 39: 598–610. DOI:10.1093/ije/dyp392.
45. Dessinioti C, Geller AC, Whiteman DC, et al. Not all melanomas are created equal: a review and call for more research into nodular melanoma. *Br J Dermatol [Internet]*

2021 [cited 2022 Apr 18]; 185: 700–710. DOI:10.1111/BJD.20388.

46. De Vries E. Melanomas in Colombia; a different reality. *Rev Colomb Cancerol [Internet]* 2013; 17: 91–92. DOI:10.1016/s0123-9015(13)70010-6.
47. Piñeros M, Abriata MG, De Vries E, et al. Progress, challenges and ways forward supporting cancer surveillance in Latin America. *Int J Cancer [Internet]* 2021 [cited 2021 Dec 6]; 149: 12–20. DOI:10.1002/IJC.33407.
48. Piñeros M, Abriata MG, Mery L, et al. Cancer registration for cancer control in Latin America: a status and progress report. *Rev Panam Salud Publica* 2017; 41: e2. DOI:10.26633/RPSP.2017.2.
49. Castañeda J, Pérez A and Gil F. Tamaño de la muestra en análisis de sobrevida. *Rev Colomb Estadística [Internet]* 2000; 23: 2346–2364.