Epidemiology of Non-Hodgkin's Lymphoma in India

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Key Words

Non-Hodgkin's lymphoma · Immune phenotype · Anti-CD20 antibody · Survival · Time trends · Cancer registry

Abstract

Non-Hodgkin's lymphoma (NHL) is a common hematological malignancy. The age-adjusted incidence rates for NHL in men and women in India are 2.9/100,000 and 1.5/100,000, respectively. These are about one fourth of the incidence rates reported from Western Europe or North America. With India, the incidence is several-fold higher in urban cancer registries compared to rural areas; the incidence being higher in metropolitan cities and Indian immigrants suggesting that urban lifestyles and economic progress may increase the cancer incidence. Compared to developed nations, the key differences in the presentation in India include: median age of 54 years (almost a decade less), higher male to female ratio, higher proportion of patients with B-symptoms (40–60 vs. 20–30%), poor ECOG performance status (≥ 2) at diagnosis (50 vs. 20–30%), higher frequency of diffuse large B-cell lymphomas (60–70 vs. <40%), lower frequency of follicular NHL (<20 vs. 30–40%) and T-cell type in 10–20 vs. <10%. The estimated mortality rate due to NHL is higher in India than in North America and Western Europe. Diagnostic and treatment delays, incorrect diagnosis and inappropriate or sub-

optimal treatment may be possible reasons for the poor outcome. Any improvement in the outcomes for NHL in India will require a nationwide approach, e.g. creation of several regional and district-level centers with expertise in lymphoma management. Collection of data on patient- and disease-related characteristics, treatment outcome, development of infrastructure, centralized review of histopathology subtype, novel treatment protocols, rigorous follow-up, training of staff, and financial support towards treatment could be possible strategies to improve the outcome.

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Introduction

The lymphomas are a heterogeneous group of disorders and accounts for up to 3% of all malignancies. According to Globocan (2012), the estimated incidence of non-Hodgkin's lymphoma (NHL) is 5/100,000 (385,741 new cases), with a mortality rate of 2.5/100,000 (199,630 deaths) worldwide [1]. The classification of NHL has undergone many changes over the last two decades. In 2001, the World Health Organization (WHO) produced a consensus classification that encompassed immunophenotype, genetic abnormalities and clinical features [2]. Currently, this is being followed globally. The prognosis and

Table 1. Incidence, mortality and prevalence of NHL in 2012

Country	Incidence		Mortality		1-year prevalence		5-year prevalence	
	n	ASR	n	ASR	n	proportion	n	proportion
<i>Men</i>								
World	217,643	6.0	115,384	3.2	123,936	4.8	463,368	17.8
Brazil	4,930	5.0	2,733	2.8	2,653	3.6	10,065	13.8
Russian Federation	3,678	4.5	2,174	2.5	2,531	4.6	9,471	17.3
India	15,883	2.9	11,071	2.0	6,592	1.5	17,961	4.0
China	26,097	3.1	16,602	2.0	11,838	2.1	42,889	7.6
South African Republic	1,208	5.4	815	4.1	562	3.2	1,986	11.3
European Union (EU-28)	42,499	10.1	16,520	3.2	29,740	14.3	115,441	55.5
USA	34,286	14.7	12,036	4.5	24,621	19.9	99,167	80.2
<i>Women</i>								
World	168,098	4.1	84,246	2.0	98,597	3.8	369,475	14.2
Brazil	4,285	3.7	2,279	1.9	2,258	2.9	8,508	11.0
Russian Federation	4,037	3.3	2,014	1.4	2,713	4.1	9,940	15.1
India	7,918	1.5	5,526	1.0	3,409	0.8	9,138	2.1
China	16,502	2.0	9,871	1.1	7,271	1.3	26,421	4.9
South African Republic	1,109	4.4	749	3.0	522	2.9	1,832	10.1
European Union (EU-28)	36,813	7.0	14,171	2.0	25,320	11.5	96,611	43.8
USA	28,780	10.2	9,696	2.6	20,522	15.9	81,675	63.4

Source: Globocan 2012 [1]. Rates are per 100,000 and age standardized. ASR = Age-standardized rate.

treatment of NHL depend on the subtype, stage and associated comorbid conditions. While adequate information is available on the epidemiology of NHL from developed nations, such data is sparse from developing countries. We have made an attempt to review the epidemiology of NHL in India.

Search and Selection Criteria

We searched PubMed, Scopus, Google Scholar, and references from relevant articles using the search terms 'lymphoma', 'NHL', 'India', 'epidemiology' and 'incidence'. Studies from India were few; we therefore included original articles reporting on ≥ 100 cases published in English after January 1, 1995. We also accessed the website of the International Agency for Cancer Research and reviewed all the online databases 'Globocan', 'Cancer Incidence in Five Continents', 'Survcan' and other publications containing information on cancer in India [1, 3–7]. We obtained additional data for the incidence and mortality from NHL in Indians living abroad based on population-based cancer registration in Singapore, the UK and the USA from recent publications [3, 8].

Cancer Registration in India

The National Cancer Control Program was initiated in 1975–1976 with emphasis on prevention, early detection, and augmentation of cancer treatment facilities in India [9]. Under this program, 27 regional cancer centers exist. Population- and hospital-based cancer registries have been established and data is collected and published periodically by the Indian Council of Medical Research. The registration of cases is entirely active. Social investigators collect data from government and private hospitals, nursing homes, clinics, consultants, radiotherapy centers, pathology laboratories, and imaging centers. Periodic as well as annual checks are performed to evaluate completeness. Though the quality of registration and data reliability have improved over time, misdiagnosis and underestimation are recognized problems for lymphoid cancers in India as in other developing countries [9].

Currently, the total population of India is over 1,300 million. Population-based cancer registries are primarily located in urban cities and cover about 30 million of the population [4, 9]. The first rural registry was set up in Barshi in 1987. More recently, two new registries at Ka-

runagappally and Ambillikkai have been added. However, so far adequate data is not available from these recently added registries. At present, about 30% of the population is urban [6] and available registries cover 10% of this population; this is close to the population covered in the USA (14%), but less than that in Europe (27%) and better than that covered in Africa (0.7%) [7]. However, because 70% of the Indian population lives in rural areas, coverage of this population by currently existing cancer registries is still limited.

Incidence of NHL

The highest incidence of NHL is reported from countries with a very high human development index, such as those in North America, Western Europe and Australia. The lowest rates are reported from South Asia and parts of Africa (table 1).

Descriptive Epidemiology

The burden of NHL in 2012 for India was estimated to have an incidence rate of 2.2/100,000 (23,801 new cases) and a mortality rate of 1.5/100,000 (16,597 deaths) (table 1). Within the country, the incidence of NHL is higher in urban areas compared to rural registries (table 2). The Ambillikkai registry in rural Tamil Nadu in South India had the lowest incidence of NHL in women in the world. From tables 1 and 2, it would appear that the incidence of all hematological cancers is highest in Delhi (capital of India), followed by Mumbai, and lowest in Barshi (rural-based cancer registry). The rural and urban populations are different with regard to environmental and socioeconomic factors. Urban cities in India, especially Delhi and Mumbai, are industrialized and fairly populated. The socioeconomic status of people is higher, and dietary habits and lifestyle tend to tilt toward Western styles. In rural areas, on the other hand, people stick to traditional eating habits and lifestyle. These factors may be responsible for the relative differences in the incidence of lympho-hemopoietic malignancies in the urban versus rural population [9].

Age and Gender Distribution

NHL is more common in men (table 1): the male to female ratio is 1.6 in Asia compared to 1.2 and 1.1 in North America and Europe, respectively. The median age of patients with NHL undergoing treatments at various

Table 2. Incidence of NHL in 12 Indian cancer registries

Population registry	Male			Female		
	cases	crude rate	ASR	cases	crude rate	ASR
India, Bangalore (2005–2007)	402	3.8	5.1	235	2.4	3.2
India, Barshi (2003–2007)	22	1.6	1.7	11	0.9	0.8
India, Bhopal (2004–2007)	123	3.5	4.7	59	1.9	2.6
India, Chennai (Madras) (2003–2007)	481	4.2	4.6	254	2.3	2.4
India, Delhi (2003–2007)	1,609	3.8	5.6	746	2.1	3.0
India, Dindigul, Ambillikkai (2003–2007)	72	1.4	1.5	28	0.6	0.6
India, Karunagappally (2003–2007)	30	3.0	2.8	22	2.0	1.9
India, Mizoram (2003–2007)	58	2.3	3.5	34	1.4	2.1
India, Mumbai (2003–2007)	1,225	3.4	4.6	690	2.4	2.8
India, Poona (2003–2007)	267	2.4	3.5	153	1.6	1.9
India, Sikkim State (2003–2007)	5	0.3	0.5	9	0.7	1.1
India, Trivandrum (2003–2007)	84	5.1	5.2	52	3.0	2.7

Source: Forman et al. [3]. ASR = Age-standardized rate.

specialized hospitals in India is lower by almost one decade compared to that of the Western population. This is similar to the median age of 54 years in other Asian countries [10–12]. The younger age at presentation in India is possibly due to the large proportion of young Indians: 65% of the population in India is under 35 years of age. The lower proportion of indolent lymphoma (predominantly occurs in the elderly population) in India is probably the result of the same bias. The most recent age-specific incidence reported by Globocan (2012) reveals that the incidence of NHL peaks at 75 years in Indian males and 70 years in Indian females [1].

Table 3. Subtype distribution of lymphoma across the world and India

Subtype	India			China	USA	Korea	Japan	Thailand
	Arora et al. [14]	Naresh et al. [13]	Sahni and Desai [31]					
LBL-T	0.42	6.06	6.9		1.09	4.79	0.7	4.11
LBL-B	2.21	0.6	0.2		3.75	13.88	0.2	0.88
Total LBL	2.81	6.67	3.1	5.2	4.85	18.68	0.9	4.99
DLBCL	46.85	33.8	50.2	41.2	31.29	37.67	36.4	51.42
FL	10.51	12.6	13.1	5.8	13.81	2.10	20.1	8.38
BL	3.38	1.8	3.0	1.91	1.42			
MALT	2.17	6.1	2.7	6.31	4.19	15.24	4.6	4.16
CLL/SLL	3.95	5.6	5.4	4.61	21.91	2.24	1.6	2.58
MCL	1.59	3.4	2.1	3.15	2.18	2.26	3.0	1.04
HCL	0.77	0.01	0.1	–	1.44	0.12	–	–
LPL	2.42	0.6	0.1	0.79	2.65	0.32	0.2	0.82
SMZL	0.32	0.2	0.5	0.35	–	0.12	0.4	–
PMBCL	0.60	0.2	0.1	–	–	0.37	0.4	0.88
NMZBCL	0.65	1.9	0.2	0.09	–	1.25	1.5	–
ENKTCL	0.92	0.7	1.1	17.1	0	5.42	1.7	–
PTCL, NOS	5.91	1.9	4.6	3.99	3.27	4.87	5.0	13.14
ALCL	5.04	4.1	4.8	3.53	1.11	2.40	2.2	3.67
AILD	1.39	1.0	0.4	3.33	0.23	1.0	5.7	1.81
ATLL	0.08	–	–	–	–	0.02	11.0	–
SPTCL	1.02	0.1	–	0.97	–	0.39	–	0.49
PCCD30+LPD	0.05	0.1	0.2	0.67	–	0.18	–	0.27
MF/SS	2.17	0.9	0.6	0.25	2.29	0.48	0.5	1.26
HSL	0.55	0.01	–	0.25	–	0.07	–	–
EATCL	0.025	–	–	0.13	–	0.39	–	–
Others				–	9.34	1.87	3.0	1.04
Total, n	4,026	2,773	935	5,549	77,490	4,337	2,260	1,826

Values are percentages, unless indicated otherwise. AILD = Angioimmunoblastic T-cell lymphoma; ALCL = anaplastic large-cell lymphoma; ATLL = adult T-cell lymphoma/leukemia; CLL/SLL = chronic lymphocytic leukemia/small lymphocytic lymphoma; DLBCL = diffuse large B-cell lymphoma; EATCL = enteropathy-associated T-cell lymphoma; ENKTCL = extranodal NK/T-cell lymphoma, nasal type; FL = follicular lymphoma; HCL = hairy cell leukemia; HSL = hepatosplenic T-cell lymphoma; LBL = lymphoblastic lymphoma; PTCL-NOS = peripheral T-cell lymphoma not otherwise specified; MCL = mantle-cell lymphoma; NMZBCL = nodal marginal zone B-cell lymphoma; SPTCL = subcutaneous panniculitis-like T-cell lymphoma; LPL = lymphoplasmacytic lymphoma; PCCD30+LPD = primary cutaneous CD30-positive lymphoproliferative disorders; SMZL = splenic marginal zone B-cell lymphoma; MF/SS = mycosis fungoides/Sézary syndrome; BL = Burkitt's lymphoma; PMBCL = primary mediastinal B-cell lymphoma.

Subtypes of NHL

The subtypes of NHL in several hospital-based studies are summarized in table 3. B-cell NHL make up 80–85% of all NHLs in India [10, 13, 14]. Diffuse large B-cell NHL is the most common subtype (60%) followed by indolent lymphoma (12–20%). T-cell lymphomas account for 10–15% of cases. Peripheral T-cell lymphoma not otherwise specified, lymphoblastic lymphoma and anaplastic large-cell lymphoma are the three common subtypes of T-cell NHL seen in the Indian subcontinent.

The frequency of extranodal NK/T-cell lymphoma in India is usually higher than that in Western countries, but lower than that in other Asian countries, e.g. China, Hong Kong and Taiwan [11, 12, 15, 16]. The frequencies of T- and NK-cell lymphomas seem to increase from West to East Asia. Adult T-cell leukemia/lymphoma is a rarely described lymphoma in India, but a recent study from South India (Kerala) documents for the first time a series of 8 patients with adult T-cell leukemia/lymphoma [17].

The exact cause for the variable distribution of NHL subtypes in different parts of the world remains unknown. Many infective agents have etiologically been correlated with lymphomas including endemic Burkitt's lymphoma, human T-cell lymphotropic virus-1 (adult T-cell lymphoma leukemia), human herpes virus-8 [Kaposi's sarcoma (KS) and multi-centric Castleman's disease], *Helicobacter pylori* [gastric mucosa-associated lymphoid tissue (MALT) lymphoma] [9]. The actual relationship and the mechanism by which these viruses or bacteria contribute to the development of lymphomas remain unknown.

Geographic Variations

Geographic variations in NHL histologic subtypes are well documented. Examples include higher rates of gastric lymphoma in northern Italy, endemic form of Burkitt's lymphoma in children in equatorial Africa, nasal T-cell lymphomas in China, certain small intestinal lymphomas in the Middle East, and adult T-cell leukemia/lymphoma in Southern Japan and the Caribbean [8]. The distribution of NHL subtypes in India shows important differences compared to that in the rest of the world. A study from Mumbai [13] of 2,773 lymphomas using REAL and WHO classifications revealed lower frequencies of follicular lymphoma (12.6%) and mantle-cell lymphoma (3.4%) in India compared to Europe and the USA, but they were similar to the frequencies in other developing countries. Diffuse large cell lymphoma, accounting for 34%, is the most common subtype, higher than the proportion seen in Europe and the USA but similar to the series from Korea and Thailand; higher frequency, however, may be relative as a result of lower frequency of indolent B-cell lymphoma. Recent hospital-based studies indicated a higher proportion of indolent lymphomas [10].

Mortality and Survival

Although the incidence rate of NHL in India is lower compared to that in developed countries, the mortality rate is nearly same. According to the Globocan (2012) data, the ratio of mortality to incidence in India is 69.7%. This reflects the poor overall 5-year survival below the global average [1]. Delayed diagnosis resulting in advanced stage of NHL, inadequate or improper treatments due to limited facilities, affordability of chemotherapy drugs, lack of expertise at district hospitals, the inability

Fig. 1. Age-adjusted survival rates of NHL in India and Asia.

to complete the NHL treatments, and poor follow-up are the possible inherent factors responsible for the higher mortality in India [9, 18]. A comparative study of population-based NHL survival rates in Africa, Asia, and Central America indicate substantially lower survival rates in parts of Africa, India, and the Philippines than in Singapore, South Korea, and parts of China (fig. 1).

Dikshit and colleagues [18] estimated the cancer mortality rate in India for 2010 in a nationally representative sample survey that employed verbal autopsy in one million Indian homes from 2001 to 2003. This million death study (MDS) revealed that the age-standardized mortality for lymphoid and hematological neoplasms in rural and urban India were 5.6 and 6.3 per 100,000 in men and 6.3 and 5.9 per 100,000 in women, respectively. Although the population-based cancer registry data from India shows a very low incidence of NHL in rural India, the MDS shows that the mortality rate in rural India is equal to that in urban India.

Analytical Epidemiology

Most of this data is available from cross-sectional studies done in tertiary hospitals.

Infectious Causes of NHL

India has a large burden of patients with human immunodeficiency virus (HIV) infection and acquired im-

mune deficiency syndrome (AIDS) [19]. However, there are few reports on NHL associated with HIV from India. The most enigmatic finding is the non-existence of KS. The UNAIDS report on global AIDS epidemic estimated 2.5 million Indians to be HIV infected in 2007 [19–23]. One review of cancer in persons with HIV/AIDS estimated that 3–4% will develop cancer during their course in India as compared to 34% in the developed countries [21]. This may be attributed to the high premature mortality from infectious diseases, which shortens survival and prevents progression to severe immunodeficiency when the risk for NHL and KS goes up. The reported incidence of co-infection with KS-associated herpes virus is low in India. In a tertiary cancer hospital-based study from Mumbai, the seroprevalence of HIV was 1.2% in cancer patients. NHL was the commonest malignancy in Indian persons with HIV/AIDS [22], with high-grade B-cell immunoblastic and Burkitt's lymphomas as the most frequent subtypes [23]. Human herpesvirus 8 is associated with the development of primary effusion lymphoma that almost exclusively develops in HIV patients. This subtype is rare in Indian series.

H. pylori infection is a cause of gastric adenocarcinoma and MALT lymphomas of the stomach. Although over 80% of middle-aged Indians are seropositive for *H. pylori*, and gastric cancer is common in many parts of India, gastric MALT lymphomas are uncommon [3, 12, 13]. This is probably due to the fact that other environmental and dietary factors play a role in the development of MALT lymphomas.

Lifestyle and Personal Factors

Lifestyle factors such as tobacco use (smoking/chewing), alcohol abuse, diet, and body mass index have been evaluated in some Indian studies. One hospital-based case control study from Mumbai reported an association between smoking and NHL. The odds ratio was two-fold for cigarette smokers and three-fold for bidi smokers [24]. The same case control study did not find any association between alcohol consumption and NHL. However, another study did not find association between smoking and NHL risk [25].

The consumption of meat and other foods of animal origin did not emerge as a risk factor for NHL unlike for many other cancers. Similar to earlier reports, a study from Mumbai did show a seven-fold higher risk in red-meat eaters [23]. High consumption of fruits and vegetables was associated with a reduced risk of NHL, particularly follicular lymphoma, among women but not among men. Coffee drinking showed a 50% reduction in the risk

Fig. 2. Projected increase in the incidence of NHL in India.

of NHL, probably due to its protective activity as an anti-carcinogen. Consumption of milk increased the risk six-fold, and this needs to be further investigated with respect to the type of milk consumed. Pesticide workers had an excess risk of three-fold for NHL, and further research on the type of pesticide in a larger setting would be appropriate. Based on these initial findings, it is possible to conclude that the prevention of tobacco use and the limited use of certain dietary items could prove to be beneficial in the prevention of NHL.

Family History and Genetic Factors

An increased risk of NHL, especially indolent lymphomas, among persons with relatives previously diagnosed with NHLs has been reported [24], but no hereditary factors are hypothesized to account for a small percentage of NHL. However, one case control study [23] from India did not show a significant difference for those having a family history of hematopoietic cancers.

Time Trends

The incidence rates of NHL have been rising in India like in other parts of the world. Between 1960 and 1990, an increase in the incidence of NHL was noted in the high-income countries [26–28]. A similar increase was found in India as well. The reasons for this pattern are largely unknown, although a part of the increase has been attributed to diagnostic improvements [29] as well as AIDS-related neoplasms following the HIV epidemic [30]. A significant increase in the incidence of NHL has been found in South Asians males in the USA. All these

reports suggest that urban living and economic prosperity contribute towards an increased incidence of NHL. Globocan estimates that the NHL burden of India will double by 2035 (fig. 2). Most of this increase is due to demographic transition with a larger older population.

Studies among Immigrants

Multi-ethnic populations living in countries with comprehensive cancer registration and a unified health-care system provide a unique opportunity to study the role of ethnic factors in the development of several cancers. Data for Indian immigrants is available from Singapore, the UK and the USA [3, 7, 8]. NHL is more common in Indian immigrants in developed countries and the mortality rate is lower.

In Singapore, the nationwide incidence rates of NHL adjusted to the world population are 5.5/4.4, 9.3/5.6, and 10.4/8.5 per 100,000 for Indian, Chinese, and Malay men/women, respectively [3]. Shirley et al. [7] compared and reported the differences in hematolymphoid cancer rates among Indians, Pakistanis, Bangladeshi, and other racial groups using nationwide data from the UK. The incidence of mature B-cell NHL was the lowest among South Asians and Chinese, the rates being 20–40% lower than those of the White population. No significant difference was observed among the South Asian immigrants. For follicular lymphoma, the rates were lowest among Chinese and Blacks, intermediate among South Asians, and highest among Whites. Among the South Asian groups, Pakistanis showed the highest rates followed by Indians and Bangladeshis (incidence rate ratios of 1.11, 0.68, and 0.54, respectively). For chronic lymphocytic leukemia/small cell lymphocytic lymphoma, the incidence was considerably lower among South Asians, around 60% of the rates in Whites. The lower incidence of low-grade NHLs in South Asians suggests that genetic differences may have some role. Studies have shown that migrants from low-incidence countries do not adopt the rates of their host country. This suggests that there may be strong evidence for the role of heritable risk factors in this group of patients; further studies are needed. For mature T-cell neoplasm, the incidence rate for South Asians compared to Whites was close to unity. The study also showed that the incidence was higher in the migrant group than in the host country.

In the USA, the SEER registry data provides some interesting findings on the occurrence of NHL in South Asians (Indians and Pakistanis) [8, 30]. The Incidence of

NHL between 1998 and 2002 (adjusted for the US population in 2000) in men/women of South Asian, Chinese, and White non-Hispanic origin was 15.8/9.4, 14.8/10.0, and 24.6/17.2, respectively [26]. The SEER data also indicates that the incidence of NHL has been rising significantly among male South Asian immigrants with an annual percentage change of 0.8 per year [30]. The urban and immigrant data suggests that the low incidence of NHL reported in Globocan 2012 is linked to urbanization and economic prosperity.

Conclusions

There is paucity of nationally representative incidence and mortality data on lymphomas from India. Available studies indicate that NHL is emerging as an important cause of cancer mortality in India. The incidence of NHL in Indians living in Indian metropolitan cities and in developed countries are several-fold higher, indicating that the national cancer burden is set to rise with India's economic progress. Currently, the outcomes of NHL in India are disproportionately lower than the world average. There is an urgent need for establishment of centers of excellence for treating lymphomas in all states and conducting nationwide education and training in the management of NHL.

Disclosure Statement

R.N. has received research grants and educational grants from Dr. Reddy Laboratory pharmaceuticals and Roche Pharmaceutical India Ltd.

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