A Population-Based Study of Retinoblastoma Incidence and Survival in Argentine Children

Florencia Moreno, MD,[1]* Banafsheh Sinaki, MPH,[2] Adriana Fandiño, MD,[3] Verónica Dussel, MD, MPH,[1,4,5] Liliana Orellana, PhD,[6] and Guillermo Chantada, MD, PhD[7]

Background. An increased incidence of retinoblastoma in some developing countries has been reported but no conclusive data are available from population-based studies at national level. ***Purpose.*** To report the incidence and survival of retinoblastoma in Argentina from the National Pediatric Cancer Registry (ROHA) and the influence of socio-economical indicators on outcome. ***Procedure.*** Cases reported to the ROHA (2000–2009) were analyzed. Incidence rates were calculated using National Vital Statistics and survival was estimated. The extended human development index (EHDI) was used as a socio-economical indicator. ***Results.*** With 438 patients reported, an incidence of 5.0 cases per million children 0–14 years old (95% CI 3.5–6.4) was calculated. Median age at diagnosis was significantly higher for children from provinces with lower EHDI; (24 vs. 35 months for unilateral, ($P = 0.003$) and 9 versus 11.5 months for bilateral retinoblastoma ($P = 0.027$). The 3-year probability of survival was 0.87 and 0.94 for unilateral and bilateral retinoblastoma, respectively. Residents in provinces with higher EHDI had a better 3-year survival (0.93 vs. 0.77 for lower EHDI, $P < 0.0001$). Probability of survival was higher for patients treated at tertiary level institutions ($P = 0.0015$). The combination of low EHDI residence province with no treatment at a tertiary institution was associated with the worst survival outcome. For both, unilateral and bilateral disease, children who died were in average diagnosed at older age. ***Conclusions.*** The incidence of retinoblastoma in Argentina is comparable to that of developed countries. Retinoblastoma is diagnosed later and survival is lower in the less developed areas of the country. Pediatr Blood Cancer 2014;9999:1–6.

Key words: cancer; children; retinoblastoma; survival

INTRODUCTION

Retinoblastoma, a rare tumor affecting about 3% of children younger than 15 years, can be considered as a paradigm of human cancer genetic susceptibility. It was one of the first pediatric tumors whose molecular mechanisms has been elucidated through the presence of 13q abnormalities that led the path to discovery of the retinoblastoma (*RB1*) gene [1]. Tumors develop when both alleles of the *RB1* tumor suppressor gene undergo loss-of-function mutations abrogating cell cycle control. It presents as bilateral, or hereditary, disease at a median age of 14 months; or unilateral, usually sporadic disease, diagnosed at a median age of 23 months [2]. Even though the North American Survival Epidemiology and End Results (SEER), the European Automatic Childhood Cancer Information System and other registries have tabulated the incidence and survival of children with retinoblastoma accurately [3–10], the situation in developing countries has not been so well documented [11]. In addition, many studies reported a higher incidence of retinoblastoma in developing countries [12–15], but exact figures are unknown.

In developed countries, children with retinoblastoma have a disease-free survival greater than 90% [3,6,8]. Children living in developing countries have a lower probability of disease-free survival, with reports as low as 10–30% [11]. Reasons for this differential might include late diagnosis, inaccessibility to specialized care, and/or poor adherence to recommended therapy [11,16]. Most of the reports from developing countries, including our previous data [17,18], come from single institutions, so the full picture of national incidence and survival outcomes remains largely unknown. In order to obtain more representative data, population-based studies in developing countries are needed. Argentina is an upper middle-income country with an average of about 1,200 cancer cases per year in children under 15 years of age. Its national childhood cancer registry, Registro Oncopedátrico Hospitalario Argentino (ROHA) [17,18], provides reliable incidence and survival data since 2000 [17]. Vital statistics in Argentina are also reliable, therefore, good quality estimations of retinoblastoma incidence and survival can be obtained. In addition, socioeconomic indicators are available for the different regions allowing their influence in cancer incidence and survival to be assessed.

In this article, we report on the incidence, clinical presentation, and 3-year survival of retinoblastoma cases reported to the Argentinean National Registry (ROHA) in a 10-year period. In addition, we investigated whether living in disadvantaged regions was associated with a different disease profile and outcome.

METHODS

Setting and Study Population

Argentina is a large country, stretching over 2.8 million square km. Its population is mainly urban (90%) and highly concentrated: 46% live in the capital city or Buenos Aires province [19]. The country has a well-developed public health system that coexists with a social security system and a private

[1]Registro Onco-pediatrico Hospitalario Argentino (ROHA, Hospital-based Pediatric Cancer Registry from Argentina), Instituto Nacional del Cáncer, Buenos Aires, Argentina; [2]Department of Pediatrics, New York Medical College, New York, New York; [3]Ophthalmology Service, Hospital JP Garrahan, Buenos Aires, Argentina; [4]Institute for Clinical Effectiveness and Health Policy, Buenos Aires, Argentina; [5]Department of Psychosocial Oncology and Palliative Care, Dana-Farber Cancer Institute, Boston, Massachusetts; [6]Instituto de Cálculo, University of Buenos Aires, Buenos Aires, Argentina; [7]Hematology-Oncology Service, Hospital JP Garrahan, Buenos Aires, Argentina

Conflict of Interest: Nothing to report.

*Correspondence to: Florencia Moreno, Registro Onco-pediatrico Hospitalario Argentino (ROHA, Hospital-based Pediatric Cancer Registry from Argentina), Instituto Nacional del Cáncer, Av Julio A. Roca 781 Piso 11, Buenos Aires C1067 ABC, Argentina. E-mail: roha@roha.org.ar

Received 3 September 2013; Accepted 10 March 2014

DOI 10.1002/pbc.25048
Published online in Wiley Online Library (wileyonlinelibrary.com).

sector; approximately 41% of the population lacks health insurance so they are managed at the public health sector [20]. Regardless their insurance status, 80% of the children with cancer is treated in public institutions, with 50% being treated at one of the three tertiary level pediatric public hospitals [21]. About 40% of the children with cancer need to migrate to a large city to receive treatment [22]. Unlike some other developing countries, cancer treatment is granted without cost to all children; however, because of significant socio-economic disparities and transport-related limitations, there is still unequal access to cancer care, especially in the early phases of diagnosis, across the country [23]. Argentina's estimated population of children younger than 15 years for 2005 was 10,204,619; 68% lived in the Central, 26% in the North, and 6% in the South region (Fig. 1). The number of live births for the same year was 694,803. Population estimates were obtained from the National Census Bureau (INDEC) [24].

Case Definition, Information Sources and Variables

A case was defined as a child under the age of 15 who was diagnosed with retinoblastoma between January 1, 2000, and December 31, 2009, and lived in Argentina at the time of such diagnosis. Cases were identified from the ROHA. The registry collects data from multiple sources validated internationally. Factors considered in the analyses included: laterality of the disease (uni or bilateral); age at diagnosis; level of the treating hospital, dichotomized as tertiary yes/no; calendar year at diagnosis grouped as 2000–2003, 2004–2006, 2007–2009; and a socioeconomic indicator of the province where the child resided at the time of diagnosis. The Extended Human Development Index (EHDI) of each Argentinean province in 2006, as calculated by the United Nations Development Program (UNDP) [25] was used as a socioeconomic indicator. The EHDI is based on the Human Development Index a commonly used composite measure of development that combines indicators of health, education, and living standards [26]. By adding some new variables to each of these domains, the EHDI aims to better reflect regional disparities, as well as quality aspects and the dynamic nature of development [27]. Specifically, the EHDI provides information about how each jurisdiction is performing on: long and healthy life (life expectancy and infant mortality due to preventable causes), education (literacy rate, school enrolment rate, over-age rate, and educational quality rate), and decent standard of living (annual total family income per capita, employment rate, and unemployment rate). Provinces were classified in two groups based on whether their EHDI was above or below the country EHDI (0.704); 13 provinces had EHDI above and 11 had EHDI below the country average (Fig. 1).

Statistical Analysis

Numerical factors are summarized using medians and percentiles 25 and 75; categorical variables are reported as counts and percentages. Categorical variables were compared using the chi-square test or Fisher's exact text and numerical variables using the Kruskal–Wallis's rank test. Incidence and mortality rates were calculated using Epidat (version 3.0). We report age-standardized incidence rates (ASR), directly standardized to the world standard population and expressed per million children under 15 years of age. Survival curves and probability of survival at 1 year and 3 years were estimated using Kaplan–Meier method. The Cox proportional hazards model was used to evaluate association between 3-year survival and age at diagnosis, level of the treating hospital and EHDI of the residence province.

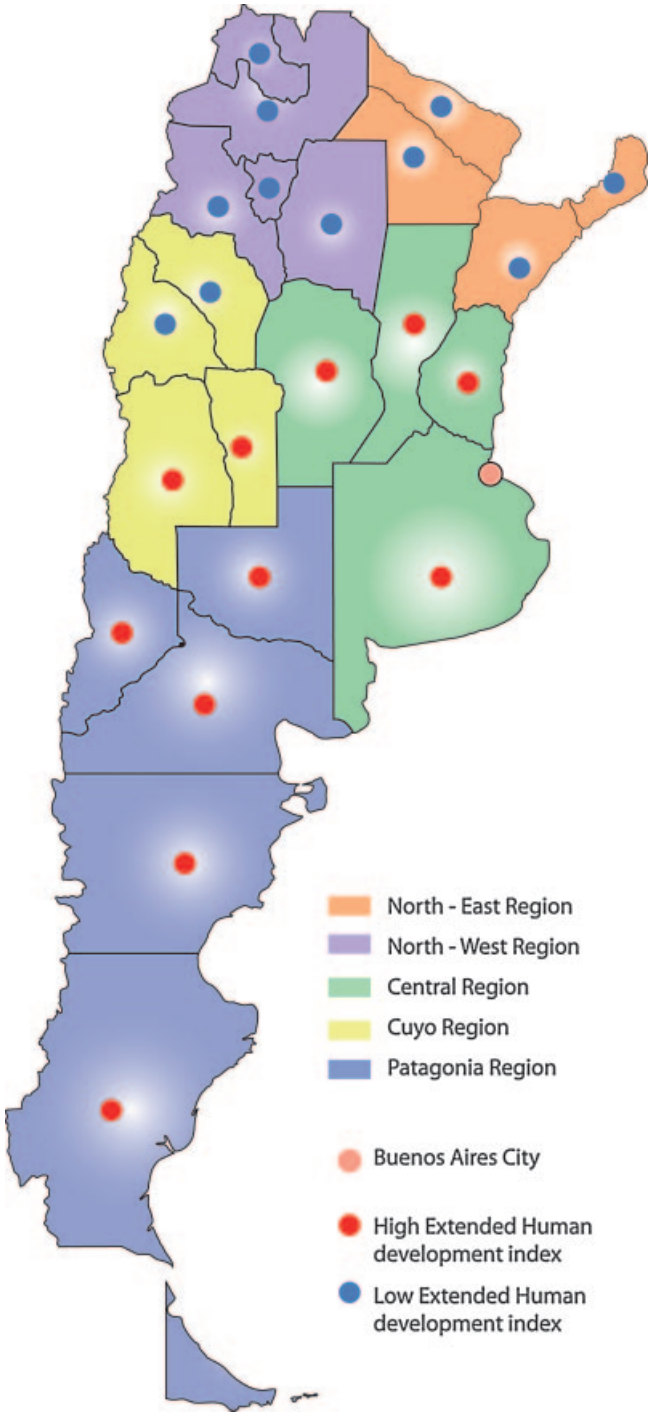

Fig. 1. Argentina by regions and extended Human development index.

RESULTS

Patient Description, Incidence and Mortality Rates

Over this 10-year period, a total of 438 cases of retinoblastoma patients were reported to the ROHA, making up an average of 43.8 cases per year. Six cases (1.36%) were detected by death certificate

TABLE I. Main Characteristics of the 438 Cases of Retinoblastoma in Argentina, 2000–2009

	Unilateral N = 299	Bilateral N = 139	*P*-value
Factor	N (%)	N (%)	Chi-square test
Gender			
Female	145 (48.5)	61 (43.9)	
Male	144 (51.5)	78 (56.1)	0.368
Disease extension			
Localized	291 (97.3)	133 (95.7)	0.0624[c]
Metastatic	8 (2.7)	3 (2.2)	
Pineal	0	3 (2.2)	
Region of residence			
Central	194 (64.9)	100 (71.9)	0.523
Northwest	33 (11)	11 (7.9)	
Northeast	27 (9)	13 (9.4)	
Cuyo	28 (9.4)	8 (5.8)	
Patagonia	17 (5.7)	7 (5)	
Low extended human development index	69 (23.1)	26 (18.7)	0.301
Treated at tertiary hospital	189 (63.2)	108 (77.7)	0.003
Cohort at diagnosis			
2000–2003	112 (37.5)	40 (28.8)	0.205
2004–2006	97 (32.4)	52 (37.4)	
2007–2009	90 (30.1)	47 (33.8)	
Dead by 12 months after diagnosis[a]	28 (9.4)	4 (2.9)	0.015
Dead by 36 months after diagnosis[a]	33 (11)	7 (5)	0.042
	Median IQR[b]	Median IQR[b]	
Age at diagnosis	26 (13–42)	10 (5–19)	<0.001[d]

[a]Cumulative incidence calculated assuming no loss to follow up for vital status. [b]IQR, inter quartile range = (Percentile 25%, Percentile 75%). [c]Fisher's exact test. [d]Kruskal–Wallis test.

only. There were 299 (68.3%) unilateral and 139 (31.7%) bilateral, 3 of whom (2.1%) developed trilateral disease. About 5% of children diagnosed initially with unilateral develop a metachronous tumor in the fellow eye. Since we collect information at the time of diagnosis, these cases would be possible included in the unilateral group. ASR for the whole country was 5.0 cases per million children under the age of 15 years (95% CI: 3.5–6.4). The estimated incidence was stable over time: 4.2 (95% CI: 3.2–5.1), 5.1 (95% CI: 4.1–6.2), and 4.8 (95% CI: 3.8–5.8) for cohort of children diagnosed at 2001–2003, 2004–2006, and 2007–2009, respectively.

Table I presents the main characteristics of the children diagnosed with unilateral and bilateral disease. There were 11 patients (2.6%) that presented metastatic disease in the central nervous system at diagnosis. The male/female ratio was 1.12. Cases with bilateral disease were more likely to be treated at tertiary hospitals ($P = 0.003$). In both, unilateral and bilateral disease age at diagnosis was significantly higher for children residing in provinces with lower EHDI (Fig. 2). Median age at unilateral disease diagnosis was 24 months for high income versus 35 months for low-income province cases ($P = 0.003$). For patients with bilateral disease median age at diagnosis was 9 months in high EHDI provinces versus 11.5 months in low EHDI provinces ($P = 0.027$). A total of 46 children died (36/299 with unilateral retinoblastoma and 10/139 with bilateral retinoblastoma). Two of the three children with trilateral disease died. All children who presented CNS dissemination died. Overall 8/299 children with unilateral disease had CNS metastasis at diagnosis and all died. Of them 4/226 lived in provinces with higher EHDI (1.74%) and 4/65 lived in provinces with lower EHDI (5.8%) ($P = 0.08$).

For this population the estimated 3-year survival probability was 0.90 (95% CI: 0.86–0.92) (Fig. 3, Global curve). No differences in survival were observed among the three cohorts defined according to year of diagnosis (2001–2003, 2004–2006, and 2007–2009). The estimated 3-year probability of survival was significantly higher in bilateral than in unilateral disease (0.94 and 0.87, respectively, $P = 0.035$). Probability of survival was higher for patients treated at tertiary level institutions (Fig. 3, $P = 0.0015$). Additionally, patients from provinces with higher socioeconomic level, as measured by EHDI, had also a higher 3-year probability of survival compared with those residents in lower developed areas (0.93 and 0.77, respectively, $P < 0.0001$). Figure 4 shows survival curves for the strata defined by the combination of the following two factors, level of the treating institution and EHDI of the residence province. The combination of both risk factors (low EHDI and non-tertiary level treating institution) results in a very low survival probability, even at 1-year after diagnosis (Fig. 4). Children who died by 3 years were older at diagnosis than those who survived. For unilateral retinoblastoma the median age at diagnosis was 25.5 and 28 months for survivors and deceased, respectively ($P = 0.40$). For bilateral disease, median age at diagnosis was 9 and 20 months for survivors and deceased, respectively ($P = 0.013$).

DISCUSSION

Our study showed that there are no major differences in the incidence of retinoblastoma in Argentina compared to developed countries. Other studies from the region reported increased incidence rates in areas of Mexico [12] and Northern Brazil [13].

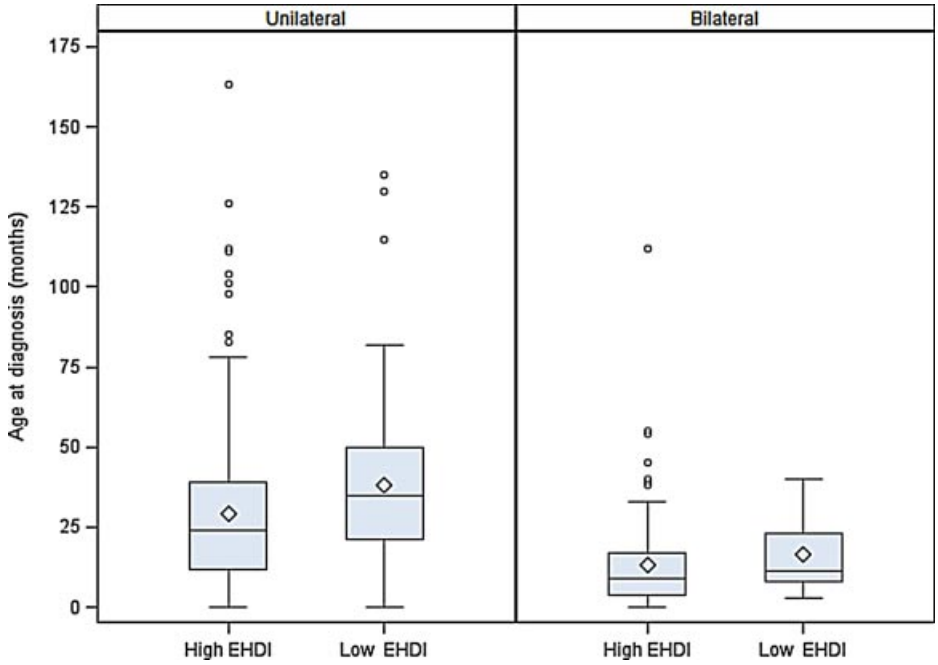

Fig. 2. Age at diagnosis according to the socioeconomic level, extended human development index (EHDI) of the province of residency in unilateral and bilateral diseases.

Reports from developing countries in other regions of the world also suggested an increased incidence [14,15,28]. The reasons for a probable geographic variation in the incidence of retinoblastoma in certain populations are unknown. Environmental factors such as the potential role of HPV infection were postulated to explain the possible increased incidence of retinoblastoma in some developing countries [29]. However, further evaluation of this association yielded controversial results [30]. Others reported maternal dietary habits such as low folate intake, or parental occupation as risk factors for retinoblastoma [31,32]. Ethnical variations might also affect the incidence of retinoblastoma but no distinct pattern is clearly evident. An increased incidence in Native Alaska population was reported [33]. Ethnical factors are difficult to assess in Argentina where a meltdown of many ethnical groups that migrated to our country more than a century ago compose its society. However, the situation in other Latin American countries with other ethnic background may be different and other registries may consider collecting this information to obtain relevant data from their particular background. Retinoblastoma was reported to be more frequent in areas with lower development indicators with the highest incidence rates reported from Equatorial Africa [15]. Data from North American and European population based registries

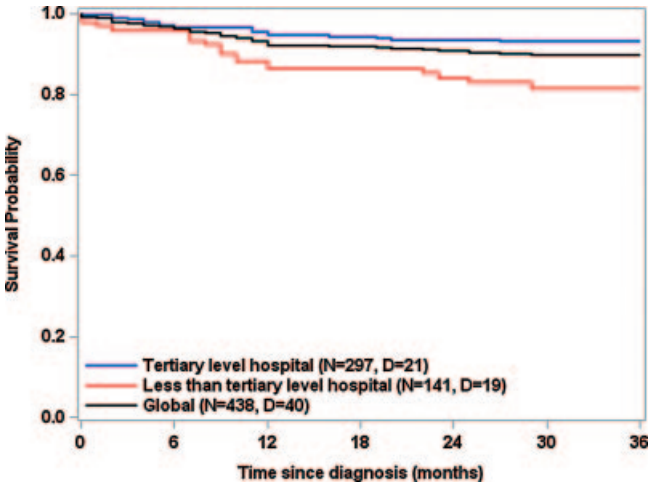

Fig. 3. Survival of children with retinoblastoma diagnosed in Argentina 2000–2009 according to type of treatment center.

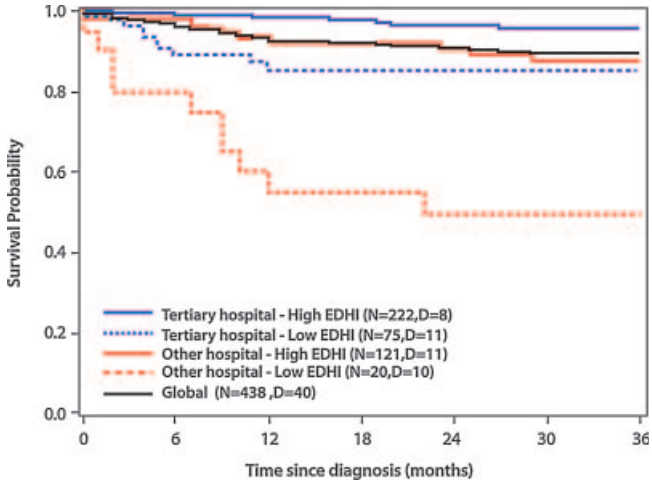

Fig. 4. Survival of children with retinoblastoma diagnosed in Argentina 2000–2009 according to socio-economic factors and to type of treatment center.

TABLE II. Standardized Incidence Rates, Relative Frequencies at Age 0–14 Years and Retinoblastoma

	Europe 1988–1997		USA SEER 1999–2010		Argentina 2000–2009		Canada 1992–2006	
	ASR[a]	%RF[b]	ASR[a]	%RF[b]	ASR[a]	%RF[b]	ASR[a]	%RF[b]
Retinoblastoma	4.1	2.4	4.3	2.5	5.0	3.5	3.9	2.4

[a]ASR, age standardized rate per 1,000,000 population aged 0–14 years. [b]RF, Relative frequencies (%).

have reported an incidence of retinoblastoma in the range of 4–6 cases per million children younger than 15 years (Table II) [4,6–8]. However, rates from 10 to 20 cases per million were reported from developing countries [15,34]. Nevertheless, these data were seldom reported from population-based registries with national coverage and represent different regions in the same country. National population-based cancer registries in developing countries are scarce and they face numerous logistic problems such as lack of infrastructure, problems in diagnosis of children with cancer and limitations of patient's access to care in local hospitals, poor registration of patients treated at specialist hospitals, geographical barriers to reach distant rural areas, and poor quality national demographic data [23,35]. In addition, in many developing countries, vital data such as birth and death certificates which are crucial for the estimation of cancer incidence are not mandatory or not enforced. Methodological issues may also affect the estimations of retinoblastoma incidence. There is no general agreement on which is the best method for estimating the incidence of retinoblastoma [4]. Because of its low incidence, a small number of children are diagnosed every year, so case ascertainment in relatively small populations might lead to inaccurate estimations. Some studies reported incidence rates as cases every 10,000 live births and others report cases every million children 0–4 or 0–14 years. The use of estimations using the live births in the denominator as reported from Scandinavia may not be accurate in developing countries with higher infant mortality rates and, on the other hand, delayed diagnosis would exclude children diagnosed at an older age in developing countries (7.5% of our population) when only children younger than 5 years are considered. Thus, we used the standard calculation of cases every million children 0–14 years old, as reported by most registries. Most of these sources of bias are limited in our analysis since the ROHA collects more than 90% of all the pediatric cancer cases which are highly centralized, national demographic data are reliable and 1% of our cases were ascertained from death certificates. Our results failed to find a significant increase in the incidence of retinoblastoma in our 10-year evaluation. In addition, the sex distribution and laterality are in line with previous population-based reports from developed countries [7]. We were not able to detect differences in incidence according to the region of the country where the family lived, however this is not a conclusive result as some of the regions are not densely populated and the number of cases are low. We only observed an increased incidence in the Buenos Aires area (the most developed district in the country, not shown in Table I) which we interpret is related to migration to receive adequate therapy. Our study is distinctive in that it presents population-based data about the incidence of trilateral retinoblastoma in a developing country. The results appear to confirm those reported from a single institution in Brazil [36]. This figure appears to be lower than that from developed countries which reported up to 6–13% [37], but in line with a recent single institution estimation [38].

We have detected important differences in the diagnosis and outcome of patients according to the area of residency development index. Children living in the least developed areas of the country are diagnosed at a significantly older age and have a significantly higher risk of dying of retinoblastoma. This difference is more evident in the population with unilateral disease where affected children are diagnosed 10 months later than the country median. Altogether, since retinoblastoma presents at a narrow age range, these data seem to indicate that delayed diagnosis is probably the most likely factor underlying these observations [39,40]; however, a particular biology of retinoblastoma in our population may also occur. The national survival rates were encouragingly over 90% as it is seen in most developed countries. However, children from the least developed areas fared significantly worse with a survival gap larger than 15%. The impact of socio-economic indicators in the survival of retinoblastoma has been reported previously based on data from European countries [8,11]. Our data show that this phenomenon is seen even within the different areas of the same country. The inequality of care that children with cancer receive in our country may explain this observation by limiting the access to high quality care of children in less developed areas, especially in the pre-diagnostic period, since children from less developed areas were diagnosed at a later age [23]. However, since the age at diagnosis showed a weaker correlation with ultimate 3-year survival, we hypothesize that effective therapies administered in tertiary care centers may have helped to reduce this gap in prognosis. This difference is narrowed in bilateral cases, where the difference in age at diagnosis is less than 2 months between those coming from provinces with higher development indicators compared to those from less developed areas. This might also explain the higher 3-year survival of children with bilateral retinoblastoma.

Our study also provided data about the influence of the treating center on the outcome of children with retinoblastoma. Current treatment of retinoblastoma, especially for bilateral retinoblastoma, is very sophisticated so few centers in developing countries can provide state of-the-art therapy. Compared to other malignancies in Argentina, care of children with retinoblastoma is highly centralized with one center providing care for 68% of the affected children. Centralizing patients in a single referral center translated in improved survival in these children justifying this approach. In Argentina, access to highly specialized centers for pediatric oncology is not restricted but families with low income may still find it impossible to migrate temporarily for treatment. Access to high quality care might have influenced the pre-diagnosis phase to a greater extent, causing delayed diagnosis in less favored areas, as was reported previously in a single institution report from our country. However, the survival difference in our country was seen mostly in unilateral disease in which, we speculate, the effectiveness of protocolized risk-tailored adjuvant therapy for preventing metastatic disease in high risk children implemented in several

prospective protocols at the central institution might explain this finding.

CONCLUSIONS

Based on population-based data from a National Registry, the incidence of retinoblastoma in Argentina is comparable to that of developed countries. Retinoblastoma is diagnosed later and survival is lower in the less developed areas of the country.

REFERENCES

1. Knudson AG, Jr. Mutation and cancer: Statistical study of retinoblastoma. Proc Natl Acad Sci USA 1971;68:820–823.
2. Potluri VR, Helson L, Ellsworth RM, et al. Chromosomal abnormalities in human retinoblastoma. A review. Cancer 1986;58:663–671.
3. MacCarthy A, Birch JM, Draper GJ, et al. Retinoblastoma: Treatment and survival in Great Britain 1963 to 2002. Br J Ophthalmol 2009;93:38–39.
4. Seregard S, Lundell G, Svedberg H, et al. Incidence of retinoblastoma from 1958 to 1998 in Northern Europe: Advantages of birth cohort analysis. Ophthalmology 2004;111:1228–1232.
5. Abramson DH. Retinoblastoma incidence in the United States. Arch Ophthalmol 1990;108:1514.
6. Moll AC, Kuik DJ, Bouter LM, et al. Incidence and survival of retinoblastoma in The Netherlands: A register based study 1862–1995. Br J Ophthalmol 1997;81:559–5562.
7. Broaddus E, Topham A, Singh AD. Incidence of retinoblastoma in the USA: 1975–2004. Br J Ophthalmol 2009;93:21–23.
8. MacCarthy A, Draper GJ, Steliarova-Foucher E, et al. Retinoblastoma incidence and survival in European children (1978–1997). Report from the Automated Childhood Cancer Information System project. Eur J Cancer 2006;42:2092–2102.
9. Tamboli A, Podgor MJ, Horm JW. The incidence of retinoblastoma in the United States: 1974 through 1985. Arch Ophthalmol 1990;108:128–132.
10. Krishna SM, Yu GP, Finger PT. The effect of race on the incidence of retinoblastoma. J Pediatr Ophthalmol Strabismus 2009;46:288–293.
11. Canturk S, Qaddoumi I, Khetan V, et al. Survival of retinoblastoma in less-developed countries impact of socioeconomic and health-related indicators. Br J Ophthalmol 2010;94:1432–1436.
12. Fajardo-Gutierrez A, Juarez-Ocana S, Gonzalez-Miranda G, et al. Incidence of cancer in children residing in ten jurisdictions of the Mexican Republic: Importance of the Cancer registry (a population-based study). BMC Cancer 2007;7:68.
13. de Camargo B, de Oliveira Santos M, Rebelo MS, et al. Cancer incidence among children and adolescents in Brazil: First report of 14 population-based cancer registries. Int J Cancer 2010;126:715–720.
14. al-Idrissi I, al-Kaff AS, Senft SH. Cumulative incidence of retinoblastoma in Riyadh, Saudi Arabia. Ophthalmic Paediatr Genet 1992;13:9–12.
15. BenEzra D, Chirambo MC. Incidence of retinoblastoma in Malawi. J Pediatr Ophthalmol 1976;13:340–343.
16. Kivela T. The epidemiological challenge of the most frequent eye cancer: Retinoblastoma, an issue of birth and death. Br J Ophthalmol 2009;93:1129–1131.
17. Moreno F, Loria D, Abriata G, et al. Childhood cancer: Incidence and early deaths in Argentina, 2000–2008. Eur J Cancer 2013;49:465–473.
18. Moreno F. Argentinean hospital-based pediatric cancer registry. Results 2000–2008. In: Kaleidos F, editor. Edition 2010.
19. Anonymous. Fuente INDEC: Encuesta Permanente de Hogares 2010, processed with Redatam + SP. In Edition. Buenos Aires; 2010.
20. National Statistics Bureau (INDEC). Percent of the population without social security or health plan coverage by age and region. Health coverage and hospital resources. In Edition 2005.
21. Moreno FDV, Abriata G, Loria D, et al. Hospital-based pediatric oncology registry (Registro Oncopediátrico Hospitalario Argentino, ROHA INC). Incidence 2000–2009, survival 2000–2007, mortality trends 1997–2010. In Edition. Buenos Aires; 2012.
22. Moreno F, Schvartzman E, Scopinaro M, et al. Hospital-based pediatric oncology registry (Registro Oncopediátrico Hospitalario Argentino, ROHA). Results 2000–2008, In: ROHA FK, editor. Edition. Buenos Aires, Argentina: ROHA; 2009.
23. Scopinaro MJ, Casak SJ. Paediatric oncology in Argentina: Medical and ethical issues. Lancet Oncol 2002;3:111–117.
24. National Statistics Bureau (INDEC). In Edition 2005.
25. Mercado R, Catterberg G. Human development in Argentina: Current trends and new challenges. In National Report on Human Development Edition 2010.
26. Klugman J, Rodríguez F, Choi HJ, et al. The real wealth of nations: Pathways to human development. In Human Development Report. 20th Anniversary Edition, Edition 2010.
27. UNDP. United Nations Development Program. Extended human development index (EHDI)-construction. Technical note—Calculating the extended human development index for Argentina. In Edition 2010.
28. Schultz KR, Ranade S, Neglia JP, et al. An increased relative frequency of retinoblastoma at a rural regional referral hospital in Miraj, Maharashtra, India. Cancer 1993;72:282–286.
29. Orjuela M, Castaneda VP, Ridaura C, et al. Presence of human papilloma virus in tumor tissue from children with retinoblastoma: An alternative mechanism for tumor development. Clin Cancer Res 2000;6:4010–4016.
30. Antoneli CB, Ribeiro KB, Sredni ST, et al. Low prevalence of HPV in Brazilian children with retinoblastoma. J Med Virol 2011;83:115–118.
31. Orjuela MA, Titievsky L, Liu X, et al. Fruit and vegetable intake during pregnancy and risk for development of sporadic retinoblastoma. Cancer Epidemiol Biomarkers Prev 2005;14:1433–1440.
32. Moll AC, Imhof SM, Kuik DJ, et al. High parental age is associated with sporadic hereditary retinoblastoma: The Dutch retinoblastoma register 1862–1994. Hum Genet 1996;98:109–112.
33. Lanier AP, Holck P, Ehrsam Day G, et al. Childhood cancer among Alaska Natives. Pediatrics 2003;112: e396.
34. Amozorrutia-Alegria V, Bravo-Ortiz JC, Vazquez-Viveros J, et al. Epidemiological characteristics of retinoblastoma in children attending the Mexican Social Security Institute in Mexico City, 1990–94. Paediatr Perinat Epidemiol 2002;16:370–374.
35. Howard SC, Metzger ML, Wilimas JA, et al. Childhood cancer epidemiology in low-income countries. Cancer 2008;112:461–472.
36. Antoneli CB, Ribeiro Kde C, Sakamoto LH, et al. Trilateral retinoblastoma. Pediatr Blood Cancer 2007;48:306–310.
37. Blach LE, McCormick B, Abramson DH, et al. Trilateral retinoblastoma—Incidence and outcome: A decade of experience. Int J Radiat Oncol Biol Phys 1994;29:729–733.
38. Ramasubramanian A, Kytasty C, Meadows AT, et al. Incidence of pineal gland cyst and pineoblastoma in children with retinoblastoma during the chemoreduction era. Am J Ophthalmol 2013;156:825–829.
39. Erwenne CM, Franco EL. Age and lateness of referral as determinants of extra-ocular retinoblastoma. Ophthalmic Paediatr Genet 1989;10:179–184.
40. Chantada G, Fandino A, Manzitti J, et al. Late diagnosis of retinoblastoma in a developing country. Arch Dis Child 1999;80:171–174.