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Thyroid Cancer – South American Experience

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Abstract

Thyroid cancer comprises a broad spectrum of diseases with variable prognoses. The diagnosis of thyroid cancer usually follows the identification of a thyroid nodule on physical examination or as an incidental finding on diagnostic imaging performed for other reasons. It is considered the most frequent endocrine cancer, and its incidence has been growing steadily during the past three decades around the world. This trend is a constant in every continent except for Africa. Thyroid cancer is the fifth most common malignancy among women and its incidence has only declined in a few countries. The incidence of thyroid cancer may be substantially different around the world, and the potential causes are related to racial, ethnic and geographical differences or to environmental differences such as excessive or deficient iodine, in addition to radiation exposure. Thyroid cancer is the sixteenth most frequent malignancy around the world, with approximately 298,000 new cases diagnosed in 2012 (2% of the total). Thyroid cancer increase has been associated to socioeconomic status, better access to healthcare and rising use of thyroid imaging. Therefore, the rise could be apparent because of the useless identification of a large reservoir of subclinical papillary lesions that will never affect patient health (over diagnosis). Although increased detection might have played a major role, some evidences suggest that true increase in incidence have also contributed to such phenomenon. The evidence indicates that the type of thyroid cancer that has experienced a substantial increase in terms of frequency is papillary cancer, with no significant changes in the frequency of the other types of cancer and histological variants. Though the increased frequency is the same for all tumor sizes, it is more evident in <1 cm tumors (micro carcinomas). However, it is also true that the information derived from tumor histology is now more accurate and complete, reducing the number of the so-called unspecific/unknown categories.

The information available for South America – except for a few countries – is limited and scattered; in countries like Brazil, Chile and Colombia the population coverage is insufficient to ensure reliable data and complete cancer records; moreover, there are no universal criteria to ensure data collection from most of the population. Though there is comprehensive information about specific populations or geographical areas, the real situation regarding thyroid cancer in the population is unknown. However, the creation of population-based cancer records has led to a more accurate vision of the problem. The objective of this review is to provide an update on the epidemiology of thyroid cancer in South America; discussing the probable causes that have led to increase in frequency in the population, for this purpose we conducted a systematic medical literature review (see "Literature search"). We find that in South America few cancer registries are based on the population; countries like Chile have sub-registries and this results in an underestimation of thyroid cancer due to an incomplete registry of cases because some of the pathologic anatomy centers failed to participate in the trial; similarly, Brazil evidences an under-registration of thyroid cancer, as a result of the difficulties to access healthcare services and of the quality of the data in the available registries. The national cancer information system has not yet been implemented in Colombia, and reporting malignant neoplasms is not obligatory, except for neoplasms present in the pediatric population.

Keywords: Cancer, Carcinoma, Thyroid, Thyroidectomy, Surgery, Epidemiology, Incidence, South America, and Colombia.

Literature Search

Systematic medical literature review of MEDLINE database, using the terms MeSH: "cancer", "carcinoma", "thyroid", "epidemiology", "global burden", "neoplasm", "thyroidectomy", "surgery" combined with conjunctions "AND", "OR" and "NOT" in addition to "also try"; data published on "any date", limiting the search to results that included the link "abstracts" and "full text" exclusively in humans, and regardless of gender. The selection was based on clinical trials, cohort studies, intervention trials, meta-analysis, clinical practice guidelines and systematic review articles. The search was limited to articles published in English and Spanish on adult population >19 years old. Additionally, a search was completed on the following databases: SciELO, Hinari, Lilacs, Imbiomed, and Latindex using the above criteria. Additionally were reviewed texts, manuals, and files containing relevant and proven information on thyroid cancer in South America. Finally, the various population registries on cancer and the different national initiatives on cancer trials were accessed, to gain the information therein discussed.

Definitions

Raw or Gross Rates: For a particular location, a raw rate is the ratio between a D number of deaths observed in one year (or in a specific period of time) and the N number of people exposed to risk in the same year (or period of time). The population exposed (people-year) in a period of time is the sum of the mean population (estimate of the population at the mid-point of the time interval) of each year in that period of time. The annual raw rate is expressed in terms of the number of cases per 100,000 males or females.

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Age adjusted rates (standardized using the direct method): In order to compare the figures observed in the various regions, time periods, or different groups, the variables that account for part of the differences identified should be considered; age being one of those known factors. The expression standardized rates-direct method is known in demographics as the typical population method, and to facilitate international comparisons, the world population has been adopted as the standard. The principle of this method consists in determining the potential rate observed in a typical population (standard or reference) with a particular demographic structure, if it were to exhibit a mortality value consistent with that of the population studied.

Introduction and Overall Cancer Burden

The term "cancer" is a generic expression encompassing a broad range of diseases that may affect any part of the body. Cancer is a term widely used to define those diseases in which the abnormal cells divide in an uncontrolled manner and may invade other tissues. The screening, diagnosis and treatment of cancer entails huge healthcare costs, regardless of the economic environment; for example, based on the aging population in the United States (US), the National Cancer Institute (NCI) at the National Institutes of Health (NIH) in the US forecasts that the cancer-related medical expenses will grow to at least 158.000 million US dollars in 2020; this amounts to 27% increase over the 2010 figures. In fact, it has been estimated that if the diagnostic and therapeutic support methods continue the same trend in terms of price escalation, the general expenditure may represent around 207.000 million dollars. Moreover, this figure may be even higher considering the loss in productivity of the affected patients [1-3]**.** According to the type of cancer, the level of cost – in descending order and expressed in millions of dollars – are: Breast cancer (16.5); colorectal cancer (14.0); lymphoma (12.0); lung (12.0); and prostate (12.0).

The estimate of new cancer cases in 2012 was 14.1 million new cases around the world: 7.4 million males and 6.7 females, with a 10:9.1 male to female ratio. The world Age Standardized Rate (ASR) showed that the incidence is 205 new cases per every 100.000 males and 165 per every 100.000 females. Over 60% of the new cases per year are attributed to Africa, Asia, Central and South America [4-7].

The ASR varies according to gender; for example, in males the ASR may show up to a four-fold variation depending on the particular region (from 79 per 100.000 in Western Africa, to 365 per 100.000 in Australia and New Zealand). Likewise, in women the variation is almost three fold (from 103 per 100.000 in South-Central Asia to 295 per 100.000 in North Eastern America). France has a higher incidence of cancer in men (385 per 100.000), whilst Denmark exhibits the highest rates for women (328 per 100.000). The incidence rate also varies depending on the Human Development Index (HDI), which is an indicator of human development in a particular country and is based on a social statistical marker comprising three parameters: long and healthy life, education, and dignified lifestyle. However, such indicator is used for the sake of statistics but does not necessarily express the particular level of development of a region. Furthermore, when considering the HDI, obviously the ASR also changes accordingly [8-10]. For 2012, the incidence rate in males varied around three fold in countries with a very high HDI (316 per 100.000) in contrast to those with a low HDI (103 per 100.000). In females, the rate varied around two fold in countries with a very high HDI (253 per 100.000) versus countries with a low HDI (123 per 100.000). Countries like Armenia, report the highest cancer mortality rate in males (210 per 100.000), while Zimbabwe exhibits the highest female rate (146 per 100.000). The mortality rate also varies with HDI; in males the mortality rate is 51% higher in countries with a very high HDI (132 per 100.000) as compared with low-medium HDI countries (87 per 100.000). In women, the rate varies only slightly among countries with a very high HDI (85 per 100.000) versus countries with a low HDI (87 per 100.000). These data should be interpreted with caution since the interpretation of the differences in the incidence of cancer based on HDI values may reflect differences in the quality of the information [11-13].

Epidemiology and Global Burden of Thyroid Cancer

Thyroid cancer is the most common endocrine malignancy (1.0-1.5% of all newly diagnosed cancers in the US every year are originally thyroid) and is the fifth most frequently diagnosed cancer in women (though in Italy is number two in women under 45 years old) with a growing incidence in the last 30 years around the world. Countries like Italy, Israel, Japan and Switzerland report the highest percentage increase in the incidence rate – particularly in women – during particular time periods, while in the United Kingdom the percentage increase is the lowest (Table 1). This trend is present practically in every continent, except for Africa, probably because the detection methods are poor for the identification of the disease. In contrast, in countries like Norway and Sweden, the incidence has declined [14,15]. The five countries with the highest incidence of thyroid cancer (in descending order per 100.000 individuals) are: Iceland (16.3); Israel (15.8); Malta (15.7); US (14.2); and Qatar (14.1).

The increased frequency in thyroid cancer is almost exclusively due to the rise in the number of papillary cancers, with no significant changes in the follicular, anaplastic, and medullary types. The typical presentation is as small tumors, though there is also increasing incidence of large tumors. The increase in incidence is measured using the Annual Percent Change (APC). In general, the APC ranges are 2-14% in women and 2-8% in men; specifically, in terms of gender and race, the APC for men and women (respectively) is 6.3% and 7.1% for Caucasians; 4.3% and 8.4% for blacks; 4.2% and 6.7% for Hispanics; and 3.4% and 6,4% for Asian and Pacific Islands populations [14,16].

It has been hypothesized that the rise in the incidence of thyroid cancer is mostly due to improved detection rather than to a real increase in frequency (Table 2). Genetic and environmental factors, as well as access to healthcare systems, may all account for the broad variability in the incidence of the condition, analyzed in terms of the geographical area and different ethnics. Despite the growing incidence, thyroid cancer mortality remains almost unchanged (around 0.5 cases per 100.000 people), though a slight increase of +0,8% in the mortality rate has been described in the APC, particularly in men, regardless of an earlier diagnosis and the current improved therapies for high-risk thyroid cancer.

According to the NCI, the number of new thyroid cancer cases in the US is 12.9 per 100.000 men and women per year, while the number of deaths is 0.5 per 100.000 men and women per year (these rates are age adjusted and are based on the cases and fatalities reported between 2007 and 2011). Additionally, it has been estimated that 1.1% of males and females may be diagnosed with thyroid cancer at some point in their lives (based on the data from 2009 and 2011), and the prevalence of thyroid cancer (in 2011) was estimated at 566.708 people living with the condition in the US (123.088 men and 443.620 women) [17,18].

In accordance with the US Census Bureau, 45.5 million Americans, representing 15% of the total population, were identified as Hispanics or Latinos in 2007. Though the people of Hispanic origin may be of any race, approximately 97% of the Hispanics living in the US are white. According to the American Cancer Society, the estimated new cases of

Country	Years		Incidence Variation (APC)	
			Females	Males
Australia	1982 1982 2000	2007 2000 2007	- 2.0 13.8	4.0 - -
Canada	1970/72 2002	1994/1996 2008	3.5 7.3	3.2 8.4
China	1983 1983	2000 2003	- 4.9	2.6 -
Denmark	1973/1977	1998/2002	81.3 §	20 §
Finland	1973/1977	1998/2002	62.8 §	29.4 §
France	1983	2000	8.98	8.13
Israel	1973/1977	1998/2002	95.2 §	34.6 §
Italy	1991/1995	2001/2005	145 §	127 §
Japan	1973/1977	1998/2002	85.7 §	52.4 §
Spain	1978 (Only papillary thyroid cancer)	2001	9.4 ¥	2.6 ¥
Switzerland	1973/1977	1998/2002	85.7 §	5.3 §
United Kingdom	1993	2008	2.3	0.6
US	1998 1997	2005 2009	7.0 7.0	6.3 -

APC: Annual Percent Change.
§: Percentage of temporary change (% increase) during the period of time indicated.
¥: Increased incidence during the period of time indicated.

Table 1: Rise in the incidence rate of thyroid cancer in various countries.

Increased incidence of thyroid cancer (Due to improved detection ability rather than to a genuine rise in incidence)	Actual increase in the incidence of thyroid cancer
Extended use of neck/thyroid ultrasound and fine needle aspiration (FNA), neck vessels Doppler ultrasound, neck CT, neck MRI, PET/CT scan, use of high-resolution ultrasound devices and the increasing number of cytological examinations on smaller nodules in size, and improved access to biochemical-molecular markers for the detection of thyroid cancer.	The higher incidence of thyroid cancer has been observed in many regions around the world, including North America, Europe, and Australia and probably reflects a general "trend", although this trend has not been documented in every geographical region.
Increased detection of incidental thyroid micro-carcinomas due to: - Growing frequency of thyroidectomies due to benign lesions - More detailed histopathological analysis - Findings of thyroid nodules at physical examination; patient referred for a different reason	The frequency of large size and advanced stage thyroid cancer has not declined, as is expected when patients are diagnosed early.
More frequent identification of micro-carcinomas	Marked increase in the frequency of thyroid autoimmunity, as well as in the frequency of overweight and obesity that have been associated to increased frequency of thyroid cancer.
Increased frequency of small size thyroid cancer in autopsies	Increased frequency of large size tumors.
The age-adjusted incidence rates show a clear birth cohort pattern, with a higher incidence of recent birth cohorts than older ones. This may be related to the high frequency of thyroid cancer in women around 55 years old and in men over 55, and also reflects changes in exposure to environmental agents.	Only papillary thyroid cancer has shown an increased frequency
	The higher incidence is not proportionally distributed by age and gender (for example, the trend is higher in women over time)
	Enhanced detection of small size papillary carcinoma
	Growing number of new carcinogens present
Improved accuracy of population-based cancer registries	Increased exposure to ionizing and cosmic radiation, to solvents and pesticides, in addition to differences in the intake of iodine among the populations studied
Better access to healthcare systems	Increased accuracy in population cancer registries should have given rise to an increased number of other types of tumors

Table 2: Reasons explaining the increased incidence of thyroid cancer.

thyroid cancer among Hispanic women (2009 estimates, excluding all the skin basal and squamous cell carcinomas and carcinomas in situ, with the exception of urinary bladder) were 3.500 (equivalent to 7%). The incidence rates and thyroid cancer mortality for 2002-2006 (the rates are expressed per 100.000 inhabitants and were age-adjusted to the standard US population for the 2000 census) were as follows: for Hispanic men, the incidence rate was 3.8; for non-Hispanic White men, the rate was 5.4; with a proportional relationship of 0.7 (this relationship is defined as the non-rounded up rate of the Hispanics divided into the non-rounded up rate of the non-Hispanic whites). The incidence rate of thyroid cancer among Hispanic women was 13.8; in non-Hispanic white women was 15.1; with a proportional relationship of 0.9. The mortality rate among Hispanic men was 0.6; in non-Hispanic white men was 0.5; and the proportional relationship reported was 1.2; the mortality rate among Hispanic women was 0.6, while in non-Hispanic white women was 0.5; and the proportional relationship was 1.3 [20-22].

Thyroid Cancer and Cancer Population Registries – The Situation in South America

The World Health Organization (WHO) has promoted the implementation of national scope programs for cancer control in developing countries. These have been defined as: "Comprehensive public health approaches, designed to reduce the cancer incidence and mortality, and to improve the quality of life of cancer patients through the systematic and fair implementation of evidence-based prevention, early diagnosis, treatment and palliation strategies, for the best utilization of the available resources."

Cancer registries are critical to the control plans and programs of this pathology, since cancer control and prevention are practically impossible to attain without epidemiologic surveillance systems to support those plans and assess the results thereof. There are over 300 population-based cancer registries around the world, and 225 of those were included in Volume IX of "Cancer Incidence in Five Continents (ci5c)" Of these 225, only 11 are in Latin America and the Caribbean, representing 4.3% of the population in the region. At present, the universal cancer registries exhibit considerable inequalities between the high and the low and medium income countries. The percentage population covered by the cancer registries included in ci5c is 83% of the North American population, 32% of the European population, while in Latin America is only 6%, in Asia 4% and in Africa 1%. On the other hand – and for similar purposes – the Globocan project gives a current estimate of the incidence, the prevalence and the mortality of the major types of cancer at the national level, for 184 countries worldwide [22-24].

However, the thyroid cancer registries in South America (except for countries like Brazil, Chile, and Colombia) fail to comply with the population coverage to ensure reliable and complete cancer registries data. Moreover, in countries like Brazil, Chile, and Colombia, there is no universality of the data to ensure the collection of information from most of the population (either comprehensive data from specific populations or geographical areas are available, or the data collected are incomplete or inaccessible) [25-27].

Since the 90s**,** Chile developed the Región de los Ríos (Valdivia) registry as the principal source of information on the incidence of cancer. Similar to other countries, the data from this registry are not representative of the country; however, Chile currently has five population-based cancer registries: *de los Ríos Region, Antofagasta Region, Bío Bío Province, Concepción Province, and the National Registry of Pediatric Cancer*. The data provided by the Department of Epidemiology of the Chilean Ministry of Health estimated the non-annualized thyroid cancer incidence at 2 cases per 100.000 inhabitants in males, and in 5.3 cases per 100.000 inhabitants from 2003-2007, based on the data input from 3 sentinel centers in the regions of Antofagasta, Bío-Bío and Los Ríos. Recently however, the results of the Thyroid Cancer Initiative (INCATIR) were published. This project is promoted by the team of the Universidad de la Frontera, with a view to estimate the incidence of thyroid cancer in Chile, and to describe its behavior in all patients undergoing total thyroidectomy at 39 out of 50 participating centers, during one year of observation (March 2011 through February 2012). Data from 2614 thyroidectomies were obtained (1309 confirmed cases of thyroid cancer). Hence, the incidence of thyroid cancer was estimated at 7.6 cases per 100.000 people/year [28,29].

In 2007, there were already 25 cities in **Brazil** with population-based cancer registries, with available validated information in 20 of those cities that represented 19% of the country's population. So, together with the hospital records (implemented in every cancer care center since 1993) the system encompasses over 80% of the high complexity units of the Healthcare System. Sao Paulo exhibits one of the highest rates of thyroid cancer in the world [even higher than the US reports, based on the pattern of incidence obtained from the Sao Paulo Cancer Registry and "The National Cancer Institute's Surveillance Epidemiology End Results (SEER) program" in the US]. The thyroid cancer rate reported in Sao Paulo was 14.9 cases per 100.000 women and 3.9 cases per 100.000 men from 1998-2002, using age-adjusted world standards. Moreover, thyroid cancer is the fourth most common cancer in women, following breast cancer, skin cancer and colorectal cancer. A comparison between the Sao Paulo and the US cancer rates indicates that the former increased at a faster rate than the latter in women (SPCR/SEER incidence rate ratio: 1.65 while in men the incidence rate ratio was 1.23). Papillary carcinoma was the most prevalent in both populations, followed by follicular and then medullary carcinoma. The rate of papillary carcinoma grew faster in Sao Paulo versus the US, with an Annual Percent Change (APC) of 10.3% in women and 9.6% in men. Regardless of gender, the rates grew particularly in young people <50 years old in Sao Paulo, but the rate of growth was even higher in people over 50 years old in the US. The papillary/follicular carcinoma ratio increased from <3 to >8 in both men and women in Sao Paulo, and increased from 9 to 12 in men and from 6 to 7 in women in the US. According to Globocan 2012, the ASR for all ages was 2.5 in men and 10 in women, with a standardized mortality rate of 0.3 and 0.4 for men and women, respectively [30-32].

In Peru, 12,359 cancer cases were registered between January and December 2012, of which 3931 were diagnosed in 2012 (31,8%). The cases reported came from 43 units at the national level. These data did not include the information from the National Institute of Neoplastic Diseases; this institution subjects the cases to various quality control steps prior to registering them at the Cancer Epidemiological Surveillance system. Thyroid cancer is number 9 among the 15 most frequent cancers. 17 male cases and 94 female cases were identified, for a total of 111 cases (frequency of 2.8% of all the types of cancer). More recently, the "Analysis of Cancer Status in Peru, 2013" found that the annual average of thyroid cancer cases reported from 2006-2011 was 492, that corresponds to 11th in frequency according to its topographical localization, exceeding other types of cancer such as ovarian, pancreatic, encephalon, and kidney. During this period, a total of 2952 thyroid cancer cases were documented, 524 in males and 2428 in women, accounting for 2.7% of all cancer types, based on topographical localization and gender. This is the fifth type of cancer in terms of the frequency of hospitalization and discharge for that period of time. The trend in the number of thyroid cancer cases discharged from hospital grew from 566 discharges in 2006 to 813 discharges in 2011. This meant a 43.6% increase in the number of hospital discharges. The adjusted mortality rate, corrected for under-registration (taking into account that the total number of thyroid cancers was analyzed together with other endocrine malignancies) was 0.7 in males and 1.5 in females, with a total adjusted rate of 1.0 [33,34]**.**

In Bolivia, the cancer registry for Peace, created in 1997 for a population of close to one million people (1976 census), identified 14 cases of males and 30 cases of females between 1988-1990. The Standardized Incidence Rate (per 100.000 inhabitants) was identified at 0.8 for males and 2.4 for women; more recently, and a total estimated population of 10.088.100 inhabitants, with a mean annual figure of 72.900 deaths, thyroid cancer was not included among the top 10 cancer-related deaths. In accordance with the GLOBOCAN 2012 data, the estimated incidence for both males and females, regardless of age, was reported at 2.8 (raw rate) and 3.4 (standardized rate by age). The raw mortality rate was 0.9 and the age-standardized rate was 1.3 [23,35]**.**

In countries like Paraguay, the information is extremely limited or absent, for an estimated population of 6.568.300 people, with 36.100 mean annual deaths. Thyroid cancer is not reported among the top seven causes of cancer: breast cancer, cervical uterine cancer, colorectal cancer, liver, lung, prostate and stomach – in descending order and based on frequency. This fact makes it even more difficult to determine its distribution, since cancer is not included in the non-communicable diseases plan, and no cancer registries are available. In accordance with GLOBOCAN 2012 data, the estimated incidence for both men and women and for all ages, the raw rate was reported at 1.9 and the ASR at 2.1. The raw mortality rate was 0.7 and the age-standardized rate was 0.9 [23].

In Venezuela, based on the figures of the Central Cancer Registry of the Ministry of Health and Social Welfare and the Yearbook of Epidemiology and Vital Statistics for 1992, thyroid cancer was 13 among the 15 primary anatomic localizations in terms of incidence in females. The male incidence was not reported, nor was thyroid cancer listed among the 15 top cancer-related deaths in men or women. There were 60 cases reported in men that year, with an ASR of 0.59. There were 182 cases in women, with an ASR of 1.799. More recently, and according to GLOBOCAN 2012, the estimated incidence rate in both men and women for all ages was 1.6 and an age-standardized rate of 1.6. The raw mortality rate was 0.5 and the age-standardized rate was also 0.5 [23,36].

In Uruguay, according to the III Atlas Of Cancer Incidence, The Honorary Commission Of Fight Against Cancer, National Cancer Registry 2002-2006, documented 137 male cases around the country, of which 75 were reported in the rural areas. The ASR was 1.49 and the raw rate was 1.75 (countrywide). In women, 599 cases were documented, of which 349 occurred in the rural areas. The ASR was 6.11 and the raw rate was 7.15 (countrywide). More recently, according to the IV Atlas OD Cancer Incidence in Uruguay, Of The Honrary Commission Of Fight Against Cancer, National Cancer Registry 2007-2011, 189 cases were reported in males around the country, of which 96 occurred in the rural areas. The ASR was 1.99 and the raw rate was 2.4 (countrywide). In women, 908 cases were reported, of which 470 occurred in the rural areas; the ASR was 9.08 and the raw rate was 10.69 (countrywide) [37,38].

In Ecuador, pursuant to the National Tumor Registry for Quito residents from 2006-2010, the raw incidence rate for males was reported at 3.9 and the ASR was 4.1. A raw incidence rate of 23.8 was reported for women in the same period of time and an ASR of 23.5. However, according to GLOBOCAN 2012, the estimated incidence for both males and females of any age was a raw rate of 7.6 and an ASR of 7.8. The raw mortality rate was 1.0 and the age-standardized rate was 1.1 [23,39].

In Argentina, the thyroid cancer incidence rate in the Capital City and Gran Buenos Aires (2003-2011) was estimated with an ASR of 6.51, representing almost tow fold increase versus 1981-1986. The ASR was higher among women (11.76) in contrast to men (2.65). Both for males and females, the highest rate was for <1 cm tumors; according to Globocan 2012, 2062 new cases were documented, with an ASR of 4.6 and a raw rate of 5.0 [24,40,41].

Tables 3 and 4 show the incidence of thyroid cancer in males and females in South America (where specific registry and data are available), in accordance with different periods of time studied. Both tables report the number of cases, the raw rate and the ASR. However, there are some differences in terms of frequency when analyzed based on the percentage of cases that were microscopically verified (MV) and in accordance with the percentage or the number of deaths from a particular type of cancer, with regards to the number of cases registered for the same period of time (Table 5).

There are 6 population-based cancer registries in **Colombia** that have a sub-national coverage in the cities of Cali, Pasto, Bucaramanga, Barranquilla, Manizales, in addition to the Antioquia cancer population registry. From 2002-2006, the raw rate for all types of cancers in Colombia, except for non-melanoma skin cancer is 150.2; with an ASR of 160.6 and an Accumulated Risk (AR) of 16.6. In terms of thyroid cancer, the data show a raw rate of 5.0; an ASR of 5.1 and AR of 0.5. Furthermore, when considering the estimated figures for thyroid cancer incidence and mortality according to Globocan 2002, Globocan 2008 and local estimates 2002-2006, for both males and females (raw rates per 100.000) the Estimated Annual Cases (EAC) in women exceeded those in men by a 3.9 ratio (according to GLOBOCAN 2002); and by a 24.58 ratio (according to GLOBOCAN 2002-2006); and 10.17 (according to GLOBOCAN 2008). The above figures indicate that the EAC women/men ratio increased by a factor of 2.6 based on the 2008 estimate, in contrast to the 2002 estimate [41-43].

Population (Age 0-85+ years)	Cases	RR	ARS
Brazil, São Paulo (2003-2007)	1261	4.9	5.0
Brazil, Aracaju (2003-2006)	40	4.3	5.2
Brazil, Goiânia (2003-2007)	79	2.8	3.1
Brazil, Belo Horizonte (2003-2005)	69	2.1	2.3
Brazil, Fortaleza (2003-2006)	54	1.2	1.7
Brazil, Cuiabá (2003-2006)	13	0.9	1.1
Colombia, Manizales (2003-2007)	33	3.7	3.6
Colombia, Bucaramanga (2003-2007)	58	2.4	2.6
Colombia, Cali (2003-2007)	107	2.2	2.3
Colombia, Pasto (2003-2007)	18	2.0	2.4
Ecuador, Quito (2003-2007)	122	3.3	3.9
Ecuador, Cuenca (2003-2007)	21	2.0	2.3
Uruguay (2005-2007)	91	1.9	1.6
Argentina, Mendoza (2003-2007)	71	1.8	1.7
Argentina, Córdoba (2004-2007)	43	1.7	1.7
Argentina, Bahía Blanca (2003-2007)	11	1.6	1.4
Argentina, Tierra del Fuego (2003-2007)	1	0.3	0.3
Chile, Valdivia (2003-2007)	14	1.5	1.4
Chile, Región of Antofagasta (2003-2007)	20	1.4	1.4
Chile, BioBío Provincia (2003-2007)	13	1.4	1.3

Table 3: Incidence of thyroid cancer in South American men (where specific registries and data are available) based on different periods of time studied – The number of cases, the Raw Rate (RR) and the Age Standardized Rate with the reference world population (ASR) are described.

Population (Age 0-85+ years)	Cases	RR	ASR
Brazil, São Paulo (2003-2007)	6530	22.9	20.9
Brazil , Aracaju (2003-2006)	191	18.2	18.6
Brazil, Goiânia (2003-2007)	460	14.7	14.8
Brazil, Belo Horizonte (2003-2005)	307	8.3	7.8
Brazil, Fortaleza (2003-2006)	387	7.8	8.7
Brazil, Cuiabá (2003-2006)	60	3.8	4.5
Ecuador, Quito (2003-2007)	654	16.6	17.6
Ecuador, Cuenca (2003-2007)	126	10.4	11.5
Colombia, Manizales (2003-2007)	140	14.1	12.1
Colombia, Cali (2003-2007)	639	11.8	11.3
Colombia, Bucaramanga (2003-2007)	269	10.1	9.6
Colombia, Pasto (2003-2007)	87	8.7	8.4
Argentina, Tierra del Fuego (2003-2007)	27	9.6	8.8
Argentina, Córdoba (2004-2007)	221	8.0	7.3
Argentina, Bahía Blanca (2003-2007)	55	7.3	6.6
Argentina, Mendoza (2003-2007)	262	6.3	5.8
Uruguay (2005-2007)	412	8.0	6.8
Chile, Valdivia (2003-2007)	71	7.6	6.7
Chile, Antofagasta Region (2003-2007)	127	9.8	9.4
Chile, BioBío Province (2003-2007)	39	4.2	3.7

Table 4: Incidence of thyroid cancer in South American women (where specific registries and data are available) based on different periods of time studied – The number of cases, the Raw Rate (RR) and the Age Standardized Rate with the reference world population (ASR) are described.

Country: Colombia (city)	Males				Females			
	Cases	VM* (%)	CD** (%)	MI§ (%)	Cases	MV (%)	DC (%)	DI (%)
Bucaramanga	58	94.8	0.0	19.0	269	97.0	0.7	9.3
Cali	107	91.6	3.7	16.8	639	95.9	0.8	7.7
Manizales	33	97.0	0.0	9.1	140	97.9	0.7	8.6
Pasto	18	88.9	5.6	27.8	87	96.6	1.1	13.8
Total cases (Colombia)	216				1135			
South America (other countries)								
Argentina. Bahía Blanca	23.0	95.7	4.3	8.7	59	94.9	5.1	5.1
Argentina. Córdoba	57	98.2	1.8	14.0	228	95.6	4.4	8.8
Argentina. Mendoza	71	94.4	4.2	22.5	262	96.6	2.7	8.8
Argentina. Tierra del Fuego	2.0	100	0.0	0.0	27	100	0.0	0.0
Brazil. Aracaju	45.0	97.8	2.2	2.2	192	99.0	1.0	2.1
Brazil. Belo Horizonte	76.0	97.4	1.3	3.9	307	99.0	0.7	4.2
Brazil. Cuiabá	15.0	100	0.0	20.0	60.0	83.3	5.0	8.3
Brazil. Fortaleza	55.0	92.7	1.8	14.5	388	94.6	1.3	7.7
Brazil. Goiânia	82.0	97.6	2.4	9.8	463	99.1	0.2	2.6
Brazil. São Paulo	1292	88.3	1.2	5.1	6544	88.2	0.5	2.1
Chile. BioBío Province	13.0	61.5	0.0	46.2	39	76.9	0.0	12.8
Chile. Antofagasta Region	20.0	95.0	5.0	15.0	127	98.4	1.6	11.0
Chile. Valdivia	14	100	0.0	7.1	71	98.6	0.0	15.5
Ecuador. Cuenca	21	85.7	9.5	52.4	126	95.2	0.8	10.3
Ecuador. Quito	124	93.5	3.2	19.4	656	97.1	1.5	7.9
Uruguay	101	92.1	5.9	20.8	416	96.6	2.4	11.8

*MV: Percentage of cases Microscopically Verified
**DC: Percentage of cases registered based on a Death Certificate
§DR: Ratio (in percentage) of the number of Deaths from a particular cancer, versus the number of cases registered in the same period of time

Table 5: Gender distribution of thyroid cancer in South America, where specific registries and data are available.

For the National Cancer Institute of Colombia (INCC), the incidence of cancer was estimated based on the Departments mortality and population data for 2002-2006, including the cancer population registries of Bucaramanga (2000-2005), Pasto (1998-2002), and Manizales (2002-2006), and the incidence figures of the Cancer Population Registry of Cali –RPCC- (1998-2002). A specific generalized Poisson lineal model was used for each location, exclusively based on the information provided by the Cancer Population Registry of Cali, since the evaluation about the quality of information of the other population registries revealed the need to correct certain flaws in terms of the completeness and validity of the information [42-45].

The INCC data did not take into account the information of the cancer population registry of Antioquia –RPCA- (where the preliminary information from 2007-2009 is analyzed). According to the RPCA, and based on the data published by vital statistics, in addition to the preliminary information of 2010 of the health and social protection secretariat of Antioquia, thyroid cancer was the 10th cause of morbidity in 2006 and became the 6th in 2007-2009. The most frequent malignant tumors in women corresponded to 80% of the total number of cases collected. These were in descending order: breast, skin, thyroid, cervix, and colorectal, amounting to 60% of the total number of cases in women. Breast cancer contributed with the highest percentage 29.3% of cases; interestingly enough, thyroid cancer was the third in importance (above cervical uterine cancer, colorectal, lung and ovarian cancer). A total of 2,259 cases were collected during that period, of which 698 corresponded to 2007; 721 to 2008; and 840 to 2009, showing rates of 12.0, 12.2 and 14.0 per 100.000 people, per each year, respectively. And, although the age distribution indicates that thyroid cancer occurs in all age groups, over 70% of the cases occur within the age group of 25-65 years [45,46]. Finally, according to the RPCC during the period from 2006-2010, 151 cases of thyroid cancer were registered in males, with a raw rate of 2.9 and an ASR of 2.9; there were 746 cases in females, with a raw rate of 13.1% and an ASR of 11.8% [47].

Discussion

The statement that the incidence of thyroid cancer has increased universally is controversial. This rise in incidence has been documented around the world, for both males and females of all ages, although the scale of the increase varies for the different regions. The evidence indicates that the type of thyroid cancer that has experienced a substantial increase in terms of frequency is papillary cancer, with no significant changes in the frequency of the other types of cancer and histological variants. Though the increased frequency is the same for all tumor sizes, it is more evident in <1 cm tumors (micro carcinomas). However, it is also true that the information derived from tumor histology is now more accurate and complete, reducing the number of the so-called unspecific/unknown categories.

Two trends support the reason for such increase (Table 2). Considering that the strategies to identify and diagnose thyroid nodular disease have contributed to establish a rate of prevalence of thyroid nodules in the population incidentally identified of 67% using neck ultrasound and of 15% using other imaging techniques (Magnetic Resonance Imaging and Computed Tomography scans). Recently, PET/CT scan has been used for cancer diagnosis worldwide. Incidental detection of the thyroid nodules on PET images is an important finding; these nodules has significantly higher incidence of cancer (20-30%). So, such lesions must be subjected to further evaluation. It is quite likely that the increase in the number of thyroid cancers is due to improved access to diagnostic methods, including ultrasonography as a screening method for thyroid disease (diffuse and/or nodular, hypo or hyper-functional) that enables the identification of a larger number of thyroid nodules amenable to cytology, and resulting in "over-diagnosis" and earlier detection of thyroid cancer. The consequences of over-diagnosing involve labeling a person with an unnecessary diagnosis for the rest of his/her life, in addition to the administration of costly treatments, increased concern and stress that does not necessarily translate into improved survival. Over-diagnosis refers to diagnosing a condition that may not cause any symptoms or death. This definition includes those very slow-growing or non-progressive cancers; so, when a rise in incidence is documented, with stable mortality rates – as is reported for thyroid cancer – over-diagnosis is a potential explanation that may even give rise to about 50% of the increased incidence [48-50].

On the other hand, the growing exposure to environmental factors (ionizing radiation, cosmic radiation, pesticides, solvents, carcinogens), as well as the increased frequency of autoimmune thyroid disease, overweight – obesity, alcohol use, cigarette smoking, a longer life expectancy and iodine intake (particularly in countries where the natural iodine deficiency has been supplemented) have all been associated with the presence of various types of cancer, including thyroid cancer, and may perfectly explain its increased incidence. However, claiming that one or other trend totally accounts for the rise in the incidence of cancer would be to neglect the importance of the counterpart; so the most feasible explanation is that both trends are additive and complementary [51-53]. Other reasons may explain the marked increase in the frequency of papillary carcinoma, including:

1. A rise in frequency may be explained (at least partially) by the change in the diagnostic criteria used until 1988, when a new classification system proposed by the WHO was recommended to reclassify the characteristics of carcinomas with follicular architecture – but with typical nuclear findings of papillary carcinoma – as genuine papillary carcinomas with the potential to artificially rise the incidence of papillary thyroid cancer (this classification replaced the classification published in 1974). The differences between both classifications until then were: a. Eliminate the subtypes of undifferentiated carcinoma, b. The revision of non-epithelial and miscellaneous tumors; and c) acknowledging that most of those tumors previously diagnosed as "small cell carcinomas" of the thyroid, were really malignant lymphomas. Both classifications failed to consider certain subtypes as tumor entities (tall cell carcinoma, islet cell, columnar, diffuse sclerosing, or follicular diffuse variant of papillary carcinoma and Hürthle cell carcinoma), though they really showed fundamental differences from the classical papillary and follicular types [54-56].

2. The increased incidence is particularly relevant in high income countries versus the low income countries, where the population has less employment opportunities and limited access to healthcare, indicating a potential association between access to healthcare systems and increased incidence of papillary thyroid cancer. One point in favor of this hypothesis is the higher incidence in upper socioeconomic classes or with extended health coverage. Since the higher incidence may also be due to improved medical care surveillance and better diagnostic methods, these may also be the reasons for the rise observed in papillary micro carcinoma. The fact that the papillary micro carcinoma / papillary carcinoma ratio practically remains unchanged for men but changes for women, could potentially explain part of the increase observed in women [57,58].

3. Among the potential factors that impact the rise in papillary cancer in women, improved diagnostic techniques should be emphasized as a differential according to gender. Proof of that would be that the rise in thyroid cancer among women is mainly due to papillary cancer that includes a higher percentage of micro carcinomas as compared to males [58,59].

4. Any situation that develops at one specific point in time (or during a particular period of time) that affects the total population (or a significant segment thereof), like for example a treatment or a preventive measure, or more comprehensive imaging and/or cytological screening (as is the case in the general study of thyroid disease) may result in an increased rate of change of an outcome, regardless of age and of the birth cohort. This phenomenon is called "period or time effect" and may explain the increased frequency in papillary thyroid cancer [60].

5. While cancer affects all age groups – the distribution of thyroid cancer by age is similar for both males and females, despite the fact that the incidence is considerably higher in women. After 10-15 years of age, the incidence in both genders begins to rise (more pronounced in females), until a maximum is reached around 60 years of age (with a rate of approximately 11 cases per 100.000) in women and a maximum

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around 55 years of age in men (with a rate of approximately 5 cases per 100.000). After this age, the incidence drops progressively). The "age effect" represents the age-associated change. Moreover, the increased life expectancy facilitates the occurrence of certain diseases (such as cancer). Cancer is a paradigmatic case: old age is considered the most powerful carcinogenic, because the time of exposure to potential harmful substances associated with this outcome increases. This effect is always relevant, since the occurrence of chronic diseases usually increases with age. Thyroid papillary cancer has been showing a continuous rise in frequency for the last 30 years, with an APC higher in women than in men, particularly with regards to micro carcinoma, with a higher incidence in women over 40 years of age, based on the different cohort trials. A "cohort effect" occurs when the mortality rates vary with the year of birth, regardless of age. The cohort effect affects successive age groups in successive periods of time and is influenced by the exposure to risk factors or lifestyles. Consequently, the increased frequency of papillary cancer may point to an "age effect" and a "cohort effect", particularly in females [61,62].

6. The notorious increase in the incidence of papillary cancer has not been translated into a significant change in the mortality rate; probably the detection programs and the statistical registry of deaths may be biased when describing the mortality due to thyroid cancer, or are not the source of quality information to establish thyroid cancer mortality [63].

The best strategy to assess the frequency of cancer in the population is through population-based cancer registries, defined as information systems that collect, store, analyze, and interpret data from every recent onset cancer case in a particular geographical region. A cancer registry entails a standardized effort to generate population-based data about the incidence and the prevalence of cancer. To ensure the validity of the date, usually a number of sources are acquired and compared, including hospital discharges, medical records, pathology files, and mortality figures. These registries may be passive or active [64-66].

In South America few cancer registries are based on the population; countries like Chile have sub-registries and this results in an underestimation of thyroid cancer due to an incomplete registry of cases because some of the pathologic anatomy centers failed to participate in the trial; similarly, Brazil evidences an under-registration of thyroid cancer, as a result of the difficulties to access healthcare services and of the quality of the data in the available registries. The national cancer information system has not yet been implemented in Colombia, and reporting malignant neoplasms is not obligatory, except for neoplasms present in the pediatric population. This has led to a global under-registration and based on certain cancer sites, inconsistencies have been documented between the base of the diagnosis and the histological findings of the various types. According to GLOBOCAN and the results of the population-based registries, the frequency of thyroid cancer has been constantly rising, specifically in women. This is consistent with the world trend that shows an increased incidence of differentiated thyroid cancer, mainly papillary. This rise, in addition to a stable mortality rate, suggests an increase in the number of cases detected, rather than a real rise in incidence. Probably there is an "over-diagnosis" of thyroid cancer in our environment as a result of an increase in the frequency of diagnosis of microcarcinomas, because of improved access to the above-mentioned imaging methods and an exponential increase in the indication for Fine Needle Aspiration (FNA). All of this may be explained on the basis of a "time effect" defined as a change in the rate of a particular condition affecting the population as a whole at a particular point in time, regardless of age or the birth cohort; in this case this reflects an increase in the imaging and cytological screening rates for nodular thyroid disease. Finally, the differences in the incidence of thyroid cancer in South America may be a reflection of a socioeconomic marker, since not every segment of the population can benefit equally from the screening processes.

Finally, the great strength of this study is that it could access almost all of the data on frequency of thyroid cancer in South America, either through databases, or through manual records. To our knowledge, this is the first study that reviews the epidemiology of thyroid cancer in South America, summarizing the available results published.

Our study also has limitations, due to lack database systematized in most countries of the region; the information does not contain socioeconomic data on individual or census-block group level (in all countries). The few population-based cancer registries and the information therein has been used as the main input for estimating cancer incidence at the national level.

Conclusion

Thyroid cancer is an increasingly frequent condition worldwide, particularly the papillary type and those cancers labeled as micro-carcinomas due to their size. It is very likely that the increased incidence is due to "over-diagnosis" as a consequence of improved access to diagnostic procedures and in some cases due to better access to the various healthcare systems. In South America, the information is insufficient and incomplete; countries like Brazil, Colombia, and Chile have population-based cancer registries that allow for a better understanding of the frequency and the rates of thyroid cancer mortality. However, there is still a considerable under-registration in the different countries and regions. In some areas, in addition to "over-diagnosis", other environmental factors such as the intake of iodine may impact the frequency of this type of cancer.

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