HAL
open science

Epidemiology of Lymphomas

Eve Roman, Alexandra Gwen Smith

To cite this version:

Eve Roman, Alexandra Gwen Smith. Epidemiology of Lymphomas. Histopathology, 2011, 58 (1), pp.4. 10.1111/j.1365-2559.2010.03696.x . hal-00610747

HAL Id: hal-00610747
https://hal.science/hal-00610747v1

Submitted on 24 Jul 2011

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Histopathology

Epidemiology of Lymphomas

Journal:	*Histopathology*
Manuscript ID:	HISTOP-09-10-0510
Wiley - Manuscript type:	Review
Date Submitted by the Author:	16-Sep-2010
Complete List of Authors:	Roman, Eve; University of York, Health Sciences Smith, Alexandra; University of York, Health Sciences
Keywords:	Hodgkin lymphoma, Diffuse large b-cell lymphoma, epidemiology, haematological maligancy

SCHOLARONE™
Manuscripts

Epidemiology of Lymphomas

Eve Roman*, Alexandra G Smith

Epidemiology & Genetics Unit,

Seebohm Rowntree Building,

Department of Health Sciences,

University of York,

YO10 5DD

*Corresponding author: eve.roman@egu.york.ac.uk

For Peer Review

Published on behalf of the British Division of the International Academy of Pathology

Abstract

Aims: Epidemiological reports on lymphomas often begin, and sometimes end, by stating that little is known about the causes of the condition(s) under study. This is slowly changing as evidence about the pathological diversity of subtypes accumulates. This review examines the epidemiology of lymphomas, focussing on the impact of the latest WHO classification.
Methods and Results: Use of appropriate disease classifications is critical to the research process; but many studies conducted in previous decades have been hampered by the need to aggregate data into the broad lymphoma groupings of Hodgkin and non- Hodgkin, either because primary source information was recorded in that way or because diagnostic standards were inconsistently applied. Population-based data on age and gender are presented using the latest WHO classification, revealing considerable sub-type heterogeneity. Aetiological factors highlighted include the unexplained male bias that is strikingly evident for many subtypes across all ages; and the relationship with autoimmune disease, which although often associated with increased lymphoma risk is generally more common in females.
Conclusion: This is an exciting time for epidemiological research into haematological malignancies; where the application of modern disease classifications is beginning to discriminate between subtypes revealing features that future aetiological hypotheses should seek to address.

For Peer Review

Introduction

Epidemiology is the basic quantitative science of public health; and as such is concerned with the distribution, determinants, treatment, management and potential control of disease. Concentrating on the first two of these, this article aims to review the epidemiology of the lymphomas - a heterogeneous group of malignancies that are estimated to account for around 3-4% of cancers world-wide (Figure 1) [1]. Before considering their epidemiology in any depth, the issue of disease classification – which permeates the discussion throughout is touched on below.

In order to originate and test hypotheses about pathogenesis it is vitally important to accurately describe and understand underlying disease patterns [2]. Implicit in this is the need to use appropriate disease classifications; and it is this requirement that continues to beleaguer epidemiological research into lymphoid malignancies. In short, the classification

Published on behalf of the British Division of the International Academy of Pathology

of haematological malignancies has changed markedly over recent decades, and will continue to do so as new diagnostic methods and techniques are developed [3]. In 2001 the World Health Organisation (WHO) produced, for the first time, a consensus classification that defined malignancies of the haematopoetic and lymphoid systems in terms of immunophenotype, genetic abnormalities and clinical features [4]. Up until then, competing classifications had often made meaningful comparison of results between epidemiological studies virtually impossible.

Although WHO's 2001 classification was adopted into clinical practice almost uniformly around the world, it did not have an immediate effect on population-based epidemiological research. This is because unlike many other cancers, haematological neoplasms are diagnosed using multiple parameters including a combination of histology, cytology, immunophenotyping, cytogenetics, imaging and clinical data. Furthermore, in practice, even within some of the best defined WHO categories there is a need to qualify the final diagnosis even further using additional clinical and biological prognostic factors before valid outcome comparisons can be made [5,6]. This range and depth of data is difficult for cancer registries and other researchers to access systematically, forming a barrier both to complete ascertainment and to the collection of diagnostic data at the level of detail required to systematically implement the latest WHO classification [4,3].

Descriptive Epidemiology

Whilst cancer registration has a long history in many countries, particularly those in the more affluent regions of the world, nearly 80% of the world's population are not covered by such systems [7]. Nonetheless, with a view to characterizing the global burden of disease, the WHO's International Agency for Research on Cancer (IARC) routinely uses the available data to estimate worldwide cancer incidence and mortality levels [1]. Misdiagnosis and undernumeration are, however, recognized problems for haematological cancers. The acute and rapidly fatal presentation of some leading to underenumertion in countries with less well developed health service infrastructures; and the intermittant and non-specific nature of symptoms associated with others [8,9] posing problems even in countries with well-developed health service systems and cancer registration processes. In addition, population-based data continue to be reported in the broad anatomical-based categories of non-Hodgkin lymphoma (NHL), Hodgkin lymphoma (HL), myeloma and leukaemia[1,10-13] since, for reasons outlined in the introduction, the laboratory data required to classify haematological malignancies

Published on behalf of the British Division of the International Academy of Pathology

For Peer Review

appropriately are hard for cancer registries to access in a timely and systematic fashion

International patterns

Incidence figures from IARC's most recent series of estimates are presented in Figures 1-3. Of the 12.68 million new cancer cases estimated to have occurred around the world in 2008, 6.64 were in men and 6.04 in women – haematological malignancies comprising 7.5% of cancers in males and 6.4% in females. In both sexes, lymphomas were estimated to have accounted for around half of all newly diagnosed haematological neoplasms (Figure 1).

<Figure 1>

The age-standardized lymphoma rates (NHL + HL) for both sexes combined are globally distributed in Figure 2. With one or two exceptions, the geographical pattern is dominated by the high rates in the more economically developed regions of the world. This is seen more clearly in Figure 3, which shows the estimated regional rates and numbers of cases of NHL and HL separately for men and women (http://globocan.iarc.fr/). Less than half of all NHL and HL diagnoses occurred in the three regions with the highest rates – Northern America, Europe and Oceania - largely reflecting the underlying world population distribution. The most striking disparity is seen for Asia, which has the lowest rates but more than a third of all of the estimated cases.

<Figure 2>

Variations with age and sex

That lymphoid malignancies are generally more common in men than in women is evident in Figure 3. For both NHL and HL the age standardized rates and numbers are consistently higher for males than females - the differences tending to be slightly more pronounced in less developed regions of the world (http://globocan.iarc.fr/) . The sex rate ratios (M/F) for HL, for example, ranged from 1.8 and 1.6 in Africa and Asia through to 1.2 and 1.1 in North America and Europe. Whether or not this gradation reflects genuine differences or biases within the data cannot be ascertained form the available information.

<Figure 3>

For Peer Review

The NHL and HL age-specific incidence patterns seen in developed regions of the world are broadly similar to the UK data shown in Figure 4. The relationship with age is, however, quite different for NHL and HL. For NHL, the age-specific male and female rates increase with increasing age, the divergence between the male and female rates becoming progressively more marked as age increases. By contrast, the HL incidence distribution has two peaks – one in young adults and one in the elderly. There is a pronounced male excess in the adult years, but with a slightly earlier peak and deeper trough in females the shapes of two curves are slightly different. These patterns reflect the fact that HL comprises several disease entities, each with its own descriptive features [3,14]. The impact of such differences on basic descriptive age and sex patterns can be seen more clearly in Figures 5-7, which present data from the Haematological Malignancy Research Network (www.HMRN.org). Established in 2004, HMRN is based in two UK cancer Networks (population 3.6 million) and comprises an ongoing population-based cohort of all patients (paediatric and adult) newly diagnosed by a single integrated haematopathology laboratory – over 2,000 patients each year with all diagnoses routinely coded to the latest WHO classification [15].

<Figure 4>

HMRN patients newly diagnosed with lymphoma in the 5-years Sept 2004-Aug 2008 are proportionately distributed by WHO diagnostic category in Figure 5, beginning with the B-cell NHLs, moving clockwise thorough the T-cell NHLs and ending with the HLs [3]. Diffuse-large B-cell (DLBCL), Follicular (FL) and marginal zone (MZL) dominate accounting for more than 70% of the total. The corresponding box-and-whisker age distributions are shown in Figure 6, and the sex-specific incidence rate-ratios (male rate/female rate) together with their standard errors in Figure 7.

<Figure 5>

Whilst most B-cell NHLs have a median diagnostic age over 70 years, a significant minority tend to be diagnosed at younger ages - follicular, Burkitt and mediastinal lymphomas having median ages of 65, 52 and 36 years respectively. Furthermore, some have much broader age ranges than others – with no patients diagnosed before the age of 48 years and a median of 74 years, the age distribution of mantle cell lymphoma shows the least variation. By contrast, with a median diagnostic age approaching 71 years, but with several sporadic paediatric cases, DLBCL covers the largest age range - the scatter of outliers at younger ages indicative, perhaps, of diagnostic heterogeneity within this subtype category. Overall, T-cell NHLs tend

Published on behalf of the British Division of the International Academy of Pathology

For Peer Review

to be diagnosed at younger ages, but in common with the B-cell form of disease there is considerable subtype heterogeneity – the tight age band for enteropathy type t-cell contrasting with that seen for anaplastic large t-cell, for example. Lastly, with a pronounced paediatric component, HL tends to be diagnosed earlier still, but again there are differences between the subtypes – the median ages within the classical Hodgkin lymphoma (CHL) category, for example, ranging from 37 years for nodular sclerosis CHL to 60 years for mixed cellularity CHL (Figure 6).

<Figure 6>

That males are far more likely to develop lymphoma than females is conspicuously clear in Figure 7 – but it is also evident that the gender disparity is much greater for some subtypes and almost absence for others. Among B-cell NHLs, roughly equal numbers of males and females were diagnosed with follicular lymphoma and with extranodal marginal zone lymphoma; but the sex-rate ratio for all other B-cell lymphomas shows a male bias – the most striking being for Burkitt lymphoma which in these and other series, is at least three times as likely to be diagnosed in males than in females. T-cell NHLs and HLs also exhibit a male bias, but again there is considerable subtype heterogeneity, with angioimmunoblastic T-cell lymphoma running counter to the trend by being more common in women (Figure 7).

<Figure 7>

The wide diversity of descriptive patterns shown in Figures 6 and 7 are indicative of different sub-type aetiologies, which many new and ongoing epidemiological studies are aiming to address. However, the continued application of site-based classification systems for routine cancer registration severely limits the use of such data in epidemiological studies. Hopefully, in the future, new insights into lymphoma epidemiology will emerge as the WHO classification becomes more widely applied.

Changes over time

Monitoring disease trends over time is fundamental to descriptive epidemiology, such analyses often yielding important aetiological clues. Indeed, there are many examples in the field of cancer epidemiology where this has been the case, particularly in relation to the

Published on behalf of the British Division of the International Academy of Pathology

For Peer Review

identification of hazardous occupational and environmental exposures [2]. In this context, the temporal changes reported for NHL in recent decades are unquestionably dramatic, as can be seen from Figure 8 which shows the estimated age-adjusted incidence rates from the Surveillance, Epidemiology and End Results (SEER) Program in the United States (www.seer.cancer.gov).

<Figure 8>

The sharp increase seen for NHL between 1970s and 1990s was reported in many developed countries and naturally captured both scientific and public attention at the time (Figure 8). In males, the doubling of the NHL rate over a 20 year period is particularly striking, and contrasts with the modest fall in HL seen in males over the same time period. Whilst it is generally recognized that changing diagnostic practises is almost certainly involved in these trends, there remains debate about whether such changes could have been responsible for all, or only part, of the increase in NHL [2,16-18]. In this context, the potential aetiological role of human immunodeficiency virus (HIV) as well as other viruses and exposures attracted considerable attention - and these factors are discussed in more detail in the section on causes below.

The rate of change in NHL slowed in the US towards the end of the twentieth century, and similar plateauing has now been reported for other developed regions of the world [18,19]. Taken at face-value, this would seem to support the notion that changes in disease detection, diagnostic practise and cancer registration procedures are all likely to have contributed to the increase seen over the 1970s and 1990s. Indeed, the UK Department of Health noted in 2003 that '*There are no precise and reliable figures for incidence and survival rates for the different forms of haematological cancer in England and Wales. Whilst the Office for National Statistics (ONS) and Wales Cancer Intelligence and Surveillance Unit do publish descriptive statistics, there are many problems with these figures. For example, there is evidence that many cases are never reported to cancer registries, so the actual number of patients could be substantially higher than national figures suggest*' [20]. Likewise, a recent report examining incidence and survival trends across Europe concluded that 'the *evolving classification and poor standardization of data collected on hematological malignancies vitiate the comparisons of disease incidence and survival over time and across regions*' [21].

Published on behalf of the British Division of the International Academy of Pathology

For Peer Review

Importantly, with respect to the examination of future time-trends, the role of changing diagnostic practice will undoubtedly remain challenging to evaluate since haematological oncology is changing rapidly, with new approaches to treatment and diagnosis continually emerging as diverse patient pathways evolve. In this regard, the use of more reliable and sensitive diagnostic techniques continues to lower the threshold of disease detection - the ability of flow cytometry to detect small populations of abnormal cells, for example, as well as the introduction of polymerase chain reaction (PCR) allowing the detection of disease at a molecular level. Hence, proportionately more of the patients diagnosed today have indolent or asymptomatic disease [6,15], and it remains possible that the increasing numbers of registrations may be due, at least in part, to the recognition of new group(s) of patients that would not have been diagnosed in previous decades.

Aetiology

As discussed above the use of appropriate disease classifications is critical to the research process; and many studies conducted in previous decades have been hampered by the need to aggregate their data into the broad groupings of NHL or HL, either because primary source information was recorded in that way or because diagnostic standards were inconsistently applied. Hence, given the underlying variations in pathologies and prognosis it is perhaps not surprising that many epidemiological reports on lymphomas often begin, and sometimes end, by stating that little is known about the causes of the condition(s) under study. However, this is beginning to change as evidence about the pathological and clinical diversity of lymphoma subtypes continues to accumulate, not only revealing descriptive differences such as those outlined in the previous section, but also other potentially immune-mediated associations. In this regard, it is generally agreed that immune dysregulation plays a pivotal role in lymphogenesis, and most epidemiological research has concentrated on factors and exposures that interact with the immune system.

Infection

It has been known for some time that immunodeficiency syndromes (inherited and acquired) predispose towards lymphoproliferative disorders; and in this regard, the strong association between human immunodeficiency virus /acquired immunodeficiency syndrome (HIV/AIDS)

Published on behalf of the British Division of the International Academy of Pathology

For Peer Review

and several B-cell lymphomas has been examined in numerous studies – the increased risks reported ranging from 10 to 300 fold, the highest risks generally been observed for the more aggressive NHL sub-types and the lowest for the HLs [22,23]. Unsurprisingly, the potential role of the HIV/AIDS epidemic was one of the factors evaluated in the context of the striking rise of NHL observed in the 1970s-90s discussed above. NHL rates had, however, begun rise before the onset of the HIV/AIDS epidemic in the 1980s (Figure 8), and even now the contribution of HIV/AIDS to the totality of lymphomas diagnosed in developed countries remains comparatively small [22].

In addition to HIV, a number of other viruses have been suggested to impact on lymphoma risk, albeit by different mechanisms. The most accepted viral associations are those with human t-cell leukaemia virus type 1 (HTLV-1) and the two herpesviruses, Epstein-Barr virus (EBV) and human herpesvirus 8 (HHV-8) – also known as Kaposi's sarcoma herpesvirus (KSHV). Infection with HTLV_1 is a necessary but not sufficient cause of adult t-cell leukaemia/lymphoma (ATLL), with ATLL developing in around 3% of those infected. ATLL principally occurs in areas where HTLV-1 is endemic, including Japan, the Caribbean and parts of central Africa; and like most other lymphomas it is more common in males than females [3,22,24,25].

In contrast to the specific nature of the HTLV-1/ATLL association, the globally ubiquitous EBV features in several lymphoma subtypes including Burkitt lymphoma and CHL, as well as those occurring in immunosuppressed individuals. EBV is invariably associated with the endemic form of Burkitt lymphoma that occurs in equatorial Africa and New Guinea; where, with a median age of around 7 years and a male to female ratio of 2:1, it is the commonest childhood malignancy. However, as can be seen from Figure 6, the median age at onset of the comparatively rare sporadic form of Burkitt lymphoma seen in other areas of the world is much later, and the male predominance is much greater (Figure 7). In contrast to endemic Burkitt's, EBV is only associated with around a third of all sporadic cases and the role of EBV in these tumours is a continuing area of research [3,24,26]. Likewise, the significance of the well-established association between EBV and CHL, observed most frequently in children and the elderly in around a third of all cases in resource rich countries - but even more commonly in less affluent parts of the world - remains an area of current investigation [3,24,25,27]. HHV-8 has been found in several comparatively rare tumour sub-types, where it sometimes occurs with EBV [25]. The nature of this association, and that of a number of other viruses, including Hepatitis C [25,28], are topics of ongoing research.

Published on behalf of the British Division of the International Academy of Pathology

For Peer Review

Bacterial infection resulting in chronic inflammation has been consistently linked with a marked increase in risk of some NHL subtypes – one of the best known associations being that between *Helicobacter pylori* and gastric mucosa-associated lymphoid tissue (MALT) extranodal marginal zone lymphoma; the presence of the bacteria increasing lymphoma risk by about 6-fold [3,29,30]. As with the viral associations (e.g. HTLV-1 and ATLL), bacterial infection very often occurs many years before MALT lymphoma development – the median age of diagnosis of all extra-marginal zone lymphomas combined in the HMRN series being just under 70 years (Figure 6) with no obvious sex bias (Figure 7). *Helicobacter pylori* infection generally occurs in childhood – the prevalence being highest in developing countries and falling as socio-economic status increases [31]. In the future, the introduction of effective *Helicobacter pylori* treatments, coupled with increasing affluence developed regions of the world, may well lead to a reduction in incidence of *Helicobacter pylori* positive gastric marginal zone lymphomas [32].

Interestingly, detailed analysis of medical records collected in a UK case-control study revealed significant increases in the frequency of non-specific infectious illness episodes more than 10 years before the diagnosis of CHL, but not of DLBCL and FL [33,34]. Whether or not the excess seen for CHL was a consequence of an underlying immune abnormality, or whether infection played a causal role could not be determined from the available data.

Autoimmune disease

Several well documented links between autoimmune disease based chronic inflammation and MALT lymphoma are also recognized - two of the strongest and most well described being that between Hashimoto thyroiditis and thyroid lymphoma and between Sjögren's syndrome and salivary gland lymphoma [3,35-37]. Consistent associations have also been reported for other chronic inflammatory rheumatic diseases, for example rheumatoid arthritis and systemic lupus erythematosus with both marginal zone and diffuse large B-cell lymphomas [35,38,39], and gastrointestinal inflammatory autoimmune conditions, such as coeliac disease and Crohn's disease, with the T-cell lymphomas [36,35,40]. Indeed, evidence linking lymphoproliferative disorders with autoimmunity continues to accumulate, the strongest associations being seen for marginal zone lymphoma, diffuse large B-cell lymphoma and T-cell lymphoma [36,35,41], and the weakest with the relatively indolent follicular lymphoma

Published on behalf of the British Division of the International Academy of Pathology

For Peer Review

[36,41,42]. Associations between chronic inflammatory rheumatic diseases and CHL, but not nodular sclerosis HL, have also been reported [35,37].

Taken as a whole, there is broad consensus that elucidating the mechanisms underpinning the link between autoimmune disease and the lymphomas could lead to fundamental insights into the biology of both groups of disorders, and there is considerable speculation about potential mechanisms in the literature [38,43-45]. In this regard routine examination of sex-specific associations could provide valuable information since it has long been known that most autoimmune conditions are considerably more common in women than men [46-48], whereas the reverse is true for the majority of lymphoproliferative malignancies [3,11,15]. Furthermore, there are well documented sex-specific variations in immune response that may well impact on the risk of these diseases [48-50].

Other factors

In addition to investigating associations with autoimmune and infectious conditions, the InterLymph consortium (http://epi.grants.cancer.gov/InterLymph/), which is an scientific forum for epidemiologic research on lymphomas established in 2001, has reviewed and published on several health related states/events and environmental exposures [51]. Thus far, relatively few notable associations have been reported; no consistent effects being seen for self-reported smoking [52], alcohol [53], and obesity [54]; and marginally reduced risks being observed for self-reported sun-exposure [55] and history of atopic infections [56]. Finally, with respect to genetic susceptibility, increased risks were confirmed among those with a self-reported family history of haematological cancers [57]; and, perhaps more importantly, polymorphisms in two immune-system related genes have been identified using the candidate gene approach, associations being seen for both DLBCL and marginal zone lymphoma [58,59].

Conclusion

This is an exciting time for epidemiological research into haematological malignancy; where the application of modern disease classifications is beginning to discriminate between subtypes revealing features that future aetiological hypotheses should seek to address.

Published on behalf of the British Division of the International Academy of Pathology

For Peer Review

1. Ferlay J, Shin H, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer [Internet]. 2010 Jun 17 [cited 2010 Aug 26];Available from: http://www.ncbi.nlm.nih.gov/pubmed/20560135

2. Boyle P, International Agency for Research on Cancer. World cancer report 2008. Lyon: IARC Press; 2008.

3. Swerdlow S, International Agency for Research on Cancer.;World Health Organization. WHO classification of tumours of haematopoietic and lymphoid tissues. 4th ed. Lyon France: International Agency for Research on Cancer; 2008.

4. Jaffe E, World Health Organization. Pathology and genetics of tumours of haematopoietic and lymphoid tissues. Lyon ;Oxford: IARC Press ;;Oxford University Press (distributor); 2001.

5. Barrans S, Crouch S, Smith A, Turner K, Owen R, Patmore R, et al. Rearrangement of MYC is associated with poor prognosis in patients with diffuse large B-cell lymphoma treated in the era of rituximab. J. Clin. Oncol. 2010 Jul 10;28(20):3360-3365.

6. Relander T, Johnson NA, Farinha P, Connors JM, Sehn LH, Gascoyne RD. Prognostic factors in follicular lymphoma. J. Clin. Oncol. 2010 Jun 10;28(17):2902-2913.

7. Parkin DM. The evolution of the population-based cancer registry. Nat. Rev. Cancer. 2006 Aug;6(8):603-612.

8. Howell DA, Smith AG, Roman E. Lymphoma: variations in time to diagnosis and treatment. Eur J Cancer Care (Engl). 2006 Jul;15(3):272-278.

9. Howell DA, Smith AG, Roman E. Help-seeking behaviour in patients with lymphoma. Eur J Cancer Care (Engl). 2008 Jul;17(4):394-403.

10. Westlake S. Cancer incidence and mortality in the United Kingdom and constituent countries, 2004-06. Health Stat Q. 2009;(43):56-62.

11. Jemal A, Siegel R, Xu J, Ward E. Cancer Statistics, 2010. CA Cancer J Clin [Internet]. 2010 Jul 7 [cited 2010 Aug 26];Available from: http://www.ncbi.nlm.nih.gov/pubmed/20610543

12. Sant M, Allemani C, Tereanu C, De Angelis R, Capocaccia R, Visser O, et al. Incidence of hematological malignancies in Europe by morphological subtype: results of the HAEMACARE project. Blood [Internet]. 2010 Jul 27 [cited 2010 Aug 26];Available from: http://www.ncbi.nlm.nih.gov/pubmed/20664057

13. Rachet B, Ellis L, Maringe C, Chu T, Nur U, Quaresma M, et al. Socioeconomic

For Peer Review

inequalities in cancer survival in England after the NHS cancer plan. Br. J. Cancer. 2010 Aug 10;103(4):446-453.

14. Mani H, Jaffe ES. Hodgkin lymphoma: an update on its biology with new insights into classification. Clin Lymphoma Myeloma. 2009 Jun;9(3):206-216.

15. Smith A, Roman E, Howell D, Jones R, Patmore R, Jack A. The Haematological Malignancy Research Network (HMRN): a new information strategy for population based epidemiology and health service research. Br. J. Haematol. 2010 Mar;148(5):739-753.

16. Hartge P, Devesa SS. Quantification of the impact of known risk factors on time trends in non-Hodgkin's lymphoma incidence. Cancer Res. 1992 Oct 1;52(19 Suppl):5566s-5569s.

17. Adamson P, Bray F, Costantini AS, Tao M, Weiderpass E, Roman E. Time trends in the registration of Hodgkin and non-Hodgkin lymphomas in Europe. Eur. J. Cancer. 2007 Jan;43(2):391-401.

18. Bosetti C, Levi F, Ferlay J, Lucchini F, Negri E, La Vecchia C. The recent decline in mortality from Hodgkin lymphomas in central and eastern Europe. Ann. Oncol. 2009 Apr;20(4):767-774.

19. Marcos-Gragera R, Pollán M, Chirlaque MD, Gumà J, Sanchez MJ, Garau I. Attenuation of the epidemic increase in non-Hodgkin's lymphomas in Spain. Ann. Oncol. 2010 May;21 Suppl 3:iii90-96.

20. National Institute for Clinical Excellence (Great Britain). Improving outcomes in haematological cancer : the manual. London: National Institute for Clinical Excellence; 2003.

21. Sant M, Allemani C, Santaquilani M, Knijn A, Marchesi F, Capocaccia R. EUROCARE-4. Survival of cancer patients diagnosed in 1995-1999. Results and commentary. Eur. J. Cancer. 2009 Apr;45(6):931-991.

22. Alexander DD, Mink PJ, Adami H, Chang ET, Cole P, Mandel JS, et al. The non-Hodgkin lymphomas: a review of the epidemiologic literature. Int. J. Cancer. 2007;120 Suppl 12:1-39.

23. Dal Maso L, Serraino D, Franceschi S. Epidemiology of AIDS-related tumours in developed and developing countries. Eur. J. Cancer. 2001 Jul;37(10):1188-1201.

24. Magrath I. The lymphoid neoplasms. Third Magrath. London: Hodder Arnold; 2008.

25. Jarrett RF. Viruses and lymphoma/leukaemia. J. Pathol. 2006 Jan;208(2):176-186.

26. Orem J, Mbidde EK, Lambert B, de Sanjose S, Weiderpass E. Burkitt's lymphoma in Africa, a review of the epidemiology and etiology. Afr Health Sci. 2007 Sep;7(3):166-175.

27. Glaser SL, Gulley ML, Clarke CA, Keegan TH, Chang ET, Shema SJ, et al. Racial/ethnic

For Peer Review

variation in EBV-positive classical Hodgkin lymphoma in California populations. Int. J. Cancer. 2008 Oct 1;123(7):1499-1507.

28. de Sanjose S, Benavente Y, Vajdic CM, Engels EA, Morton LM, Bracci PM, et al. Hepatitis C and non-Hodgkin lymphoma among 4784 cases and 6269 controls from the International Lymphoma Epidemiology Consortium. Clin. Gastroenterol. Hepatol. 2008 Apr;6(4):451-458.

29. Parsonnet J, Hansen S, Rodriguez L, Gelb AB, Warnke RA, Jellum E, et al. Helicobacter pylori infection and gastric lymphoma. N. Engl. J. Med. 1994 May 5;330(18):1267-1271.

30. Sagaert X, Van Cutsem E, De Hertogh G, Geboes K, Tousseyn T. Gastric MALT lymphoma: a model of chronic inflammation-induced tumor development. Nat Rev Gastroenterol Hepatol. 2010 Jun;7(6):336-346.

31. Suerbaum S, Michetti P. Helicobacter pylori infection. N. Engl. J. Med. 2002 Oct 10;347(15):1175-1186.

32. Luminari S, Cesaretti M, Marcheselli L, Rashid I, Madrigali S, Maiorana A, et al. Decreasing incidence of gastric MALT lymphomas in the era of anti-Helicobacter pylori interventions: results from a population-based study on extranodal marginal zone lymphomas. Ann. Oncol. 2010 Apr;21(4):855-859.

33. Newton R, Crouch S, Ansell P, Simpson J, Willett EV, Smith A, et al. Hodgkin's lymphoma and infection: findings from a UK case-control study. Br. J. Cancer. 2007 Nov 5;97(9):1310-1314.

34. Crouch S, Simpson J, Ansell P, Kane E, Howell D, Smith A, et al. Illness patterns prior to diagnosis of lymphoma: Analysis of UK medical records. Cancer Epidemiol [Internet]. 2010 Sep 8 [cited 2010 Sep 15];Available from: http://www.ncbi.nlm.nih.gov/pubmed/20832384

35. Anderson LA, Gadalla S, Morton LM, Landgren O, Pfeiffer R, Warren JL, et al. Population-based study of autoimmune conditions and the risk of specific lymphoid malignancies. Int. J. Cancer. 2009 Jul 15;125(2):398-405.

36. Ekström Smedby K, Vajdic CM, Falster M, Engels EA, Martínez-Maza O, Turner J, et al. Autoimmune disorders and risk of non-Hodgkin lymphoma subtypes: a pooled analysis within the InterLymph Consortium. Blood. 2008 Apr 15;111(8):4029-4038.

37. Kristinsson SY, Landgren O, Sjöberg J, Turesson I, Björkholm M, Goldin LR. Autoimmunity and risk for Hodgkin's lymphoma by subtype. Haematologica. 2009 Oct;94(10):1468-1469.

38. Hansen A, Lipsky PE, Dörner T. B-cell lymphoproliferation in chronic inflammatory rheumatic diseases. Nat Clin Pract Rheumatol. 2007 Oct;3(10):561-569.

39. Franklin J, Lunt M, Bunn D, Symmons D, Silman A. Incidence of lymphoma in a large primary care derived cohort of cases of inflammatory polyarthritis. Ann. Rheum. Dis. 2006 May;65(5):617-622.

Published on behalf of the British Division of the International Academy of Pathology

For Peer Review

40. Tack GJ, Verbeek WHM, Schreurs MWJ, Mulder CJJ. The spectrum of celiac disease: epidemiology, clinical aspects and treatment. Nat Rev Gastroenterol Hepatol. 2010 Apr;7(4):204-213.

41. Ansell P, Simpson J, Lightfoot, T, Kane, E, Howell DA, Newton R, et al. Non-Hodgkin lymphoma and Autoimmunity: does gender matter? Int J Cancer. 2010;

42. Smedby KE, Hjalgrim H, Askling J, Chang ET, Gregersen H, Porwit-MacDonald A, et al. Autoimmune and chronic inflammatory disorders and risk of non-Hodgkin lymphoma by subtype. J. Natl. Cancer Inst. 2006 Jan 4;98(1):51-60.

43. Goldin LR, Landgren O. Autoimmunity and lymphomagenesis. Int. J. Cancer. 2009 Apr 1;124(7):1497-1502.

44. Smedby KE, Askling J, Mariette X, Baecklund E. Autoimmune and inflammatory disorders and risk of malignant lymphomas--an update. J. Intern. Med. 2008 Dec;264(6):514-527.

45. Hellgren K, Smedby KE, Feltelius N, Baecklund E, Askling J. Do rheumatoid arthritis and lymphoma share risk factors?: a comparison of lymphoma and cancer risks before and after diagnosis of rheumatoid arthritis. Arthritis Rheum. 2010 May;62(5):1252-1258.

46. Invernizzi P, Pasini S, Selmi C, Gershwin ME, Podda M. Female predominance and X chromosome defects in autoimmune diseases. J. Autoimmun. 2009 Aug;33(1):12-16.

47. Gleicher N, Barad DH. Gender as risk factor for autoimmune diseases. J. Autoimmun. 2007 Feb;28(1):1-6.

48. Fairweather D, Frisancho-Kiss S, Rose NR. Sex differences in autoimmune disease from a pathological perspective. Am. J. Pathol. 2008 Sep;173(3):600-609.

49. Bird MD, Karavitis J, Kovacs EJ. Sex differences and estrogen modulation of the cellular immune response after injury. Cell. Immunol. 2008 Apr;252(1-2):57-67.

50. Fish EN. The X-files in immunity: sex-based differences predispose immune responses. Nat. Rev. Immunol. 2008 Sep;8(9):737-744.

51. Boffetta P, Armstrong B, Linet M, Kasten C, Cozen W, Hartge P. Consortia in cancer epidemiology: lessons from InterLymph. Cancer Epidemiol. Biomarkers Prev. 2007 Feb;16(2):197-199.

52. Morton LM, Hartge P, Holford TR, Holly EA, Chiu BCH, Vineis P, et al. Cigarette smoking and risk of non-Hodgkin lymphoma: a pooled analysis from the International Lymphoma Epidemiology Consortium (interlymph). Cancer Epidemiol. Biomarkers Prev. 2005 Apr;14(4):925-933.

53. Morton LM, Zheng T, Holford TR, Holly EA, Chiu BCH, Costantini AS, et al. Alcohol consumption and risk of non-Hodgkin lymphoma: a pooled analysis. Lancet Oncol. 2005 Jul;6(7):469-476.

For Peer Review

54. Willett EV, Morton LM, Hartge P, Becker N, Bernstein L, Boffetta P, et al. Non-Hodgkin lymphoma and obesity: a pooled analysis from the InterLymph Consortium. Int. J. Cancer. 2008 May 1;122(9):2062-2070.

55. Kricker A, Armstrong BK, Hughes AM, Goumas C, Smedby KE, Zheng T, et al. Personal sun exposure and risk of non Hodgkin lymphoma: a pooled analysis from the Interlymph Consortium. Int. J. Cancer. 2008 Jan 1;122(1):144-154.

56. Vajdic CM, Falster MO, de Sanjose S, Martínez-Maza O, Becker N, Bracci PM, et al. Atopic disease and risk of non-Hodgkin lymphoma: an InterLymph pooled analysis. Cancer Res. 2009 Aug 15;69(16):6482-6489.

57. Wang SS, Slager SL, Brennan P, Holly EA, De Sanjose S, Bernstein L, et al. Family history of hematopoietic malignancies and risk of non-Hodgkin lymphoma (NHL): a pooled analysis of 10 211 cases and 11 905 controls from the International Lymphoma Epidemiology Consortium (InterLymph). Blood. 2007 Apr 15;109(8):3479-3488.

58. Skibola CF, Bracci PM, Nieters A, Brooks-Wilson A, de Sanjosé S, Hughes AM, et al. Tumor necrosis factor (TNF) and lymphotoxin-alpha (LTA) polymorphisms and risk of non-Hodgkin lymphoma in the InterLymph Consortium. Am. J. Epidemiol. 2010 Feb 1;171(3):267-276.

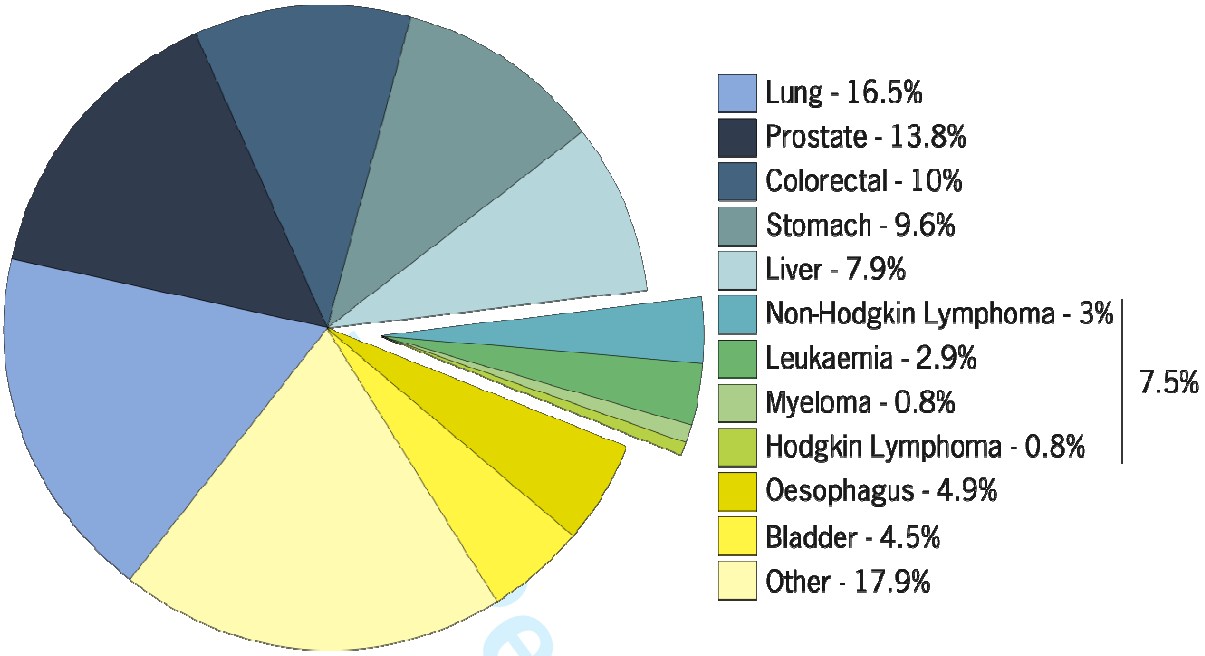
59. Rothman N, Skibola CF, Wang SS, Morgan G, Lan Q, Smith MT, et al. Genetic variation in TNF and IL10 and risk of non-Hodgkin lymphoma: a report from the InterLymph Consortium. Lancet Oncol. 2006 Jan;7(1):27-38.

For Peer Review

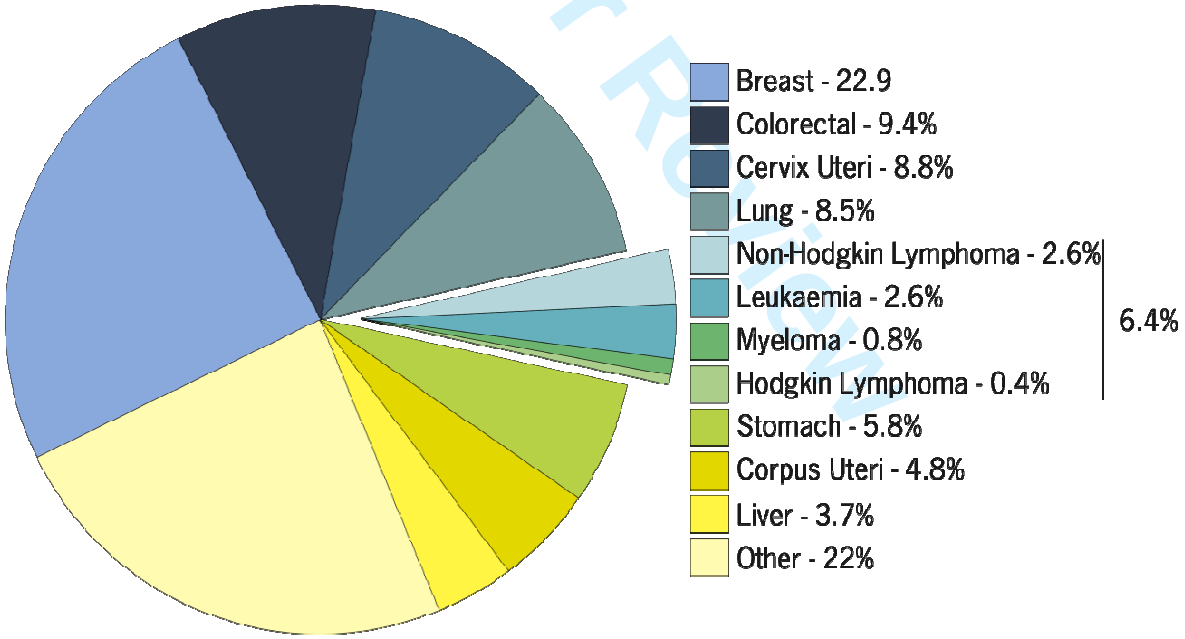
Published on behalf of the British Division of the International Academy of Pathology

Figure 1 Estimated global cancer frequency for a) males and b) females (Source GLOBOCAN)

a) Males

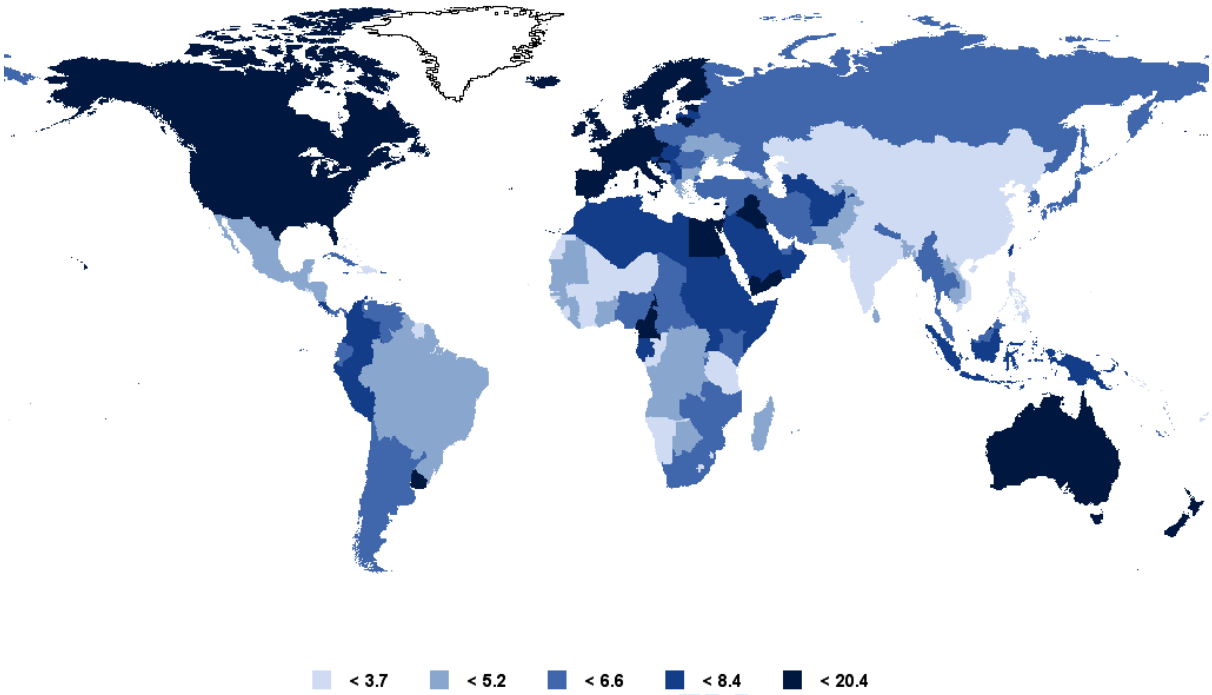


b) females



Peer Review

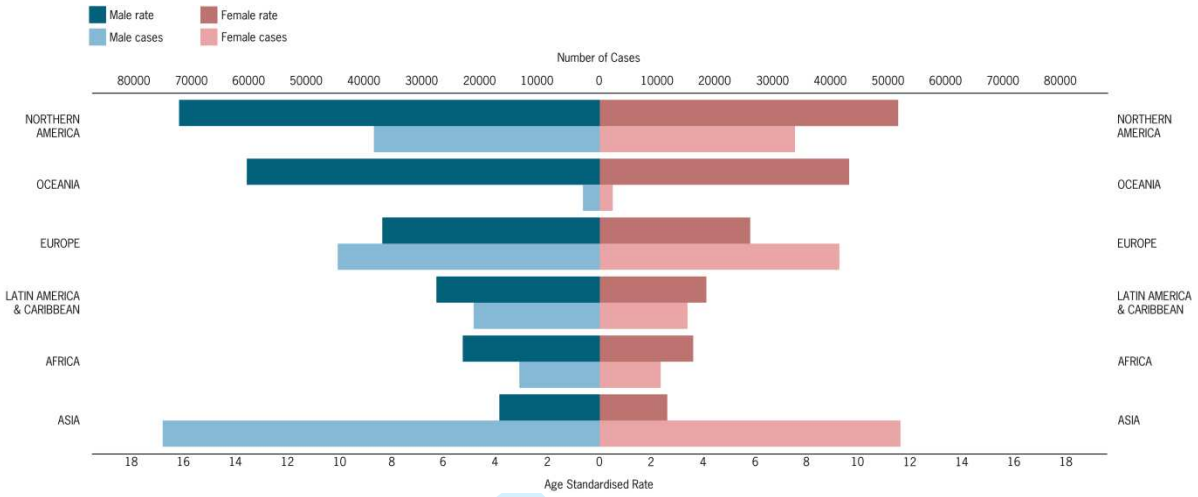
Figure 2 Estimated age-standardized (world) incidence rates for non-Hodgkin lymphoma (NHL) and Hodgkin lymphoma (HL) combined (Source GLOBOCAN)



eview

Figure 3 Estimated numbers and age-standardized (world) incidence rates by region for a) non-Hodgkin lymphoma (NHL) and b) Hodgkin lymphoma (HL) (Source GLOBOCAN)

a)



b)

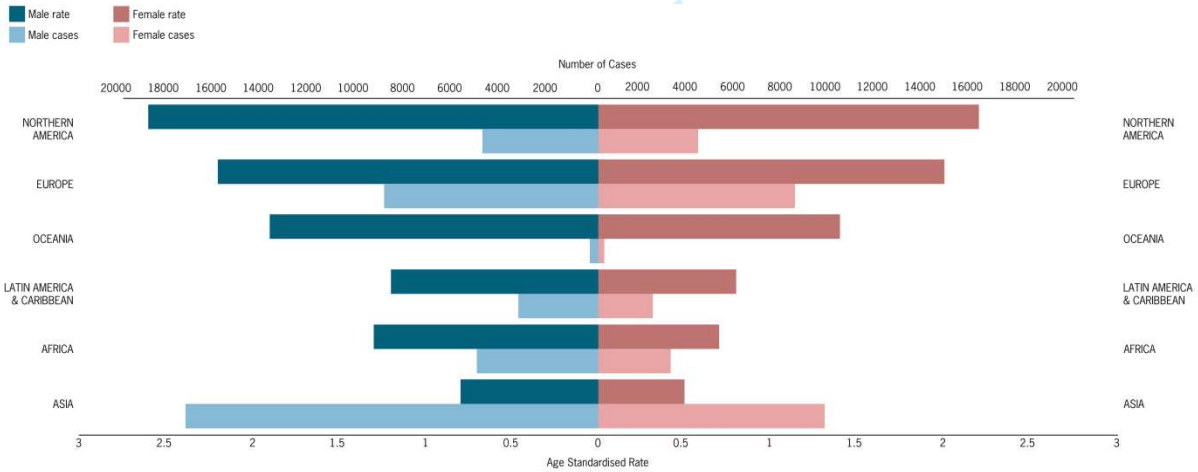
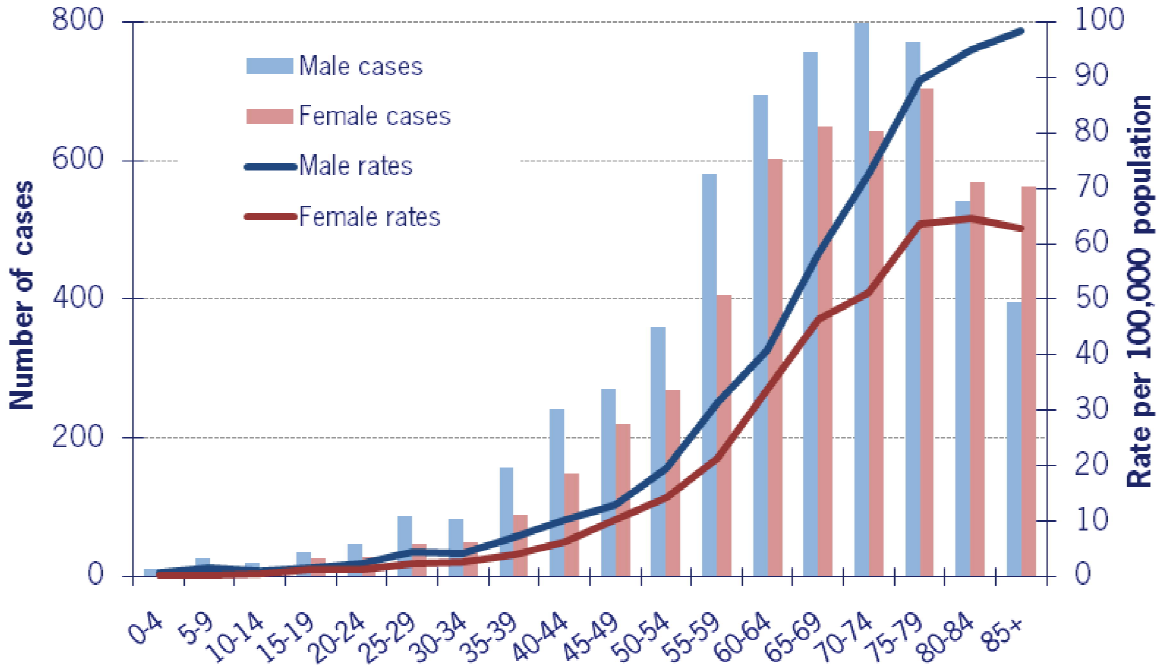


Figure 4 Numbers of new cases and age specific incidence rates, by sex, a) non-Hodgkin lymphoma and b) Hodgkin lymphoma, UK 2007

a)



b)

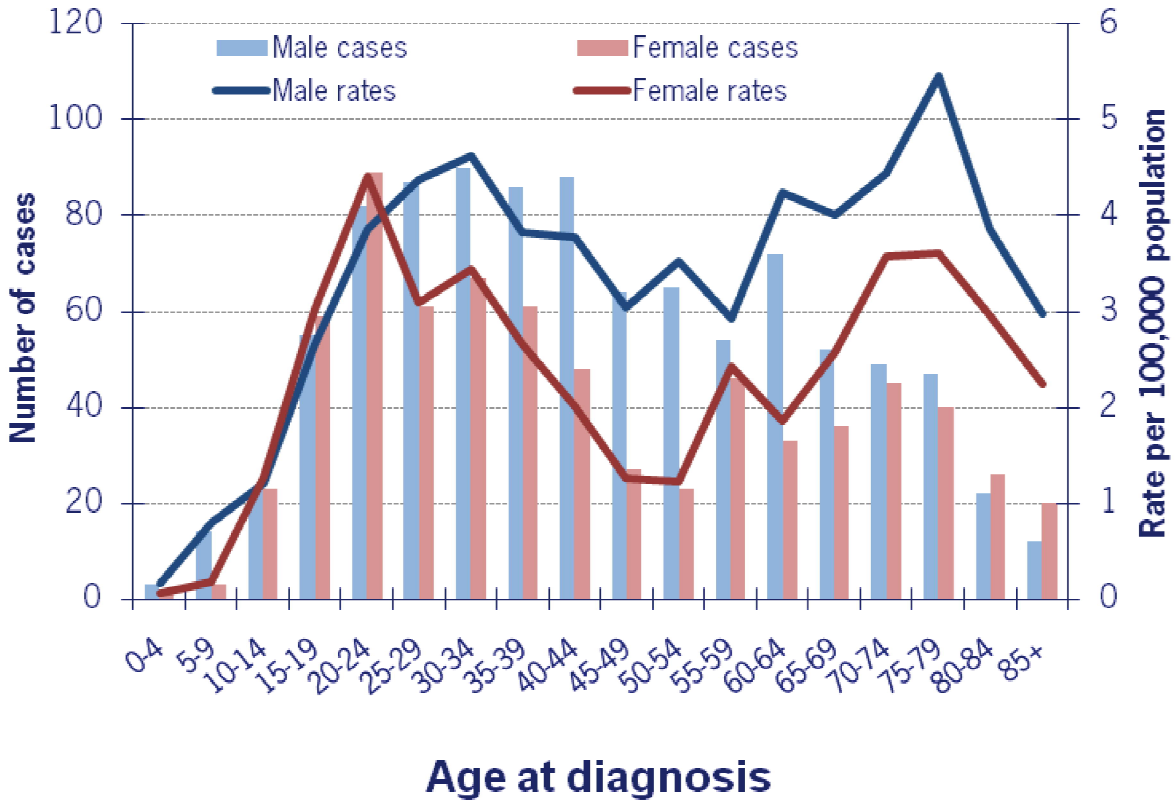
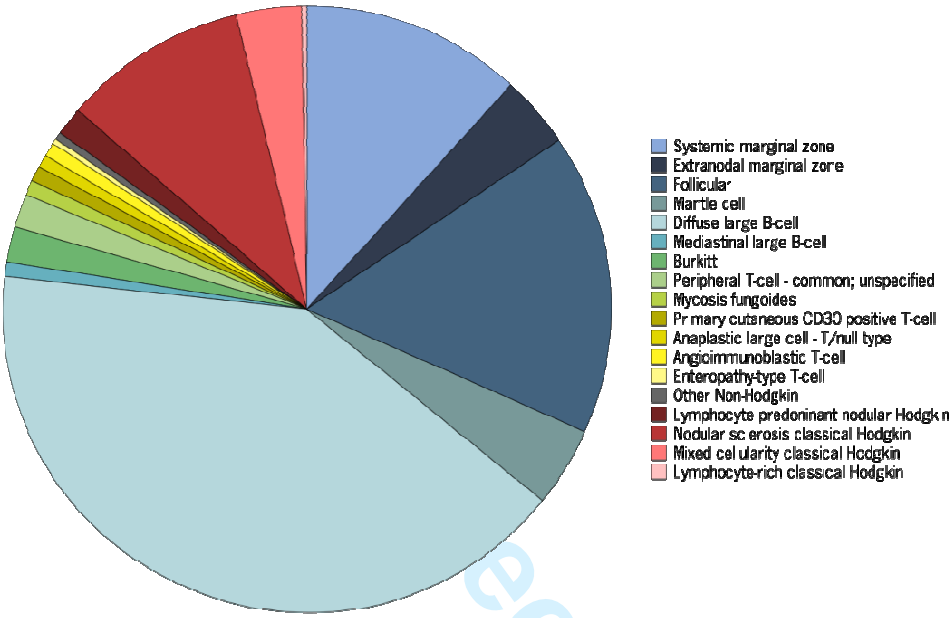
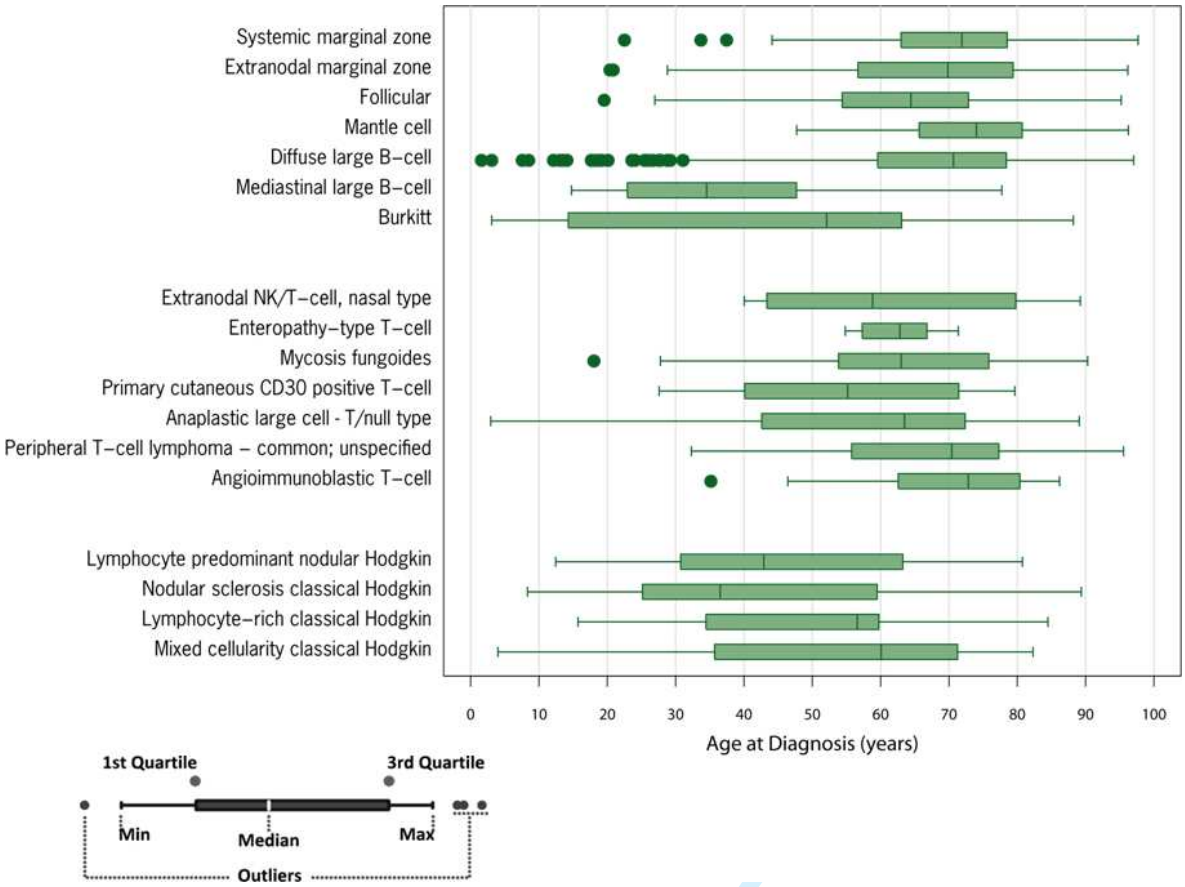


Figure 5 Lymphoma sub-type frequencies 2004-2009 (Source Haematological Malignancy Research Network (HMRN)



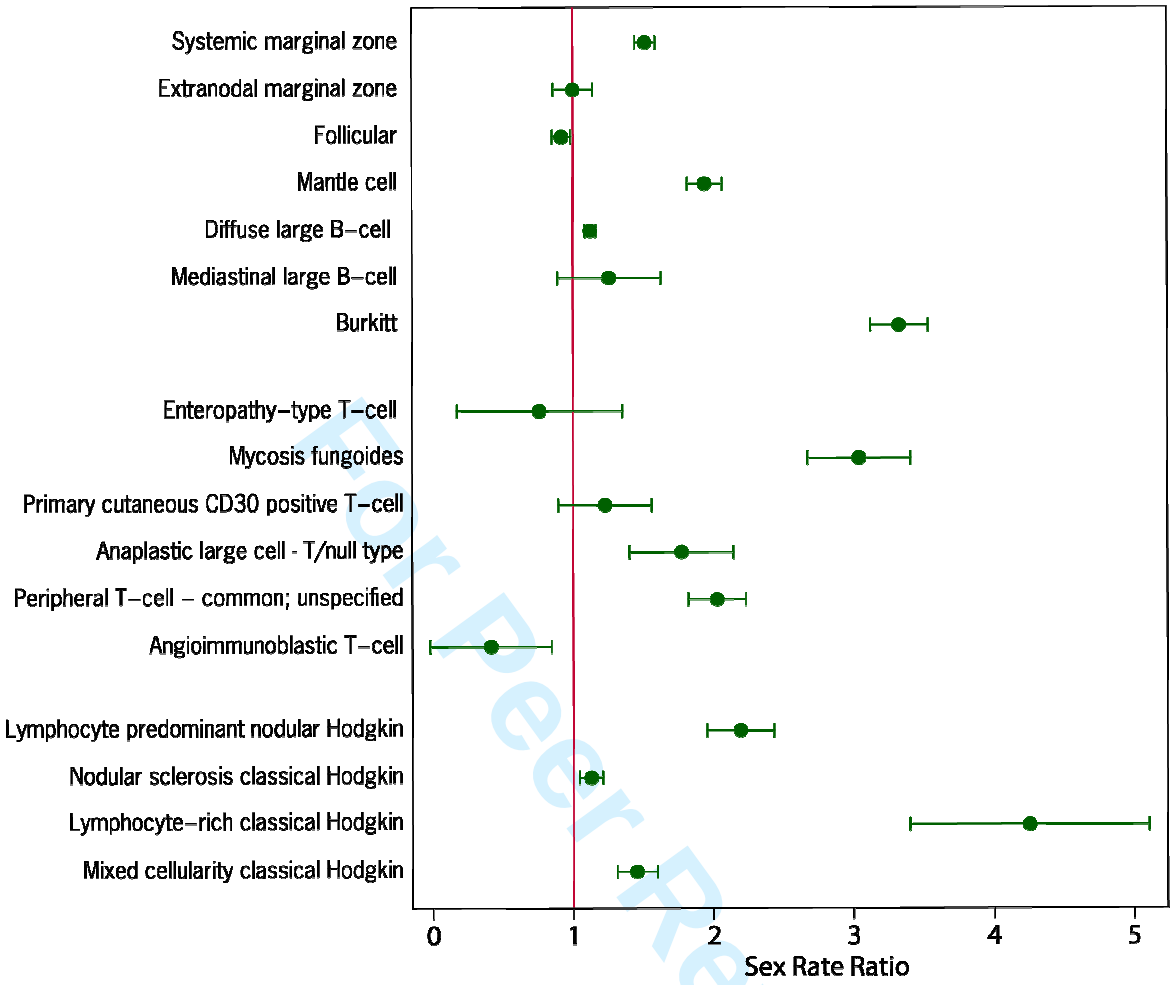
eer Review

Figure 6 Lymphoma age at diagnosis distributions 2004-2009 (Source Haematological Malignancy Research Network)



view

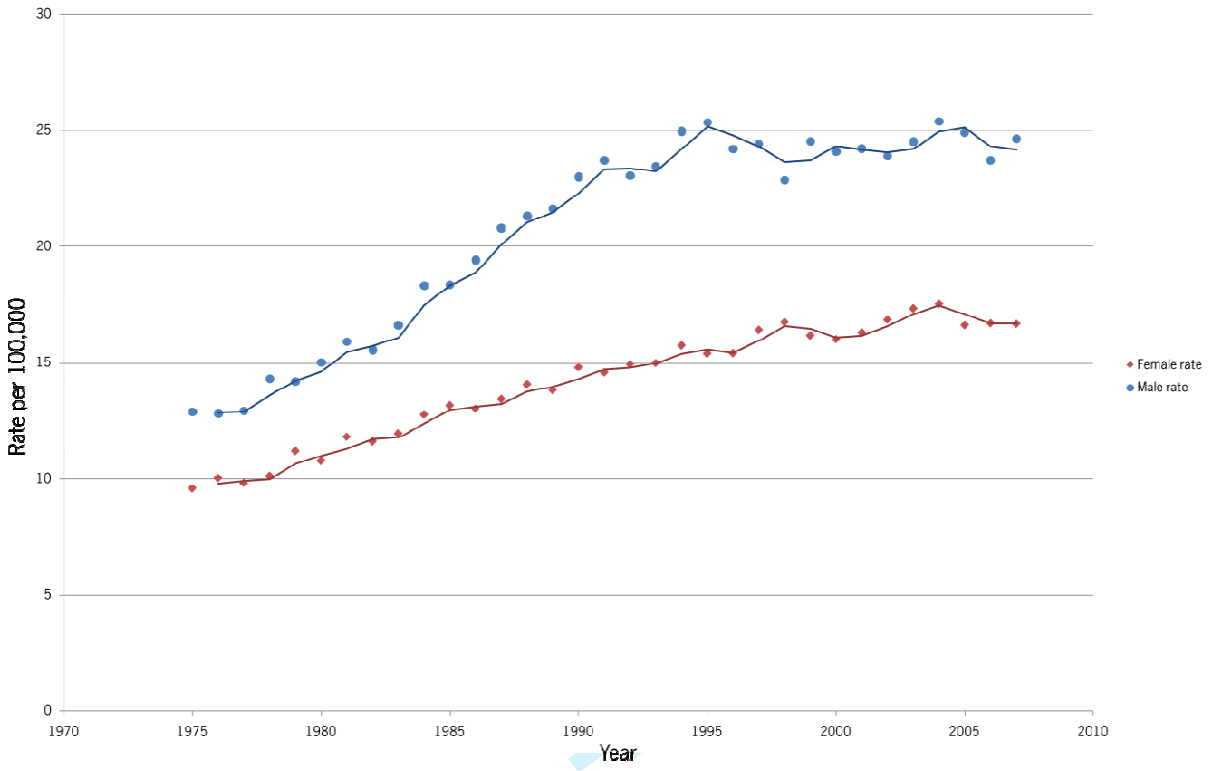
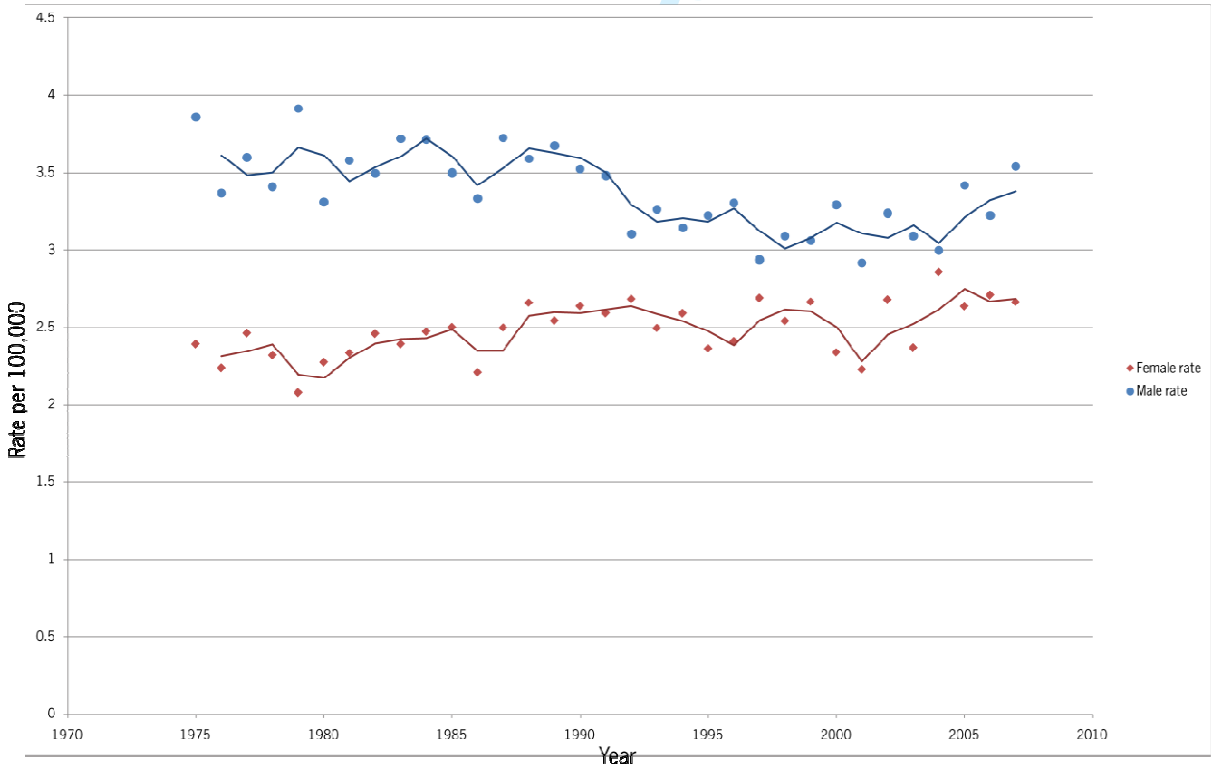
Figure 7 Lymphoma sex-rate ratios and standard errors 2004-2009 (Source Haematological Malignancy Research Network)



For Peer Review

Figure 8 Age standardized (US 2000 population) incidence rates for a) non-Hodgkin lymphoma and b) Hodgkin lymphoma (Source SEER)

a)



b)