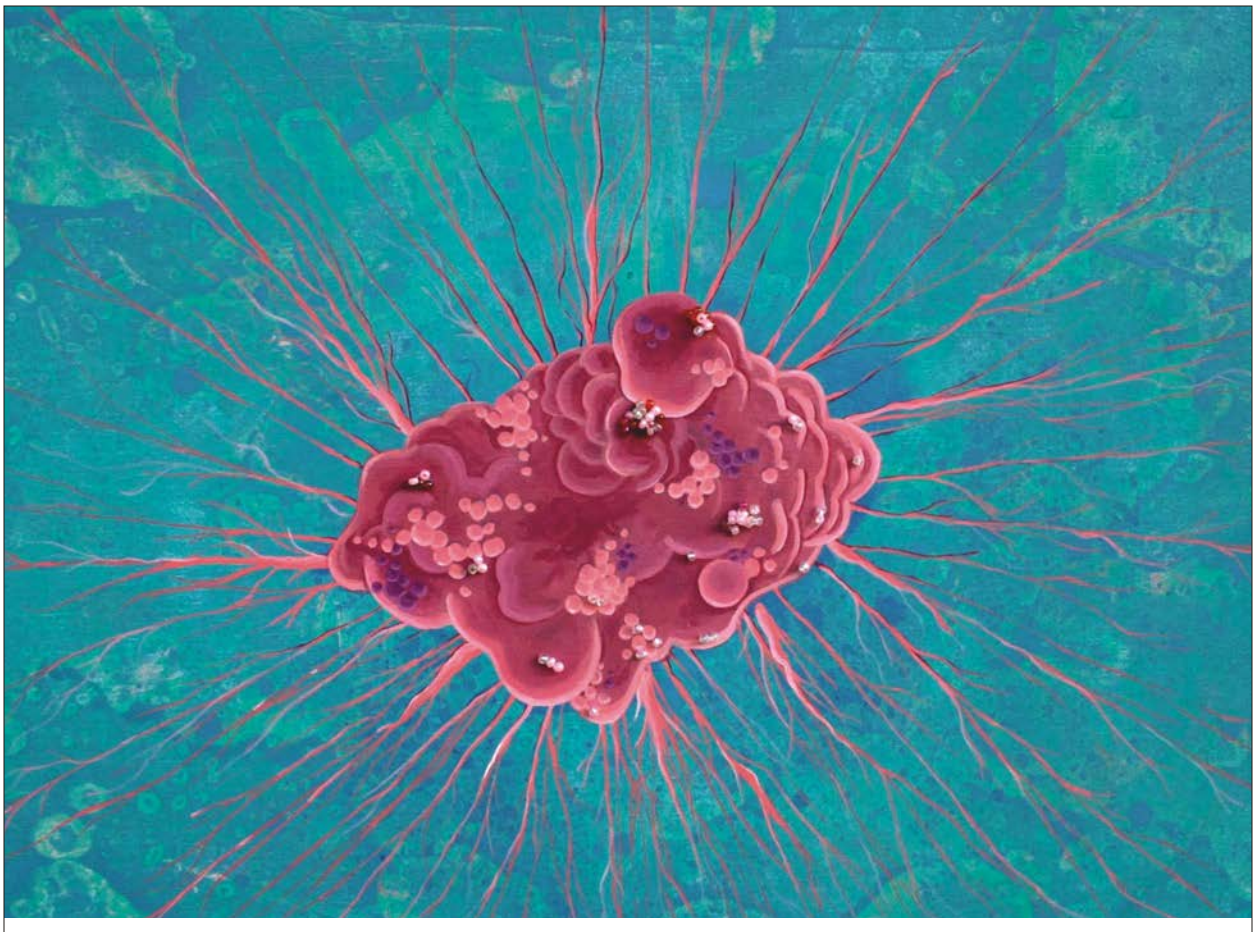

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Non-Hodgkin's lymphomas in Alexandria, Egypt: Incidence Rates and Trend Study (1995-2004)

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Abstract: The purpose of this research is to study the problem of Non-Hodgkin's lymphomas in Alexandria, Egypt: incidence rates and trend. Record reviewing for estimation of the annual incidence rates of NHL and their trends. The general incidence rate of NHL was 5.90 in 1995 and reached 8.99 in 2004, with a peak (9.40) in the year 2002. The male incidence of NHL demonstrated an obvious rise from 1995 till 1998, with a slowing from 1999 to 2002, followed by another evident rise from 2003. Females showed an increase in NHL incidence rates from 1995 till 2000, then a decline afterward till 2004. As regards the population from 15-60 years old, there was a rise through the period from 1994-1999 then a drop from 2000 till 2004. In the elderly group, the incidence rate was doubled during the 10 years (from 13.36/100,000 in 1995 to 26.65 in 2004). Conclusively, the incidence of NHL increased steadily from 1995 to 2004 in Alexandria particularly in the elderly population. The importance of developing additional strategies for screening and prevention of NHL, in this group, based on epidemiological evidences is warranted.

Key words: Non-Hodgkin's lymplomas, incidence, trend, Egypt

Introduction

Non-Hodgkin's lymphomas (NHL) are a heterogeneous group of lymphoproliferative malignancies with differing patterns of behaviour and responses to treatment (Armitage, 1993). The incidence of the most common NHL has increased dramatically worldwide during the past decades (Ekstrom Smedby *et al*., 2005; Devesa and Fears, 1992). According to the National Cancer Institute, the incidence per 100,000 persons climbed from 8.5 in 1973 to 13.7 in 1987-an increase of more than 50% (Ries *et al*., 1991). The increase in incidence has been largely confined to two age groups: men 24-54 years of age and individuals ≥ 65 years of age (Devesa and Fears, 1992). In Egypt, Non-Hodgkin's lymphoma is the 5th most common cancer in 2004 in both sexes, with a late onset of the disease (Alexandria Cancer Registry, 2004). Whatever the cause of the upward trend in NHL incidence and mortality, the studies suggest that NHL will become an increasingly important cancer over the next decade, accounting for an annual average of approximately 5% of the total cancer burden 2011/12 (Balducci and Ballester, 1996).

The purpose of this research is to study the problem of Non-Hodgkin's lymphomas in Alexandria, Egypt: incidence rates (crude and sex and age-specific) and their trend.

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Materials and Methods

Non-Hodgkin's lymphoma cases were recruited from the following sources

- Alexandria Cancer Registry (ACR)
  ACR collects data from 18 main hospitals in Alexandria city in which cancer patients will essentially pass through during their life span after diagnosis. The data are collected from these hospitals and supported by the pathology report from the pathology department.
- Hospitals (three main hospitals in Alexandria, where approximately 95% of cases were managed). These are; Alexandria Main University hospital, Gamal Abdel Nasser Health Insurance hospital and Medical Research Institute hospital

From which all new NHL cases were identified. Even cases diagnosed elsewhere were usually referred to these centers where the diagnostic and therapeutic facilities as well as the trained professional personnel were available to treat such aggressive and costly disease.

All records of NHL cases registered in Alexandria Cancer Registry (ACR) from 1st January 1995 till 31st December 2004 were reviewed. The number of NHL cases was identified for each year separately to be divided by the corresponding estimated midyear population based on the last 2 censuses. The calculated estimated midyear population was an average of both the arithmetic and geometric progression methods of census estimation.

Reviewing hospital personal data sheet was essential to complement information for every patient. An Ann Arbor staging system for lymphomas has been used for tumour staging (Hellman *et al*., 1989).

Statistical Analysis

Data were analysed using PC computer with SPSS version 11.0. The 0.05 level was used as the cut- off value for statistical significance. The time series analysis of the annual incidence of colorectal cancer in Alexandria was adopted (Simpson and Kafka, 1971). Three types of polynomial equations were used for each time series dealt with in the present study. All of them are based on the method of least squares. Trend line computed by the least square method is such that the sum of squares of the deviations of the observed values about it is minimum. These are; first degree polynomial, second degree polynomial (Quadratic equation) and third degree polynomial (third degree parabola). To test the significance of the trend equations Coefficient of determination (R^2) measures were used (Neiswanger, 1961).

Results

A total of 3284 cases of non-Hodgkin's lymphoma were registered in Alexandria Cancer Registry during the period (1995-2004). The median age was 51.6 years and the male to female ratio was 2.1:1. Clinical data were available for only 2638 cases (80.3% of the total). The most frequent histological grade was intermediate grade accounting for 1479 (56.1%) followed by 717 (27.2%) high grade and low grade of 289 (10.9%). Extranodal involvement was observed in more than one third of cases (37.9%). Most patients presented at an advanced stages as 40.0 and 30.1% were presented as stages 3 and 4, respectively. The most frequent histopathological type was diffuse large B-cell lymphoma (31.0%) followed by follicular lymphoma in 22%. Burkitt lymphoma accounted for only less than 1% of all cases with a median age of 5.5 years as shown in Table 1.

Table 1: Clinical profile of Non-Hodgkin's lymphoma in Alexandria, Egypt (1995-2004) n = 2638

Clinical data	Number	(%)
Nodal status		
Nodal	1636	62.1
Extranodal	1002	37.9
Grade		
Indolent (low grade)	289	10.9
Aggressive (Intermediate grade)	1479	56.1
Aggressive (high grade)	717	27.2
Miscellaneous	153	5.8
Stage*		
I	208	7.9
II	580	22.0
III	1055	40.0
IV	795	30.1
Histopathological types		
Diffuse large B-cell lymphoma	818	31.0
Follicular lymphoma	580	22.0
Small lymphocyte lymphoma	158	6.0
Mantle cell lymphoma	155	5.9
Peripheral T-cell lymphoma	153	5.8
Marginal zone B-cell lymphoma	159	6.0
Burkitt's lymphoma	23	0.9
Others	249	9.4
Unknown	343	13.0

*According to Ann Arbor staging system

Table 2: The annual incidence rates of Non-Hodgkin's Lymphoma/100,000 mid-year population by age and sex during the period (1995-2004), Alexandria, Egypt (ACR)*

	Age in years			Sex		
Years	< 15	15-60	> 60	Male	Female	General
1995	2.31	7.03	13.36	6.74	5.05	5.90
1996	2.99	8.14	16.84	7.46	6.83	7.15
1997	4.88	8.00	16.58	8.98	6.39	7.72
1998	3.24	9.24	19.58	10.28	6.50	8.44
1999	3.04	8.44	24.08	9.46	7.03	8.28
2000	3.49	8.80	23.05	9.88	7.55	8.75
2001	3.00	7.98	24.12	9.58	6.89	8.28
2002	3.22	9.27	23.12	10.63	8.09	9.40
2003	3.07	8.09	30.42	10.33	7.95	9.18
2004	3.04	7.97	26.65	11.13	6.68	8.99

*Alexandria cancer registry

Table 2 demonstrates the annual incidence rates and Table 3 shows the trend equations of Non-Hodgkin's lymphomas in Alexandria during the period (1995-2004) by sex and age. From Table 3 and Fig. 1, it is evident that the best fit model is the cubic ($F = 24.25$, $p = 0.001$, coefficient of determination $R^2 = 0.92$ and the mean absolute deviation MAD = 0.219). This model revealed a sharp increase in the first years (1995-1998), followed by a slow increase during the next six years (1999-2004). The general incidence rate was 5.90/100,000 in 1995 and reached 8.99/100,000 in 2004, with a peak (9.40) in the year 2002. The male incidence of NHL demonstrated an obvious rise from 1995 till 1998, with a slowing from 1999 to 2002, followed by another evident rise from 2003. As seen from the cubic model which was the best to fit data ($F = 21.80$, $p = 0.001$, $R^2 = 0.92$ and MAD = 0.297). Regarding females, the best fit model was the quadratic, showing an increase in NHL incidence rates from 1995 till 2000, then a decline afterward till 2004 ($F = 6.86$, $p = 0.022$, $R^2 = 0.66$ and MAD = 0.428) (Fig. 2 and 3).

None of the tested trend models was significant in the age group < 15 years of age. Through the incidence rates increased from 2.31/100,000 in 1995 to reach 3.04/100,000 in 2004, with the minimum rate (2.99) in 1996 and the maximum (4.88) in 1997 (Fig. 4).

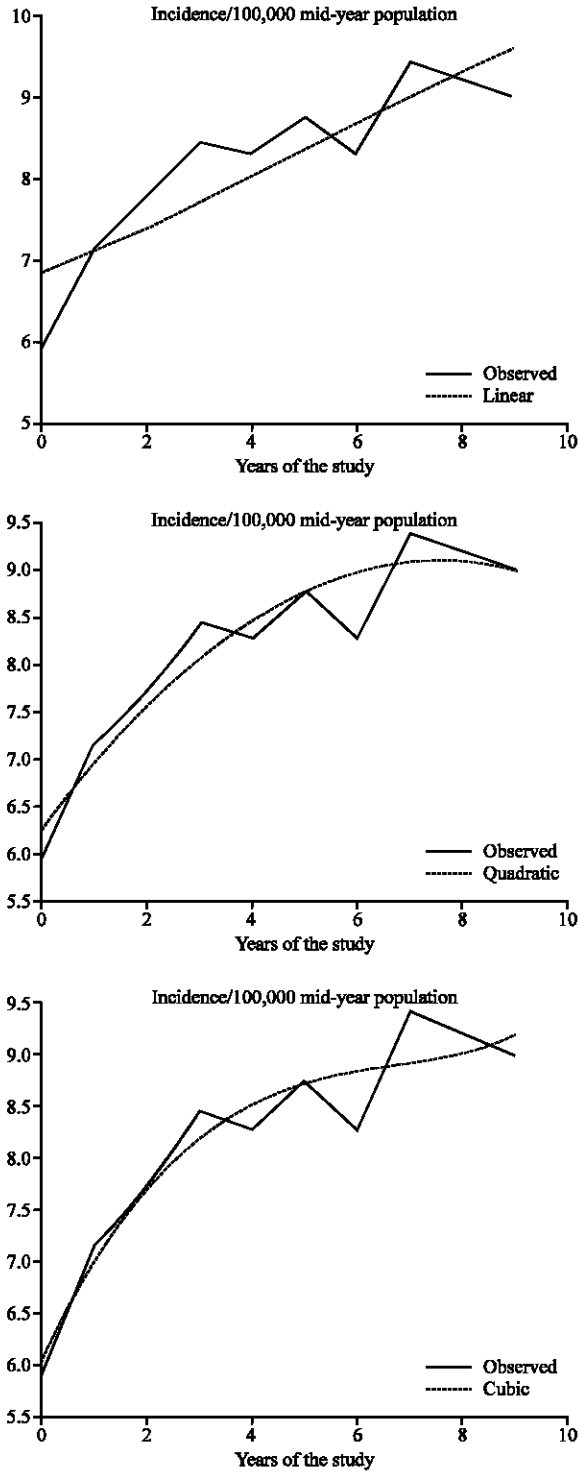

Fig. 1: General incidence of NHL in Alexandria (1995-2004)

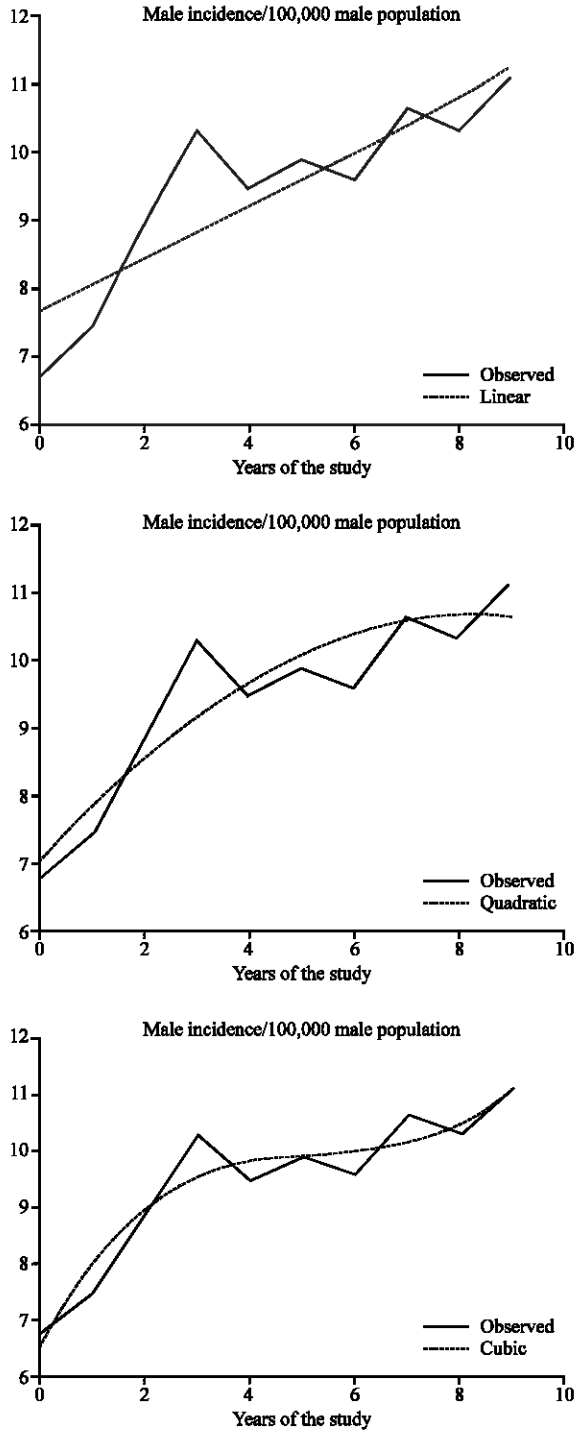

Fig. 2: Incidence of NHL in males in Alexandria (1995-2004)

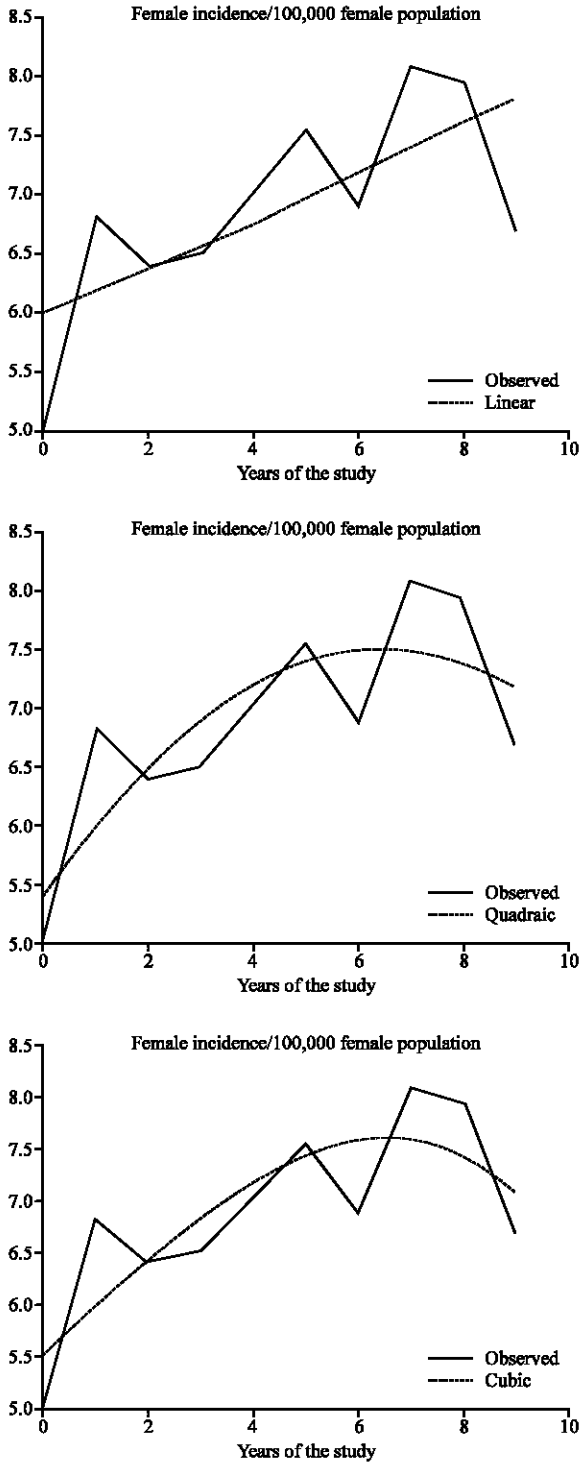

Fig. 3: Incidence of NHL in females in Alexandria (1995-2004)

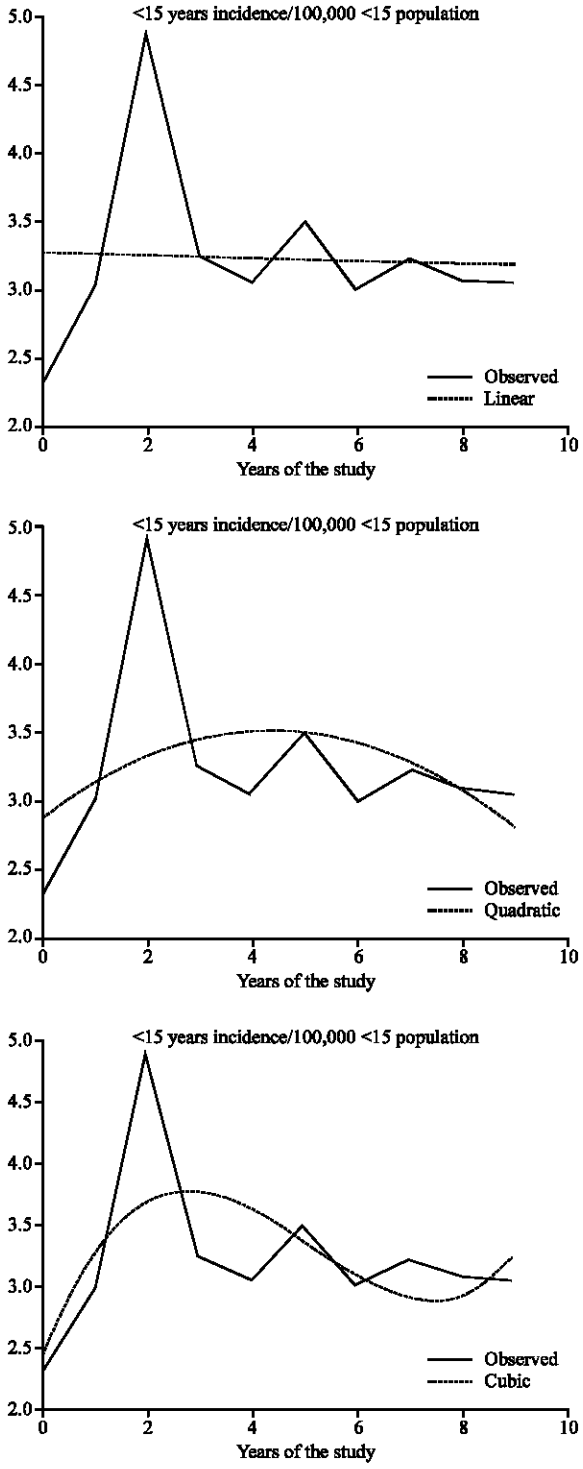

Fig. 4: Incidence of NHL in < 15 years of age in Alexandria (1995-2004)

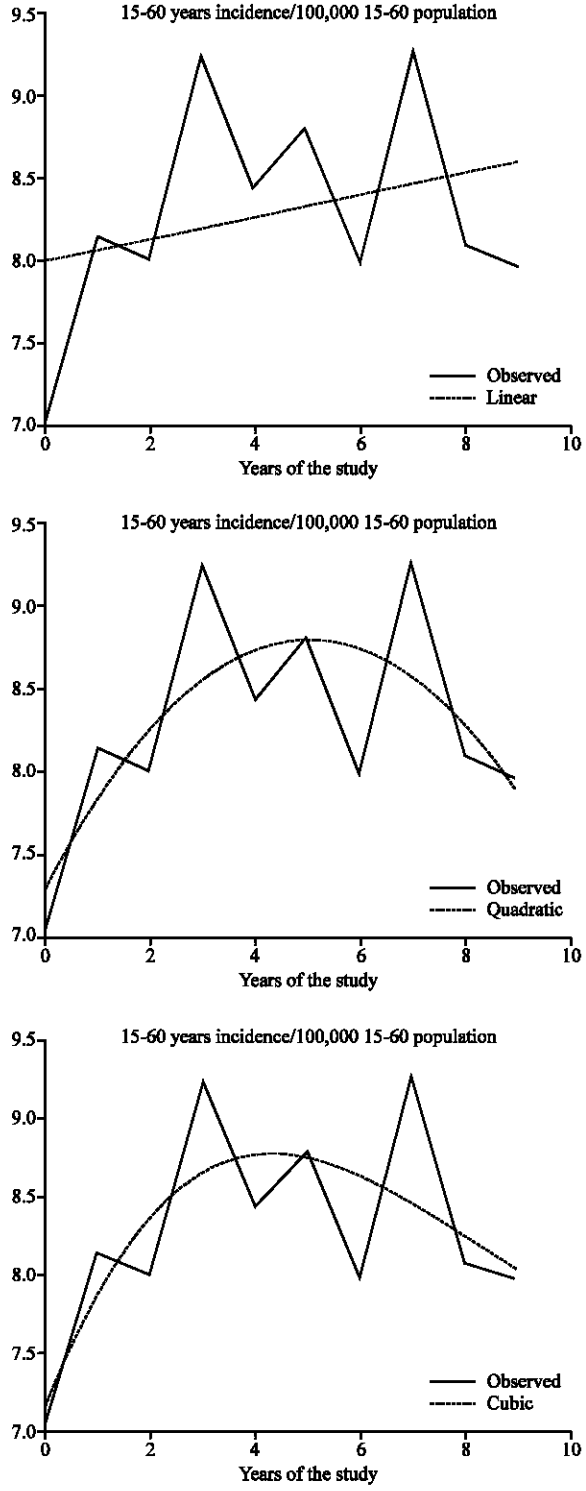

Fig. 5: Incidence of NHL in 15-60 years of age in Alexandria (1995-2004)

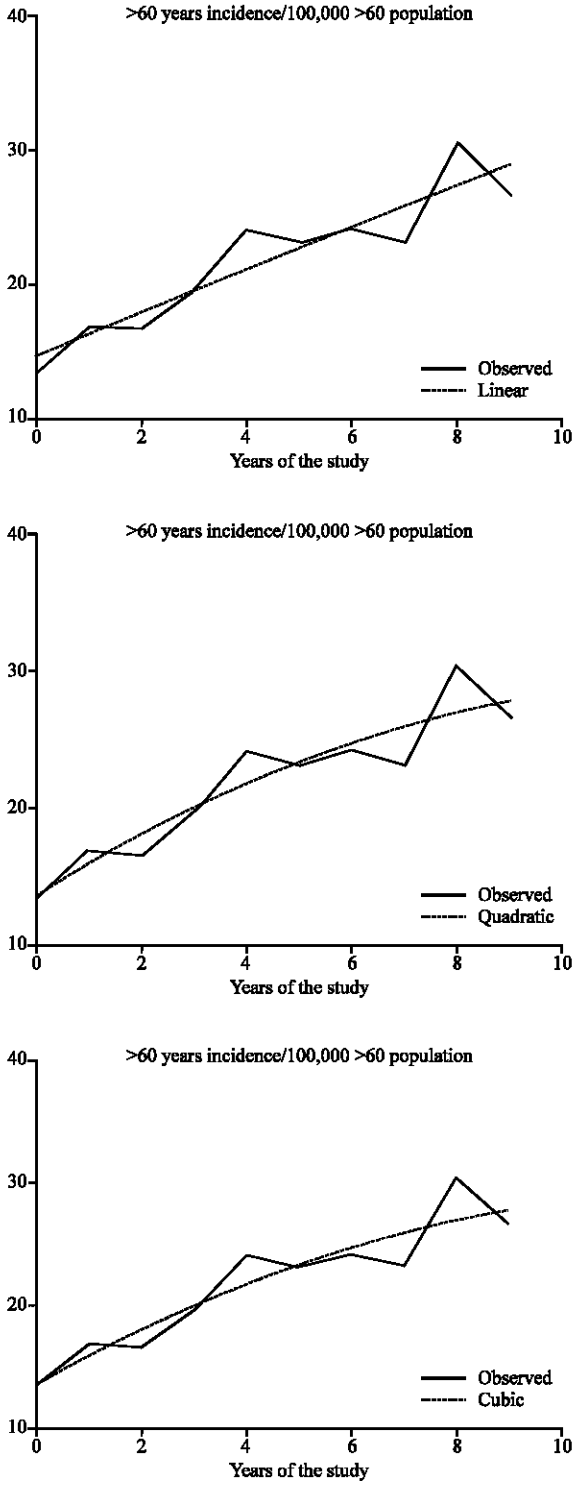

Fig. 6: Incidence of NHL in > 60 years of age in Alexandria (1995-2004)

Table 3: The trend equations for NHL incidence rates in Alexandria by age and sex (1995-2004)

Variables	Trend model	Equation	F	p-value	MAD	R^2
General	Linear	Y = 6.83+0.31b	26.58	0.001	0.403	0.769
	Quadratic	Y = 6.23+0.76-0.05b2	32.86	0.000	0.244	0.904
	Cubic	Y = 6.02+1.13b-0.16b2-0.01b3	24.25	0.001	0.219	0.924
Sex						
Male	Linear	Y = 7.64+0.40b	25.74	0.001	0.519	0.763
	Quadratic	Y = 7.01+0.87b-0.05b2	19.06	0.001	0.427	0.845
	Cubic	Y = 6.51+1.79b-0.32b2+0.02b3	21.80	0.001	0.297	0.916
Female	Linear	Y = 6.00+0.20b	7.16	0.028	0.496	0.472
	Quadratic	Y = 5.40+0.65b-0.05b2	6.86	0.022	0.428	0.662
	Cubic	Y = 5.52+0.43b+0.01b2-0.01b3	4.10	0.067	0.402	0.672
Age (years)						
<15	Linear	Y = 3.27-0.01b	0.01	0.916	0.382	0.001
	Quadratic	Y = 2.87+0.29b-0.03b2	0.62	0.565	0.365	0.151
	Cubic	Y = 2.43+1.10b-0.27b2+0.02b3	1.31	0.355	0.359	0.396
15-60	Linear	Y = 7.99+0.07b	0.80	0.398	0.515	0.091
	Quadratic	Y = 7.29+0.59b-0.06b2	3.99	0.398	0.355	0.533
	Cubic	Y = 7.14+0.87b-0.14b2+0.01b3	2.54	0.153	0.341	0.560
>60	Linear	Y = 14.69+1.58b	46.85	0.000	1.487	0.854
	Quadratic	Y = 13.57+2.42b-0.09b2	24.16	0.001	1.358	0.873
	Cubic	Y = 13.51+2.51b-0.12b2+0.01b3	13.82	0.004	1.355	0.874

As regards the population from 15-60 years old, the best fit model was the quadratic (F = 3.99, p = 0.07, R^2 = 0.533 and MAD = 0.355). This model revealed a rise through the period from 1994-1999 then a drop from 2000 till 2004 (Fig. 5). In the elderly group, the cubic model showed the least MAD, although all models were significant. Generally, the fit line showed a rise through the whole period. It was doubled during the 10 years (from 13.36/100,000 in 1995 to 26.65 in 2004) (Fig. 6).

Discussion

The median age for NHL was 51.6 years, in this study, which is slightly higher than that reported in Saudi Arabia (46 years) (Koriech and Al-Kuhaymi, 1994). In Ethiopia, the peak occurrence of NHL was reported in the age group of 50-54 years (Bekele and Ergete, 2000). In USA, from 1998-2002, the median age at diagnosis for non-Hodgkin lymphoma was 66 years of age (Ries *et al*., 2005).

In Saudi Arabia, only 5% of all NHL were of low-grade histological variety, while 49% were intermediate grade and 46% high-grade histological variety (Koriech and Al-Kuhaymi, 1994). In Ethiopia, The most frequent histological grade was high grade accounting for (43.6%) followed by (29.9%) low grade and intermediate grade (25.5%) (Bekele and Ergete, 2000). In SEER report, low histological grade accounted for 30-40% while intermediate grade (50%) and high grade accounted for only 10% (Ries *et al*., 2005). In this study, the most frequent histological grade was intermediate grade accounting for (56.1%) followed by (27.2%) high grade and low grade (10.9%). Most patients in our study presented at an advanced stage. The same has been reported in Saudi Arabia (Koriech and Al-Kuhaymi, 1994). Primary sites of NHL varied considerably from those in the West. In the west, extranodal presentation was reported in 20-30% of cases (Ries *et al*., 2005). In Saudi Arabia, over 65% of their patients presented with extranodal disease (Koriech and Al-Kuhaymi, 1994). In our study, extranodal presentation was reported in more than one third of our patients (37.9%). Burkitt lymphoma accounted for less than 1% of all lymphomas with a median age of 5.5 years. In Saudi Arabia, a rate of 5% has been reported with a median age of 6 years (Koriech and Al-Kuhaymi, 1994).

The increased incidence of NHL around the world has been documented by numerous publications since the 1980s (Cartwright *et al*., 1999, 2005; Clarke and Glaser, 2002) including Egypt (US Census Bureau, 2004). In agreement with the aforementioned reports, present study revealed a significant

incidence trend of NHL in Alexandria throughout the study period (1995-2004). NHL is ranked fifth among both male and female cancers. The same has been reported recently in USA, (Fisher, 2004) with about 14 new cases for every 100,000 persons in USA each year as compare to nine in our study. In New Zealand, it is ranked sixth and seventh among males and females, respectively (Tobias *et al*., 2002). NHL shows a fairly typical age distribution, with half or more of registrations occurring in older people. The rate is much higher among persons over the age of 60, 68 and 27/100,000 in USA and Egypt, respectively. The cause of the historical trend in NHL incidence are unclear: some of the apparent increase may be art factual, reflecting changes in diagnostic classification and ICD coding rules for the lymphomas and related cancers (Armitage and Weisenburger, 1998). In some countries at least part of the increase is attributable to HIV/AIDS; however, this is at most only a minor cause of NHL in Egypt.

Data from the Surveillance Epidemiology and End Results (SEER) registry of the National Cancer Institute have shown that the average age-adjusted incidence of NHL is higher among individuals ≥ 65 years of age than in younger age group (Baranovsky and Myers, 1986). The incidence of NHL increases with age in both men and women (Newell *et al*., 1987). Present results are in accordance with the SEER data. Although the reasons for this increase are unclear; several explanations are possible. For instance, increasing age is associated with a greater preponderance of immunologic deficits (Whisler *et al*., 1991), with abnormalities in T-cell proliferation (Beckman *et al*., 1990) and with changes in B-cell/T-cell interactions as well as in immunoglobulin gene selection in animal studies (Klinman, 1990). In addition, the risk of NHL is affected by long-term exposure to chemicals such as pesticides in the environment (Levine and Hoover, 1992; Pearce and Bethwaite, 1992).

HCV-associated lymphomas have been observed, but whether they are caused by HCV remains to be shown definitively. There is a suggestion that some B-cell NHL associated with HCV arise from clonal expansion of B-cells with particular immunoglobulin gene rearrangements specific for the E2 protein of the HCV envelope, (Quinn *et al*., 2001; Ivanovski *et al*., 1998) which is consistent with the hypothesis that lymphomas develop when B cells proliferate in response to antigen (Quinn *et al*., 2001). However, no biological mechanism of HCV-associated lymphomagenesis has been definitively elucidated

An estimated 12-15% of Egyptians, or 8-10 million people, have serological evidence of HCV infection, with higher rates in older age groups and residents of rural areas in Lower and Middle Egypt (Frank *et al*., 2000). Most of the studies reported to date that failed to find an association of HCV with NHL were conducted in areas where the prevalence of HCV was extremely low, leaving open the possibility that such an association actually exists but could not be detected because neither cases nor controls had adequate opportunity for exposure (Cowgill *et al*., 2004). Most of the published reports, examined the association of HCV with NHL, support such association of HCV with various types of NHL in Egypt as model of a transition country (Cowgill *et al*., 2004; Ascoli *et al*., 1998; Vallisa *et al*., 1999).

Conclusively, in light of the aging of the Egyptian population, the increasing prevalence of NHL in the elderly is of growing concern. This study showed that NHLs are a heterogeneous collection of lymphoreticular malignancies having wide age coverage and various peculiar histological types. Unlike in the Western Countries, patients presented mostly in advanced stages. A properly designed prospective study is recommended to observe the stage, prognostic markers and treatment outcome of NHL.

References

Alexandria Cancer Registry, 2004. Medical Research Institute, Alexandria University, Annual Report.
Armitage, J.O., 1993. Treatment of non-Hodgkin's lymphoma. N. Eng. J. Med., 328: 1023-1030.

Armitage, J.O. and D.D. Weisenburger, 1998. New approach to classifying non-hodgkin's lymphomas: Clinical features of the major histologic subtypes. Non-Hodgkin's Lymphoma Classification Project. J. Clin. Oncol., 16: 2780-2795.

Ascoli, V., F. Lo Coco, M. Artini, M. Levrero, M. Martelli and F. Negro, 1998. Extranodal lymphomas associated with hepatitis C virus infection. Am. J. Clin. Pathol., 109: 600-609.

Balducci, L. and O.F. Ballester, 1996. Non-Hodgkin's lymphoma in the elderly. Cancer Control, 3: 5-14.

Baranovsky, A. and M.H. Myers, 1986. Cancer incidence and survival in patients 65 years of age and older. CA Cancer J. Clin., 36: 26-41.

Beckman, I., K. Dimopoulos, Xu. Xiaoning, J. Bradley, P. Henschke and M. Ahernet, 1990. T cell activation in the elderly: Evidence for specific deficiencies in T cell/accessory cell interactions. Mech. Ageing Dev., 51: 265-276.

Bekele, A. and W. Ergete, 2000. The histologic pattern of non-Hodgkin's lymphomas in Ethiopians. Ethiopian J. Health Develop., 14: 345-352.

Cartwright, R., H. Brincker, P.M. Carli, D. Clayden, J.W. Coebergh, A. Jack, R. McNally, G. Morgan, S. De Sanjose, R. Tumino and M. Vornanen, 1999. The rise in incidence of lymphomas in Europe 1985-1992. Eur. J. Cancer, 35: 627-633.

Cartwright, R., H. Wood and M. Quinn, 2005. Non-Hodgkin's lymphoma (Chapter 16). In: Cancer Atlas of the United Kingdom and Ireland 1991-2000. Quinn, M., H. Wood, N. Cooper, S. Rowan (Eds.), Published by Palgrava Macmillan, pp: 173-182.

Clarke, C.A. and S.L. Glaser, 2002. Changing incidence of non-Hodgkin lymphomas in the United States. Cancer, 94: 2015-2023.

Cowgill, K.D., C.A. Loffredo, S.A. Eissa, N. Mokhtar, M. Abdel-Hamid, A. Fahmy and G.T. Strickland, 2004. Case-control study of non-Hodgkin's lymphoma and hepatitis C virus infection in Egypt. Intl. J. Epidemiol., 33: 1034-1039.

Devesa, S.S. and T. Fears, 1992. Non-Hodgkin's lymphoma time trends: United States and International Data. Cancer Res., 52(suppl 19): 5432s-5440s.

Ekstrom Smedby, K., H. Hjalgrim, M. Melbye, A. Torrang, K. Rostgaard, L. Munksgaard, J. Adami, M. Hansen, A. Porwit-MacDonald, B.A. Jensen, G. Göran Roos and B.B. Pedersen *et al*., 2005. Ultraviolet radiation exposure and risk of malignant lymphomas. J. Natl. Cancer Inst., 97: 199-209.

Fisher, S.G., 2004. The Epidemiology of non-Hodgkin's lymphoma. Lymphoma Research Foundation.

Frank, C., M.K. Mohamed, G.T. Strickland, D. Lavanchy, R.R. Arthur, L.S. Magder, T. El Khoby, Y. Abdel-Wahab, E.S. Aly Ohn, W. Anwar and I. Sallam, 2000. The role of parenteral antischistosomal therapy in the spread of hepatitis C virus in Egypt. Lancet, 355: 887-891.

Hellman, S., E.S. Jaffe and V.T. DeVita Jr, 1989. Hodgkin's Disease, In: Cancer, Principles and Practice of Oncology. DeVita, V.T., S. Hellman and S.A. Rosenberg (Eds.). Philadelphia: J.B. Lippincott, pp: 1696-1740.

Ivanovski, M., F. Silvestri, G. Pozzato, S. Anand, C. Mazzaro, O.R. Burrone and D.G. Efremov, 1998. Somatic hypermutation, clonal diversity and preferential expression of the VH 51p1/VL Kv325 immunoglobulin gene combination in hepatitis C virus-associated immunocytomas. Blood, 91: 2433-2442.

Klinman, N.R., 1990. Discussion: Aging and the expression of the B cell repertoire. Aging: Immunol. Infect. Dis., 2: 139-142.

Koriech, O.M. and R. Al-Kuhaymi, 1994. Profile of cancer in Riyadh Armed Forces Hospital. Ann. Saudi Med., 14: 187-194.

Levine, P.H. and R. Hoover, 1992. The emerging epidemic of non-Hodgkin's lymphoma: Current knowledge regarding etiological factors. Cancer Epidemiol. Biomark. Prev., 1: 515-517.

Neiswanger, W.A., 1961. Analysis of Time Series. In: Elementary Statistical Methods. New York: Prentice- Hall, Inc., pp: 477-605.

Newell, G.R., F.F. Cabanillas, F.B. Hagemeister and J.J. Butler, 1987. Incidence of lymphoma in the US classified by the Working Formulation. Cancer, 59: 857-861.

Pearce, N. and P. Bethwaite, 1992. Increasing incidence of non-Hodgkin's lymphoma: Occupational and environmental factors. Cancer Res., 52(suppl 19): 5496s-5500s.

Quinn, E.R., C.H. Chan, K.G. Hadlock, S.K. Foung, M. Flint and S. Levy, 2001. The B-cell receptor of a hepatitis C virus (HCV)-associated non-Hodgkin lymphoma binds the viral E2 envelope protein, implicating HCV in lymphomagenesis. Blood, 98: 3745-3749.

Ries, L.A.G., B.F. Hankey, B.A. Miller, A.M. Hartman and B.K. Edwards, 1991. Cancer Statistics Review 1973-1988. Bethesda, M.D., National Cancer Institute; NIH Publication, II.34-II.35:2789-91.

Ries, L.A.G., M.P. Eisner, C.L. Kosary, B.F. Hankey, B.A. Miller, L. Clegg, A. Mariotto, E.J. Feuer and B.K. Edwards, 2005. SEER Cancer Statistics Review, 1975-2002. National Cancer Institute. Bethesda, M.D., http://seer.cancer.gov/csr/1975_2002/, based on November 2004 SEER data submission, posted to the SEER web site.

Simpson, G. and F. Kafka, 1971. Introduction to Time Series Analysis. In: Basic Statistics. A Textbook for the First Course; 1st Edn. Calcutta Bombay New Delhi Oxford: IBH Publishing Co., pp: 221- 301.

Tobias, M., E. Hodgen and J. Cheung, 2002. Cancer in New Zealand: Trends and projections. Public Health Intelligence, Ministry of Health.

US Census Bureau, 2004. International Data Base.

Vallisa, D., R. Berte, A. Rocca, G. Civardi, F. Giangregorio, B. Ferrari, G. Sbolli and L. Cavanna, 1999. Association between hepatitis C virus and non-Hodgkin's lymphoma and effects of viral infection on histologic subtype and clinical course. Am. J. Med., 106: 556-560.

Whisler, R.L., J.W. Williams Jr and Y.G. Newhouse, 1991. Human B cell proliferative responses during aging: Reduced RNA synthesis and DNA replication after signal transduction by surface immunoglobulins compared to B cell antigenic determinants CD20 and CD40. Mech. Ageing Dev., 61: 209-222.