

RESEARCH ARTICLE

Incidence Trend for Non-Hodgkin Lymphoma in the North Tunisian Population, 1998-2009

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Abstract

Background: In 2008, non-Hodgkin lymphoma ranked tenth among other malignancies worldwide with an incidence of around 5 cases per 100,000 in both genders. The latest available rates in Tunisia are from 2006. **Materials and Methods:** This study aimed to provide an update about NHL incidence for 2009 and its trend between 1998 and 2009 as well as a projection until 2024, using data from the Salah Azaiz Institute hospital registry and the North Tunisia cancer registry. **Results:** In 2009, the NHL incidence in the north of Tunisia was 4.03 cases per 100,000, 4.97 for men and 3.10 for women. Diffuse large B-cell lymphoma (DLBCL) accounted for 63.2% of all NHL subtypes. Between 1998 and 2009, the overall trend showed no significant change. When we compared the trend between two periods (1998-2005 and 2005-2009), joinpoint regression showed a significant decrease of NHL incidence in the first period with an annual percentage change (APC) of -6.7% (95% CI: [-11.2%; -2%]), then the incidence significantly increased from 2005 to 2009 with an APC of 30.5% (95% CI: [16.1%; 46.6%]). The analyses of the different subtype trends showed a significant decrease in DLBCL incidence between 1998 and 2000 (APC: -21.5; 95% CI: [-31.4%; -10.2%]) then the incidence significantly increased between 2004 and 2007 (APC: 18.5; 95% CI: [3.6%; 35.5%]). Joint point analysis of the age-period-cohort model projection showed a significant increase between 2002 and 2024 with an APC of 4.5% (95% CI: [1.5%; 7.5%]). The estimated ASR for 2024 was 4.55/100 000 (95% CI: [3.37; 6.15]). **Conclusions:** This study revealed an overall steady trend in the incidence of NHL in northern Tunisia between 1998 and 2009. Projection showed an increase in the incidence in NHL in both genders which draw the attention to the national and worldwide burden of this malignancy

Keywords: Incidence - malignant non-Hodgkin lymphoma - large B-cell diffuse lymphoma - trend

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Introduction

The International Agency for Research on Cancer estimates that, in 2008, 199 600 new cases of Non-Hodgkin Lymphoma (NHL) in men and 156 300 in women has occurred worldwide, which represent respectively 3% and 2.6% of all estimated new cases of cancer. The age-standardized estimated rate per 100,000 for both genders was 5, 1; It was 4, 2/100 000 for women and 6,1/100 000 for men (Ferlay J and al, 2010). In Tunisia, the latest available data are from 2006. Our study aims to give an update about NHL incidence for 2009 and its trend between 1998 and 2009 as well as NHL incidence projection for 2024.

Materials and Methods

This study used North-Tunisia Cancer Registry (NCR) data. Created in 1997, this registry gathers data from public and private health structures located in the eleven departments of the north of the country from a total

of twenty four Tunisian departments. NHL incidences were calculated as cases per 100,000 people and age-standardized rate (ASR) were calculated on the basis of WHO population standard.

In order to analyze trends by age-adjusted incidence, the Joinpoint Regression Analysis program, version 4.2.0.2, was used. Joinpoint fits a linear regression model to the data to detect when statistically significant changes in the trend occur. A significance level of 0.05 was used for the permutation test which determines the minimum number of "joinpoints" necessary to fit the data (Kim et al., 2000). The annual percent change (APC) of the incidence was calculated with 95% confidence intervals. To perform incidence projection for 2024, an age-period-cohort (APC) model was employed assuming a Poisson distribution for the counts of cases (Jürgens et al., 2014).

Results

Descriptive epidemiology

For the 2009, NHL incidence in the north of Tunisia

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was 4.03 cases per 100 000; it was 4.97 for men and 3.10/100 000 for women. Diffuse large B-cell lymphoma (DLBCL) represented 63.2% of all NHL subtypes, MALT lymphoma 12.9%, Peripheral T-cell lymphoma 6.5%, Mantel cell lymphoma 4% and Malignant lymphoma NOS 6%. Burkitt lymphoma represented 2.5% of all diagnosed lymphoma in 2009.

Incidence Trends

Between 1998 and 2009, the overall trend showed no significant change (Figure1). When we compared the trend between two periods (1998-2005 and 2005-2009), joinpoint regression showed a significant decrease of NHL incidence in the first period with an APC of -6.7% (95% CI: [-11.2%;-2%]), then the incidence significantly increase from 2005 to 2009 with an APC of 30.5 % (95% CI: [16.1%; 46.6%]) (Figure2).

The analyses of the different subtype trends showed a significant decrease in the NHL NOS incidence (APC:-15.6; 95% CI: [-21.4%;-9.3%]). A significant decrease was found in DLBCL incidence between 1998 and 2000(APC:-21.5; 95% CI: [-31.4%;-10.2%]) then the incidence significantly increased between 2004 and 2007(APC: 18.5; 95% CI: [3.6%; 35.5%]). As for Burkitt lymphoma, there was a significant decrease of the incidence between 1998 and 2009 (APC:-10.3; 95% CI: [-15.4%; -4.9%], while there was no significant change in Mantel lymphoma

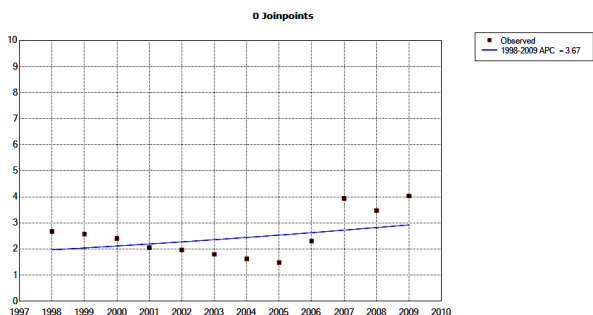


Figure 1. Joinpoint regression of 1998-2009 NHL ASR in Northern Tunisia

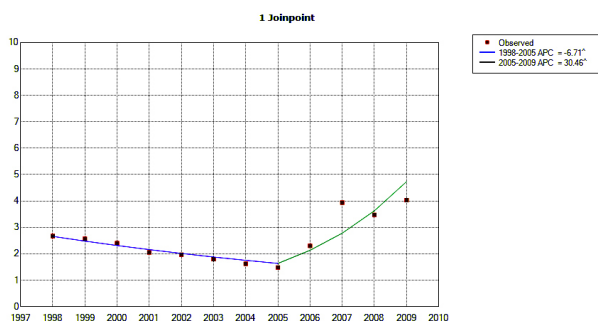


Figure 2. Joinpoint regression of 1998-2005 and 2005-2009 NHL ASRs in Northern Tunisia

within this period (Figure 3).

Projection

The number of NHL new cases predicted by the age-period-cohort model would attend 290 cases of NHL around 2024 (Table 1). Jointpoint analyze of the age-period-cohort model projection showed a significant increase between 2002 and 2024 with an APC of 4.5% (95% CI: [1.5%; 7.5%]). The estimated ASR for 2024 was 4.55/100 000 (95% CI: [3.37; 6.15]). There was a significant increase in NHL incidence among women

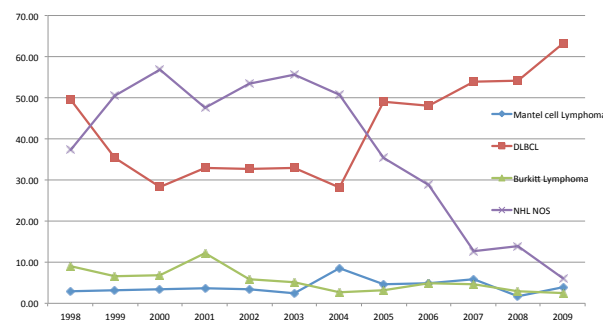


Figure 3. Incidence Trends of Four NHL Subtypes in Northern Tunisia for 1998-2009

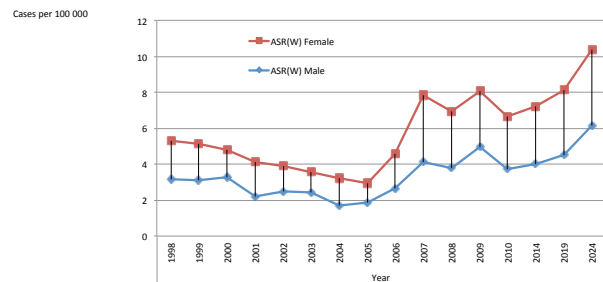


Figure 4. Age-Period-Cohort Model Projection for 2024 of NHL ASR (w) among Men and Women in Northern Tunisia

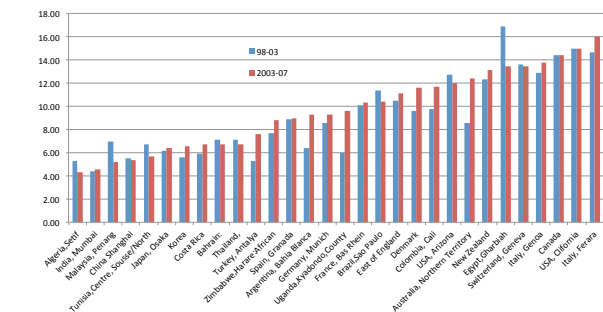


Figure 5. Age-Standardized Non-Hodgkin Lymphoma Incidence Rates in Males in Several Countries for the Periods 1998-2003 and 2003-2007

Table 1. Estimated number of new cases of NHL in northern Tunisia for 2014 and 2024

year	Predicted number of new cases					
	Both genders	95% CI	Male	95% CI	Female	95% CI
2014	186.551	[179.670; 302.176]	112.025	[83.221;151.309]	90.347	[62.6426; 131.773]
2024	290.536	[215.916; 391.480]	170.816	[116.053;251.981]	145.966	[90.8752; 236.371]

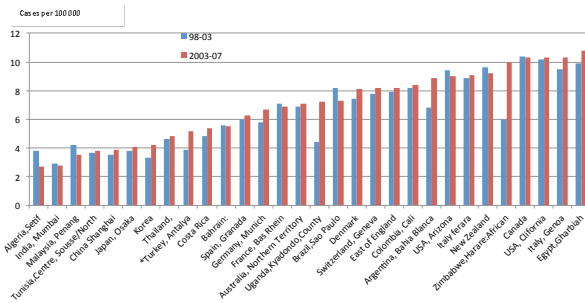


Figure 6. Age-Standardized Non-Hodgkin Lymphoma Incidences in Females in Several Countries for the Periods 1998-2003 and 2003-2007

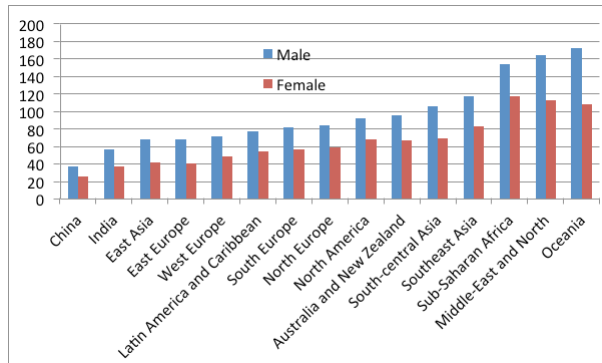


Figure 7. NHL's Age-Adjusted DALY Rates per 100,000 by Region, 2008

between 2007 and 2024 (APC: 1.9%; 95% CI: 0.3%; 3.4%) with an estimated ASR of 4.25/100 000 (95% CI: [2.61; 6.99]) in 2024. Among men, the increase was also significant (APC: 2.4%; 95% CI: [0.2%; 4.6%]). The estimated ASR for 2024 was 6.14/100 000 (95% CI: [4.18; 9.03]) (Figure 4).

Discussion

Non-Hodgkin lymphoma (NHL) represents the tenth most common malignancy in the world after the bladder cancer and the esophageal cancer (Ferlay et al., 2010). According to the study results, NHL incidence level in North Tunisia was 4.0/100 000; there was no significant change of Non-Hodgkin lymphoma incidence trend between 1998 and 2009. Compared to incidence level observed in other countries NHL incidence in North Tunisia was relatively low, and it was more near to developing countries incidence levels.

In fact, non-Hodgkin lymphoma is more frequent in developed countries than in less developed ones with rates slightly higher in male than in female; The age-standardized estimated rate per 100,000, for 2008 in developed countries was 10,3 for men and 7/100000 for women (Ahmedin J et al.,2011). In the U.S the age-standardized rate per 100,000 for the period between 2008 and 2012 was 19, 2, it was slightly higher in male than in female (respectively 23.1 and 16) (North American Association of Central Cancer Registries (NAACCR). 2016). Worldwide, the highest age-standardized incidence rates for NHL were noted in Italy for both men and women (respectively 16 and 12.2 cases per 100000); the lowest

rates were registered in Ukraine for both men and women (respectively 4 and 2.4 cases per 100000) (Ferlay et al., 2014). In our population, the NHL occupies the sixth rank of the most common cancer among Tunisian women after the ovary cancer and in the eighth rank among most common cancer in Tunisian men after the stomach cancer (Ferlay et al., 2014) while it occupies the sixth rank in Africa with an age-standardized rate per 100,000 of 6, 3 in men and 4, 1 in women.

Variation with subtypes

The lack of consensual classification impeded significant comparative epidemiological studies of NHL. According to the universally accepted World Health Organization classification, there are 36 subtypes of non-Hodgkin lymphoma (21 of B cell and 15 of T-cell type) excluding entities of uncertain malignant potential (Elias Campo et al., 2011). The occurrence of NHL subtypes differs by area location. In our study, the most common subtype around 2009, in both genders, was diffuse large B-cell lymphoma (63.2%) which is consistent with a study conducted in Spain during 10 years (from 2000 to 2009) were diffuse large B-cell lymphoma represented the most common subtypes of non-Hodgkin lymphoma with a proportion of 30 % followed by follicular lymphoma (about 20%) (Novelli et al., 2013). In the other hand, peripheral T-cell lymphoma is the most common subtype derived from T cells and accounts for about approximately 50% of T-cell NHLs (Morton et al., 2007). In a Kuwaiti study conducted between 1998 and 2006, DLBCL represented the most common subtype of all NHL cases (Ameen et al., 2010).

About 60% of NHLs subtypes are derived from B cells such as diffuse large B-cell lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma and follicular lymphoma (Morton et al., 2007; Morton et al., 2014). Follicular lymphoma constitutes 30% of cases in Western countries but is relatively rare in developing countries as well as in China and Japan (Vose et al., 2002). (DLBCL) is the most common of the aggressive NHLs in the United States (Vose et al., 2002) and it contributed the most to NHL mortality (Howlader et al.,2016). In Australia, around 2006, the most common lymphoma was also DLBCL (18%) followed by follicular lymphoma (12%) (Van Leeuwen et al., 2014).

Geographic differences in etiologic or host factors may play a role in these international differences (Anderson et al., 1998). For instance, the geographic distribution of HIV has influenced geographic patterns of NHL (Hooper et al., 2001). The effect of HIV varies by NHL subtype, with risks particularly increased for diffuse large B-cell lymphoma and Burkitt lymphoma (Engels et al., 2006). Immunodeficiency associated with the presence of EBV can induce a chronic antigenic stimulation which causes the proliferation of B lymphocytes and lead to the development of B cell NHL (Glaser et al., 1997). Even there is no elucidated link with Plasmodium Falciparum infection, Burkitt lymphoma is founded to be more common in tropical Africa where malaria is endemic (Johnston WT et al., 2014). Several studies established the link between gastric infection with Helicobacter

pylori, and mucosa-associated lymphoid tissue (MALT) tumors in the stomach (Vineis et al., 1999; Smedby et al., 2011). In a case control study, MALT lymphomas were significantly associated with a previous diagnosis of *H. pylori* (OR=7.33, CI 95%: 2.84-18.9) (Becker et al., 2005), indeed the geographic distribution of malt lymphoma can be explained by the variance observed in the prevalence of helicobacter infection. The overall prevalence of *H. pylori* in developed countries is lower than the one observed in less developed ones, where over 80% of the population may be infected by this pathogen (Eusebi et al., 2014). In our population MALT lymphoma represents the second most prevalent subtype of NHL. As for Adult T cell lymphoma, it occurs more frequently in Japan and the Caribbean where HTLV-1 is endemic (Proietti et al., 2005). As another risk factor, the disparity in dietary patterns may have influenced the incidence variation between countries. Although some studies showed an association between fat and protein intake and the risk of NHL (Mozaheb et al., 2012), an Italian case control study conducted between 1998 and 2004 found that neither adherence to Mediterranean diet nor a frequent intake of its individual components conveyed protection from NHL (Campagna et al., 2015).

Likewise, the pattern of subtypes varies between genders; mantle cell lymphoma, for instance, is found to be preponderant in men worldwide, while follicular lymphoma is more frequent among women (Ferlay et al., 2010).

In order to provide more evidence that would enlighten further etiologic studies it is wise to compare NHL's incidence trends between countries. Though the overall trend showed no significant change in the incidence for the decade between 1998 and 2009, the joinpoint analyses revealed a difference between two periods taken separately. In fact, there was a significant decrease in the incidence from 1998 to 2005; in return, the incidence significantly increased from 2006 to 2009.

Since the 1970s there has been a dramatic increase in NHL incidence worldwide (Baris et al., 2000; Cancer, 2008). The highest increase was observed in Denmark, where the rate doubled between 1970 and 1985 (Coleman et al., 1993). This increase was not limited to developed countries, but has been also observed in India, Japan, Brazil, Singapore and Puerto Rico (Devesa et al., 1992). From the late 1990s onwards the rate of the increase has slowed especially in the developed areas (Adamson et al., 2007; Sandin et al., 2006). In Australia, for example, the incidence of NHL increased significantly by 2.5%/year (95% CI 2.2-2.8%) during 1982-1996, and was stable during 1997-2006 (0.4%, 95% CI 0.2-0.9%) [13]. A hypothesis was given by Hardell and Eriksson to explain this trend; in fact they associated the decline in NHL incidence to the reduced exposures to several pesticides and persistent organic pollutants that studies have associated with elevated risk of NHL (Hardell et al., 2003).

High rate of increase was consistently observed in Korea between 1999 and 2008 in both men and women (Park et al., 2012), which is consistent with the trend observed in our population from 2006 to 2009 where the

increase was significant with an APC of 30.5. This trend has also involved both genders. The analyses of data emanating from five continents registries between 1998 and 2007 (Curado et al., 2007; Forman et al., 2007), shows an overall increase in the incidence of NHL in both genders more remarkable in Denmark and Australia for male, and in Uganda and Zimbabwe for female (Figures 5, 6).

As for NHL subtypes, epidemiologic studies are scarce. In the US Diffuse large B cell lymphoma was marked by an upswing between 1973 and 1990 in the U.S from 3 to 4% each year (Herrinton et al., 1998; Shipp et al., 1997) this trend could be related to the AIDS epidemic which marked that era. The increase was less prominent for Burkitt and follicular lymphoma. A decrease in the incidence of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) and unspecified lymphoid neoplasms was noted in the US from 1992 to 2001 (Devesa et al., 1992). Those trends are broadly similar with the ones reported in other western countries. The interpretation of this change should be done carefully because we should take in consideration the refinement in the techniques of diagnosis, particularly with the introduction of immuno-histochemical staining of cycline D1 (Vasef et al., 1997), and the improvement in the data registration as well as in NHL subtypes classification (Hartge et al., 1992). The increase in the number of people with human immunodeficiency virus (HIV) infection, also contributed to the modification of the NHL trend as it is the only established risk factor that changes over time (Patel et al., 2011). In Africa, there was no significant increase in the incidence of NHL in the late 80's compared to the USA. In fact this period was marked by the HIV epidemic. The decreased longevity of people living with AIDS, who died from infectious complications, prevented the subsequent development of NHL. In addition, the lack of diagnosis techniques led to consider other pathologies such as tuberculosis as the etiology of lymphadenopathies, in those people, rather than lymphoma (N. Clumeck et al., 1984). In our population there was no significant change in the incidence of Mantle cell lymphoma, whereas diffuse large B cell lymphoma incidence has increased since 1998 especially between 2004 and 2007 where the increase was significant. This may be explained by the fact that our region represents an endemic area for hepatitis B that studies find to have a significant association with DLBCL (Marcucci et al., 2012). In the other hand Burkitt's lymphoma incidence decreased significantly within this period. The decrease in the incidence of this subtype was also observed in some region in Africa and it was interpreted as a result of malaria prevention (Orem et al., 2007; God et al., 2010).

Although data projection showed a consistent increase in the estimated number of NHL new cases as well as in the incidence from 2009 onward, NHL trend is expected to slow down by 2024. In fact, the APC for the period between 2009 and 2024 was lower compared to the one calculated for 2006-2009. Those results were consistent with NHL prediction in both developed and less developed countries. The estimation of The International Agency for Research on Cancer for the year 2025 showed an increase in the number of new cases of NHL. Worldwide, the

predicted number of new cases is 517442 cases for both genders, NHL new cases is expected to attend the amount of 225921 in more developed countries and the amount of 266769 of case in less developed countries (Ferlay et al., 2010), those prediction may be explained by the growth and aging in the population.

To assess the burden of NHL or any other pathology, in addition to its incidence, we need to have an idea about its Disability-adjusted life-years (DALYs). Three regions are concerned with a high amount of DALYs and they are the Sub-Saharan Africa, Oceania and the Middle- East and finally, the region of our interest, North Africa (Figure 7). In fact NHL represents the fourth major contributor to the DALY burden from cancer in this region after the lung and the breast cancer (Soerjomataram et al., 2012). The Inter-country gap observed in NHL burden is explained by the differences in this malignancy mortality between regions (Ilic et al., 2014).

In conclusion, The update data provided by this study about NHL epidemiology in northern Tunisia revealed an overall steady trend in the incidence between 1998 and 2009. With an age standardized rate around 4 cases per 100 000, Tunisia ranked among the regions with a relatively low incidence of NHL. DLBCL had the predominant proportion among all other NHL subtypes, which was the case in other countries such as the US. As for the developed and less developed countries, future estimation showed an increase in both number of new cases and rates of NHL which emphasize in the worldwide burden of this malignancy and in the need of further etiologic studies about NHL that could guide an eventual prevention program.

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