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Keywords: epidemiology; lymphoma; non-Hodgkin; Hodgkin; lymphoproliferative; cancer registration

Lymphoma incidence, survival and prevalence 2004–2014: sub-type analyses from the UK's Haematological Malignancy Research Network

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Background: Population-based information about cancer occurrence and survival are required to inform clinical practice and research; but for most lymphomas data are lacking.

Methods: Set within a socio-demographically representative UK population of nearly 4 million, lymphoma data ($N=5796$) are from an established patient cohort.

Results: Incidence, survival (overall and relative) and prevalence estimates for >20 subtypes are presented. With few exceptions, males tended to be diagnosed at younger ages and have significantly ($P<0.05$) higher incidence rates. Differences were greatest at younger ages: the <15 year male/female rate ratio for all subtypes combined being 2.2 (95% CI 1.3–3.4). These gender differences impacted on prevalence; most subtype estimates being significantly ($P<0.05$) higher in males than females. Outcome varied widely by subtype; survival of patients with nodular lymphocyte predominant Hodgkin lymphoma approached that of the general population, whereas less than a third of those with other B-cell (e.g., mantle cell) or T-cell (e.g., peripheral-T) lymphomas survived for ≥ 5 years. No males/female survival differences were detected.

Conclusions: Major strengths of our study include completeness of ascertainment, world-class diagnostics and generalisability. The marked variations demonstrated confirm the requirement for 'real-world' data to inform aetiological hypotheses, health-care planning and the future monitoring of therapeutic changes.

The lymphomas comprise a heterogeneous group of cancers with diverse aetiologies, treatment pathways and outcomes (Swerdlow *et al*, 2008; Campo *et al*, 2011). Critically for research, appreciation of the similarities and differences between the various sub-types only surfaced in recent decades as biological understanding about the relationship between these complex malignancies, the bone marrow, the immune system and the cellular and genetic basis of malignant transformation increased (Harris *et al*, 2000; Jaffe *et al*, 2001; Swerdlow *et al*, 2008; Jaffe, 2009; Campo *et al*, 2011). Even now, this area of oncology remains one of the most rapidly

evolving fields; with developments in genomics, diagnostic technologies and targeted therapies meaning that existing lymphoma definitions are continually subject to change (Puvvada *et al*, 2013; Dunleavy and Wilson, 2014; O'Connor and Tobinai, 2014).

The pace and recency of scientific advances, coupled with the breadth of laboratory investigations required to make an accurate diagnosis, mean that dependable comprehensive population-based information about the underlying patterns of incidence and survival of clinically meaningful lymphoma subtypes is limited (Morton *et al*, 2006; Sant *et al*, 2010, 2014; Marcos-Gragera *et al*, 2011;

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Smith *et al*, 2011; Olszewski and Castillo, 2013; Nabhan *et al*, 2014). Such ‘real-world’ data are, however, required not only to inform aetiological hypotheses and plan future health-care services, but also to monitor the impact of therapeutic changes in the general patient population. This need is particularly pertinent in fast-moving areas like haematological oncology where treatment protocols are subject to rapid change, and ‘gold standard’ randomised controlled trials are invariably restricted to specific patient sub-groups; often younger patients with fewer co-morbidities (Rothwell, 2005, 2010; Elting *et al*, 2006; Janson *et al*, 2009; Al-Refaie *et al*, 2011; Freemantle *et al*, 2013; Van de Water *et al*, 2014). Furthermore in some countries, particularly those where universal health-care coverage is lacking, the likelihood of trial participation usually varies with socio-economic status, gender and ethnicity (Murthy *et al*, 2004; Penberthy *et al*, 2012; Kwiatkowski *et al*, 2013; Mohd Noor *et al*, 2013; Unger *et al*, 2013). Such biases impact on the external validity of experimental treatment trials; and ‘real-world’ observational data are increasingly being used to provide context and evaluate treatment effectiveness across the whole patient population (Sehn *et al*, 2005; Armstrong, 2012; Hershman and Wright, 2012; Kodeda *et al*, 2013; Tripathy *et al*, 2013; Smith *et al*, 2014).

In the case of lymphomas, an added dimension is provided by the fact that the pathways of patients diagnosed with incurable but comparatively indolent subtypes, such as follicular lymphoma and marginal zone lymphoma, may begin with a period of ‘active-monitoring/watch and wait’. The resulting patient pathways can be complex and diverse, with individual patients differing widely in their need for, and response to, different treatment regimens; some having long periods of observation, and others having multiple courses of chemotherapy (Dreyling *et al*, 2013, 2014; Michallet *et al*, 2013). In such a circumstance, extrapolating survival data derived from specific treatment trials to the general patient population is problematic and may result in misleading estimates. In addition, depending on the data feeds used for case ascertainment, the fact that some lymphoma patients are not treated can pose further challenges for cancer registries, and the frequency estimates (incidence and prevalence) they produce.

The UK’s population-based Haematological Malignancy Research Network (HMRN) was specifically established in 2004 to address the needs outlined above, by producing ‘real-time’ generalisable data that would inform contemporary clinical practice and research (Smith *et al*, 2010). With nearly 4 million people, representing 6% of the UK population, the socio-demographic composition (age, gender, deprivation) of the regional population mirrors that of the UK as a whole. All diagnoses (> 2200 a year) are made and coded by clinical specialists working within a single integrated haematopathology laboratory, irrespective of the patient’s age, treatment intent, or management within the National Health Service or private sector (Smith *et al*, 2011). With its emphasis on completeness and utilisation of primary-source information, HMRN’s data are increasingly being used to provide ‘gold-standard’ information to facilitate decision making (NCIN/ECSG, 2014; NICE, 2014). The present paper reports incidence, survival and prevalence estimates on over 20 lymphoma subtypes traditionally categorised topographically as being either Hodgkin or non-Hodgkin (World Health Organization, 1992). Providing the best available up-to-date population-based information, the lymphomas included were diagnosed over the period 2004–2012 and followed-up through to March 2014.

METHODS

Data are from the UK’s population-based Haematological Malignancy Research Network (www.hmrn.org). Initiated in

2004, full details of its structure, data collection methods and ethical approvals have been previously described (Smith *et al*, 2010). Briefly, within HMRN, patient care is provided by 14 hospitals organised into five multi-disciplinary teams; and clinical practice adheres to national guidelines. As a matter of policy, all diagnoses are made and coded by clinical specialists at a single integrated haematopathology laboratory—the Haematological Malignancy Diagnostic Service (www.hmds.info); cited in the UK’s Department of Health’s Cancer Reform Strategy (2007) as ‘the model for delivery of complex diagnostic services’. HMRN has Section 251 support under the NHS Act 2006, and all patients have full-treatment, response and outcome data collected to clinical trial standards; all are ‘flagged’ for death and subsequent cancer registrations at the national Medical Research Information Service (MRIS) and routinely linked to nationwide information on Hospital Episode Statistics.

For analytical purposes, area-based population counts were sourced from the Office National Statistics (Office for National Statistics, 2001). All analyses were conducted either in the statistical package Stata 12 (Stata-Corp, 2011) or R (R Core Team, 2013). Incidence rates and their 95% confidence intervals (CIs) were estimated by Poisson regression. Directly age-standardised rates (European) were calculated using the Stata command ‘dstdize’ and corresponding standardised sex rate ratios and their 95% confidence intervals were estimated (Jensen, 1991). The overall survival was calculated using standard time to event analyses and the program *strel* (v1.2.7) was used to estimate relative survival; age- and sex-specific background mortality rates were obtained from national life tables (Cancer Research UK, 2006). Prevalence estimates (3, 5 and 10 year) and corresponding confidence intervals were calculated from incidence and survival data using R’s ‘survival’ and ‘rms’ libraries; 3 and 5 year estimates were calculated directly from the patient cohort, and Monte-Carlo simulation techniques were employed to generate the larger 10-year values (Crouch *et al*, 2014).

RESULTS

The 5796 lymphomas diagnosed September 2004 to August 2012 are distributed by sub-type and gender in Table 1; with frequencies and median ages at diagnosis being given for subtypes that had 10 or more diagnoses during the 8-year period. The traditional categories of non-Hodgkin and Hodgkin are shown first, followed by the more meaningful cell-of-origin groupings. Mature B-cell malignancies, which comprise around 94.7% ($N=5488$) of the total, occurred far more frequently than the rarer T-cell subtypes ($N=308$); with diffuse large B-cell lymphoma accounting for around 4 out of 10 lymphoma diagnoses, followed by the more indolent follicular and marginal zone subtypes, which when combined accounted for a further 3 out of 10 lymphoma diagnoses.

As with many other cancers, the likelihood of an individual being diagnosed with lymphoma increases markedly with age, the median age at diagnosis being 67.2 years (interquartile range 54.9–76.5 years) for all patients combined (Table 1). However, unlike many other cancers, some lymphomas can be diagnosed at any age, with different subtypes dominating at different ages, as can be seen more clearly in Figures 1 and 2: Figure 1 showing the age-specific rates of the main subtypes, and Figure 2 the corresponding distribution within age classes. Hodgkin and Burkitt lymphomas dominate the paediatric age range (< 15 years), where there were no cases of follicular lymphoma (youngest patient 19 years), marginal zone lymphoma (youngest patient 20 years), or mantle cell lymphoma (youngest patient 39 years) within our population. By contrast, in those aged 60 years or more, diffuse large B-cell, marginal-zone and follicular lymphomas accounted for over 80%

Table 1. Lymphoma numbers and median ages (IQR) at diagnosis: Haematological Malignancy Research Network (HMRN) 2004–2012

	Total diagnoses		Males		Females		P Median age difference (male versus female)
	No (%)	Median age (IQR)	No (%)	Median age (IQR)	No (%)	Median age (IQR)	
All lymphomas	5796 (100)	67.2 (54.9–76.5)	3086 (100)	66.0 (53.1–75.4)	2710 (100)	68.8 (56.7–77.7)	0.001
Non-Hodgkin	4961 (85.6)	69.1 (58.9–77.6)	2614 (84.7)	67.9 (57.9–76.5)	2347 (86.6)	70.5 (60.7–78.5)	0.001
Hodgkin	835 (14.4)	41.3 (26.8–63.5)	472 (15.3)	42.0 (27.7–61.5)	363 (13.4)	39.6 (26.0–65.8)	0.358
B-cell	5488 (94.7)	67.4 (55.1–76.6)	2914 (94.4)	66.1 (53.4–75.5)	2574 (95.0)	68.9 (56.9–77.7)	0.001
DLBCL	2373 (40.9)	70.0 (59.6–78.2)	1243 (40.3)	68.4 (58.0–76.9)	1130 (41.7)	71.4 (61.4–79.6)	0.001
DLBCL, NOS	2312 (39.9)	70.0 (59.7–78.2)	1208 (39.1)	68.4 (58.4–77.0)	1104 (40.7)	71.4 (61.3–79.5)	0.001
T-cell/histiocyte-rich	32 (0.6)	65.5 (52.7–77.3)	17 (0.6)	59.8 (44.1–74.4)	15 (0.6)	71.3 (61.5–78.9)	0.188
Plasmablastic	24 (0.4)	70.9 (54.4–78.2)	15 (0.5)	69.2 (53.4–75.1)	9 (0.3)	76.0 (68.4–81.5)	0.482
MZL	983 (17.0)	72.4 (63.8–79.2)	537 (17.4)	71.2 (63.5–78.6)	446 (16.5)	73.4 (64.1–79.5)	0.021
Systemic MZL	772 (13.3)	72.9 (65.3–79.4)	434 (14.1)	72.2 (64.6–79.2)	338 (12.5)	73.7 (66.2–79.8)	0.117
Extranodal MZL	211 (3.6)	68.8 (57.2–77.8)	103 (3.3)	66.5 (55.8–76.9)	108 (4.0)	72.4 (57.9–79.4)	0.017
FL	923 (15.9)	64.9 (55.8–73.3)	412 (13.4)	63.1 (55.0–72.8)	511 (18.9)	66.3 (56.5–73.8)	0.001
Follicular	897 (15.5)	65.0 (55.9–73.3)	397 (12.9)	63.2 (55.4–72.8)	500 (18.5)	66.4 (56.6–73.8)	0.001
Follicular, large cell	26 (0.4)	58.5 (50.0–71.9)	15 (0.5)	59.6 (44.4–74.9)	11 (0.4)	57.4 (52.2–71.3)	0.805
MCL	247 (4.3)	73.5 (64.3–80.3)	159 (5.2)	71.0 (61.2–78.9)	88 (3.2)	75.8 (67.3–82.6)	0.006
BL	103 (1.8)	52.2 (16.9–64.8)	76 (2.5)	39.4 (12.1–63.9)	27 (1.0)	56.8 (38.9–69.2)	0.026
Intermediate DLBCL/CHL ^a	24 (0.4)	59.3 (34.2–72.1)	15 (0.5)	54.5 (26.2–66.0)	9 (0.3)	71.8 (55.8–77.9)	0.212
CHL	737 (12.7)	40.9 (26.3–64.1)	400 (13.0)	42.0 (27.3–62.8)	337 (12.4)	38.1 (25.7–65.6)	0.144
Nodular sclerosis CHL	545 (9.4)	37.0 (25.0–59.4)	283 (9.2)	39.5 (25.6–59.4)	262 (9.7)	33.9 (24.5–59.5)	0.006
Mixed cellularity CHL	173 (3.0)	59.2 (36.1–70.6)	102 (3.3)	53.2 (34.3–69.2)	71 (2.6)	65.4 (40.5–72.5)	0.004
Lymphocyte-rich CHL	18 (0.3)	49.3 (35.9–59.7)	14 (0.5)	47.8 (34.5–57.7)	4 (0.1)	59.4 (51.5–61.9)	0.195
Lymphocyte predominant nodular HL	98 (1.7)	43.6 (29.9–59.1)	72 (2.3)	41.6 (30.3–55.7)	26 (1.0)	55.2 (27.2–65.9)	0.096
T-cell	308 (5.3)	65.1 (51.8–74.8)	172 (5.6)	63.9 (49.1–73.6)	136 (5.0)	68.3 (54.4–76.6)	0.070
Peripheral—common, unspecified	91 (1.6)	68.5 (52.9–77.2)	57 (1.8)	65.9 (49.8–73.9)	34 (1.3)	71.6 (59.1–81.7)	0.295
Angioimmunoblastic	55 (0.9)	71.9 (61.6–78.4)	20 (0.6)	67.7 (55.2–75.9)	35 (1.3)	72.9 (64.6–80.1)	0.281
Anaplastic large cell	46 (0.8)	59.2 (41.3–74.3)	28 (0.9)	54.0 (40.1–73.4)	18 (0.7)	63.5 (43.2–75.7)	0.334
ALK-negative	27 (0.5)	69.0 (57.4–81.6)	15 (0.5)	72.4 (61.0–77.6)	12 (0.4)	64.4 (54.4–86.5)	0.407
ALK-positive	16 (0.3)	35.6 (24.3–43.9)	12 (0.4)	39.7 (27.3–44.4)	4 (0.1)	25.5 (15.3–36.6)	0.275
Mycosis fungoides	39 (0.7)	65.8 (53.9–75.8)	28 (0.9)	67.0 (53.8–76.0)	11 (0.4)	63.0 (54.8–70.6)	0.513
Primary cutaneous CD30+ LPD	37 (0.6)	52.9 (39.4–70.5)	19 (0.6)	61.5 (39.0–73.1)	18 (0.7)	49.3 (39.4–62.6)	0.233
Enteropathy-type	24 (0.4)	62.7 (58.6–68.1)	13 (0.4)	61.6 (58.0–64.0)	11 (0.4)	65.0 (60.6–71.4)	0.343

Abbreviations: ALK = anaplastic lymphoma kinase; BL = Burkitt lymphoma; CHL = classical Hodgkin lymphoma; DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; IQR = interquartile range; LPD = lymphoproliferative disorders; MCL = mantle cell lymphoma; MZL = marginal zone lymphoma; NOS = not otherwise specified.

^aCases classified 2009–2012 only.

of diagnoses, and the common childhood lymphomas only occurred occasionally. As with B-cell lymphomas, the rarer T-cell lymphomas span the full age range, but again there is considerable heterogeneity by subtype (Table 1): the median age of patients with ALK-positive anaplastic T-cell lymphoma being 35.6 (IQR 24.3–43.9) and those with angioimmunoblastic T-cell lymphoma being 71.9 years (IQR 61.6–78.4).

In general, males tend to be diagnosed with B-cell lymphomas at younger ages than females (Table 1) and, with one or two exceptions, experience higher rates of disease at all ages; the male/female sex rate ratio (Figure 2) being highest in those diagnosed before the age of 15 years (2.2; 95% CI 1.3–3.4). Indeed, as is evident from Table 2, males are almost three times as likely to develop some B- and T-cell cancer subtypes: the European age standardised sex-rate ratios being 2.57 (95% CI 2.3–2.88), 2.95 (95% CI 2.3–3.78), 3.49 (95% CI 1.53–7.97) and 2.96 (95% CI 2.28–3.84), respectively, for mantle cell, Burkitt, lymphocyte-rich classical Hodgkin and lymphocyte predominant nodular Hodgkin (B-cell lymphomas); and 2.97 (95% CI

1.12–7.89) and 2.69 (95% CI 1.62–4.46), respectively, for ALK-positive anaplastic large cell and mycosis fungoides (T-cell lymphomas).

Amongst the lymphomas, there are marked outcome differences by subtype, as is evident from the 5-year overall and relative survival estimates given in Table 3 and the survival curves shown for the eight main B-cell lymphoma categories in Figure 3. At one extreme, the survival of patients with nodular lymphocyte predominant Hodgkin lymphoma approaches that of the general population (Figure 3); and with no deaths among women in the follow-up period, gender-specific data are not presented in Table 3. By contrast, around three-quarters of patients with mantle cell lymphoma die within 5 years of their diagnosis; the similarity between the overall and relative survival curves confirming that most patients with this cancer die from their disease. With respect to differences between males and females, no statistically significant differences are evident either for overall or relative survival; the sex-specific relative survival estimates, which take account of the fact that women tend to live longer than men,

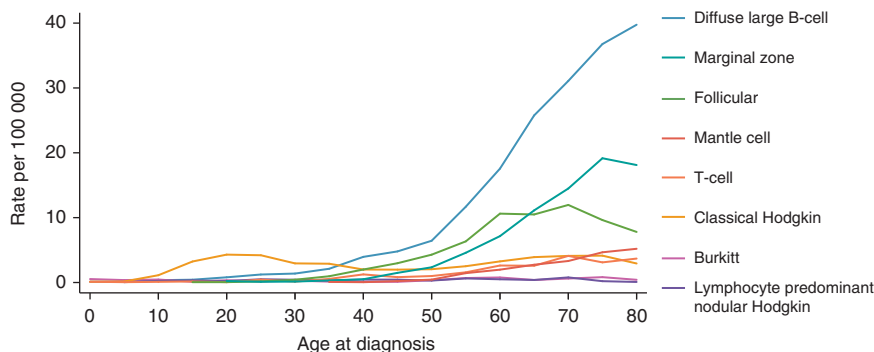


Figure 1. Age-specific rates per 100 000 by subtype: Haematological Malignancy Research Network (HMRN) 2004–2012.

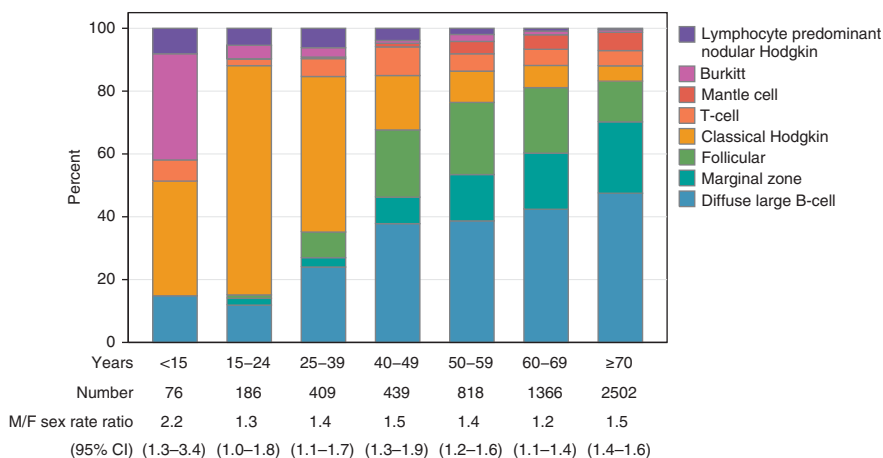


Figure 2. Numbers of cases and sex-rate ratios by sub-type and age: Haematological Malignancy Research Network (HMRN) 2004–2012.

tending to be more similar to each other than the overall survival estimates (Table 3).

Prevalence estimates (3, 5 and 10 year) generated from incidence and survival data are given for the main lymphoma subtypes in Table 4; and the sex-specific estimates of the main B-cell lymphoma subtypes are shown side-by-side in Figure 4. Data for lymphocyte predominant nodular Hodgkin lymphoma are not shown because the numbers of deaths were too few to generate reliable estimates. For all lymphomas combined, prevalence ranged from 48.0 (95% CI 45.8–50.3) per 100 000 population within 3 years of diagnosis, through to 72.5 (95% CI 69.7–75.3) per 100 000 within 5 years and 123.7 (95% CI 120.0–127.4) within 10 years. For some lymphomas, such as diffuse large B-cell lymphoma where the corresponding 3-, 5- and 10-year point estimates are 17.6, 25.9 and 43.3 per 100 000, respectively, the prevalent pools will contain individuals who have been cured of their cancer; the proportion falling as the time-frame lengthens. On the other hand, for chronic incurable lymphomas like follicular lymphoma where the 3, 5 and 10 year estimates are 9.7, 14.8 and 25.2, respectively, the prevalent pools will be comprised of individuals who are either being actively monitored or who are receiving treatment for their disease.

The male to female prevalence differences evident in Table 4 and Figure 4, are largely due to differences in both age at diagnosis and underlying incidence patterns: males tend to be diagnosed at younger ages (Table 1) and have higher disease incidence levels (Table 2). Given these, it is perhaps not surprising that, with the exception of follicular lymphoma, the 3, 5 and 10 year prevalence estimates for males tend to be higher than those of females across all main subtypes; resulting in 10-year prevalence estimates for all lymphomas combined of 138.3 (95% CI 132.7–144.0) and 109.9 (95% CI 105.1–114.8) per 100 000 for males and females

respectively—a difference of almost 30 per 100 000. It is also important to note that these differences are not due to differential survival: the 5-year relative survival estimates for all lymphomas combined being 67.2 (95% CI 65.0–69.2) and 67.8 (95% CI 65.5–69.9) respectively (Table 3).

DISCUSSION

This paper presents contemporary sex-specific incidence, prevalence and survival estimates for more than 20 lymphoma subtypes, providing much needed ‘real-world’ data to better inform practitioners and researchers. To our knowledge, this is the first time that reliable population-based occurrence and survival estimates for several clinically meaningful lymphoma subtypes have been presented side-by-side. The benefits of this are immediately apparent. Within categories that are often lumped together, outcome varied markedly from one subtype to another; patients with some disease subtypes tending to have near normal lifespan, whereas those with others often died rapidly from their disease. Furthermore, strong differences between males and females were observed with respect to subtype incidence and prevalence frequencies, as well as age at cancer onset. Such differences have clear implications not only for aetiological hypotheses and clinical practice, but also for health service planning.

With respect to descriptive patterns, mature B-cell neoplasms dominated our data; the commonest subtype being diffuse large B-cell lymphoma (median diagnostic age 70.0 years), which accounted for 40% of the total, and the rarest T-cell ALK-positive

Table 2. Lymphoma crude and age standardised (European) incidence rates per 100 000 (95% confidence interval): Haematological Malignancy Research Network (HMRN) 2004–2012

	Total Diagnoses		Males		Females		Age std. sex rate ratio (M/F)	P M/F age std rate difference
	Annual rate (95% CI) per 100 000		Annual rate (95% CI) per 100 000		Annual rate (95% CI) per 100 000			
	Crude	Age standardised (European)	Crude	Age standardised (European)	Crude	Age standardized (European)		
All lymphomas	20.29 (19.77–20.82)	16.84 (16.68–17.00)	22.3 (21.52–23.10)	19.95 (19.7–20.2)	18.40 (17.71–19.11)	14.29 (14.08–14.49)	1.40 (1.37–1.42)	<0.0001
Non-Hodgkin	17.37 (16.89–17.86)	14.01 (13.87–14.16)	18.89 (18.17–19.63)	16.63 (16.4–16.85)	15.93 (15.3–16.59)	11.92 (11.74–12.11)	1.39 (1.37–1.42)	<0.0001
Hodgkin	2.92 (2.73–3.13)	2.83 (2.70–2.90)	3.41 (3.11–3.73)	3.32 (3.21–3.43)	2.46 (2.22–2.73)	2.36 (2.27–2.45)	1.41 (1.34–1.48)	<0.0001
B-cell	19.21 (18.71–19.73)	15.92 (15.77–16.08)	21.06 (20.3–21.83)	18.82 (18.57–19.06)	17.48 (16.81–18.16)	13.56 (13.36–13.75)	1.39 (1.36–1.42)	<0.0001
DLBCL	8.31 (7.98–8.65)	6.60 (6.60–6.70)	8.98 (8.49–9.50)	7.85 (7.69–8.01)	7.67 (7.23–8.13)	5.60 (5.47–5.73)	1.40 (1.36–1.45)	<0.0001
DLBCL, NOS	8.09 (7.77–8.43)	6.43 (6.33–6.53)	8.73 (8.24–9.24)	7.63 (7.47–7.79)	7.50 (7.06–7.95)	5.48 (5.36–5.60)	1.39 (1.35–1.44)	<0.0001
T-cell/histiocyte-rich	0.30 (0.20–0.42)	0.10 (0.07–0.12)	0.33 (0.19–0.52)	0.12 (0.07–0.17)	0.27 (0.15–0.45)	0.08 (0.05–0.11)	1.52 (0.82–2.81)	0.183
Plasmablastic	0.11 (0.07–0.17)	0.07 (0.05–0.09)	0.11 (0.06–0.18)	0.10 (0.06–0.14)	0.12 (0.06–0.23)	0.04 (0.02–0.06)	2.44 (1.22–4.90)	0.012
MZL	3.44 (3.23–3.66)	2.62 (2.56–2.68)	3.88 (3.56–4.22)	3.30 (3.20–3.41)	3.03 (2.75–3.32)	2.11 (2.03–2.19)	1.56 (1.49–1.64)	<0.0001
Systemic MZL	2.70 (2.52–2.90)	2.03 (1.97–2.08)	3.14 (2.85–3.45)	2.64 (2.55–2.73)	2.29 (2.06–2.55)	1.57 (1.51–1.64)	1.68 (1.59–1.78)	<0.0001
Extranodal MZL	0.74 (0.64–0.85)	0.60 (0.57–0.63)	0.74 (0.61–0.90)	0.67 (0.61–0.73)	0.73 (0.60–0.89)	0.54 (0.49–0.59)	1.23 (1.08–1.40)	0.002
FL	3.23 (3.03–3.45)	2.81 (2.74–2.88)	2.98 (2.70–3.28)	2.73 (2.63–2.83)	3.47 (3.18–3.78)	2.89 (2.79–2.98)	0.95 (0.90–0.99)	0.02
Follicular	3.14 (2.94–3.35)	2.73 (2.66–2.79)	2.87 (2.59–3.17)	2.63 (2.54–2.73)	3.39 (3.10–3.71)	2.82 (2.72–2.91)	0.93 (0.89–0.98)	0.006
Follicular, large cell	0.13 (0.09–0.20)	0.09 (0.07–0.11)	0.12 (0.07–0.20)	0.10 (0.06–0.14)	0.15 (0.07–0.27)	0.07 (0.04–0.10)	1.44 (0.79–2.64)	0.235
Mantle cell	0.86 (0.76–0.98)	0.65 (0.62–0.69)	1.15 (0.98–1.34)	0.99 (0.93–1.05)	0.60 (0.48–0.74)	0.39 (0.35–0.42)	2.57 (2.30–2.88)	<0.0001
BL	0.36 (0.29–0.44)	0.36 (0.32–0.39)	0.55 (0.43–0.69)	0.54 (0.47–0.61)	0.18 (0.12–0.27)	0.19 (0.14–0.23)	2.95 (2.30–3.78)	<0.0001
Intermediate DLBCL/CHL ^a	0.22 (0.14–0.33)	0.08 (0.05–0.10)	0.29 (0.16–0.48)	0.11 (0.06–0.15)	0.16 (0.07–0.31)	0.05 (0.02–0.08)	2.30 (1.07–4.94)	0.003
CHL	2.58 (2.40–2.77)	2.49 (2.43–2.56)	2.89 (2.61–3.19)	2.82 (2.72–2.92)	2.29 (2.05–2.55)	2.20 (2.11–2.28)	1.28 (1.22–1.35)	<0.0001
Nodular sclerosis CHL	1.91 (1.75–2.07)	1.87 (1.81–1.93)	2.04 (1.81–2.30)	2.01 (1.92–2.10)	1.78 (1.57–2.01)	1.75 (1.67–1.83)	1.15 (1.08–1.23)	<0.0001
Mixed cellularity CHL	0.61 (0.52–0.70)	0.56 (0.52–0.60)	0.74 (0.60–0.89)	0.70 (0.64–0.77)	0.48 (0.38–0.61)	0.42 (0.37–0.48)	1.67 (1.43–1.96)	<0.0001
Lymphocyte-rich CHL	0.13 (0.08–0.20)	0.07 (0.05–0.09)	0.13 (0.07–0.23)	0.11 (0.07–0.15)	0.11 (0.03–0.28)	0.03 (0.01–0.06)	3.49 (1.53–7.97)	0.003
Lymphocyte predominant nodular HL	0.37 (0.30–0.45)	0.34 (0.31–0.38)	0.52 (0.41–0.66)	0.52 (0.45–0.58)	0.20 (0.13–0.30)	0.18 (0.13–0.22)	2.96 (2.28–3.84)	<0.0001
T-cell	1.08 (0.96–1.21)	0.92 (0.88–0.97)	1.24 (1.06–1.44)	1.14 (1.07–1.21)	0.92 (0.77–1.09)	0.74 (0.67–0.80)	1.55 (1.39–1.72)	<0.0001
Peripheral—common, unspecified	0.32 (0.26–0.39)	0.27 (0.24–0.29)	0.41 (0.31–0.53)	0.37 (0.32–0.43)	0.23 (0.16–0.32)	0.17 (0.13–0.21)	2.25 (1.73–2.92)	<0.0001
Angioimmunoblastic	0.22 (0.17–0.29)	0.15 (0.13–0.17)	0.19 (0.12–0.30)	0.13 (0.09–0.17)	0.24 (0.17–0.33)	0.17 (0.13–0.21)	0.77 (0.53–1.12)	0.169
Anaplastic large cell	0.17 (0.13–0.23)	0.14 (0.11–0.17)	0.23 (0.15–0.33)	0.19 (0.13–0.25)	0.12 (0.07–0.19)	0.10 (0.06–0.15)	1.82 (1.09–3.02)	0.020
ALK-negative	0.11 (0.07–0.16)	0.08 (0.06–0.10)	0.12 (0.07–0.20)	0.10 (0.06–0.13)	0.09 (0.05–0.16)	0.07 (0.03–0.10)	1.49 (0.76–2.93)	0.251
ALK-positive	0.08 (0.05–0.13)	0.06 (0.04–0.09)	0.10 (0.05–0.17)	0.09 (0.05–0.14)	0.05 (0.01–0.14)	0.04 (0.01–0.06)	2.97 (1.12–7.89)	0.029
Mycosis fungoides	0.16 (0.11–0.21)	0.12 (0.10–0.14)	0.23 (0.15–0.33)	0.18 (0.14–0.23)	0.09 (0.04–0.15)	0.07 (0.03–0.11)	2.69 (1.62–4.46)	<0.0001
Primary cutaneous CD30+ LPD	0.14 (0.10–0.19)	0.13 (0.10–0.15)	0.14 (0.08–0.21)	0.13 (0.09–0.18)	0.14 (0.08–0.22)	0.12 (0.08–0.16)	1.10 (0.68–1.78)	0.707
Enteropathy-type	0.11 (0.07–0.17)	0.08 (0.07–0.10)	0.13 (0.07–0.21)	0.10 (0.07–0.13)	0.10 (0.05–0.18)	0.07 (0.04–0.10)	1.39 (0.81–2.40)	0.238

Abbreviations: ALK = anaplastic lymphoma kinase; BL = Burkitt lymphoma; CI = confidence interval; CHL = classical Hodgkin lymphoma; DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; IQR = interquartile range; LPD = lymphoproliferative disorders; MZL = marginal zone lymphoma; NOS = not otherwise specified.

^aCases classified 2009–2012 only.

Table 3. Lymphoma 5-year OS and RS estimates (95% confidence interval): Haematological Malignancy Research Network (HMRN) diagnosed 2004–2012 and followed through to 2014

	Total diagnoses		Males		Females	
	OS (95% CI)	RS (95% CI)	OS (95% CI)	RS (95% CI)	OS (95% CI)	RS (95% CI)
All lymphomas	57.4 (56.0–58.7)	67.4 (65.9–68.9)	57.0 (55.1–58.8)	67.2 (65.0–69.2)	57.8 (55.8–59.7)	67.8 (65.5–69.9)
Non-Hodgkin	53.7 (52.2–55.2)	63.9 (62.2–65.6)	53.4 (51.3–55.4)	63.9 (61.5–66.1)	54.0 (51.9–56.2)	64.1 (61.6–66.5)
Hodgkin	78.9 (75.8–81.7)	84.9 (81.7–87.6)	77 (72.6–80.7)	82.3 (77.7–86.1)	81.5 (76.8–85.3)	87.7 (82.6–91.4)
B-cell	58.4 (57–59.8)	68.8 (67.2–70.3)	58.0 (56.0–59.9)	68.5 (66.3–70.6)	58.9 (56.8–60.9)	69.1 (66.8–71.3)
DLBCL	46.3 (44.2–48.4)	54.8 (52.4–57.1)	46.6 (43.6–49.5)	55.5 (52.0–58.8)	46.1 (43.0–49.1)	54.2 (50.7–57.5)
DLBCL, NOS	46.6 (44.4–48.7)	55.0 (52.6–57.4)	46.9 (43.9–49.9)	55.9 (52.4–59.2)	46.2 (43.1–49.2)	54.3 (50.8–57.7)
T-cell/histiocyte-rich	64.5 (45.1–78.5)	67.9 (46.8–82.0)	58.0 (31.7–77.3)	61.1 (32.5–80.5)	71.7 (41.1–88.3)	73.4 (41.1–89.8)
Plasmablastic	16.3 (4.8–33.7)	17.2 (5.1–35.5)	17.5 (3.2–41.1)	18.5 (3.4–43.2)	14.5 (1.8–39.4)	14.7 (1.8–40.0)
MZL	61.2 (57.7–64.5)	77.2 (72.9–80.8)	60.7 (55.9–65.1)	77.6 (71.5–82.5)	61.9 (56.6–66.7)	76.4 (69.9–81.7)
Systemic MZL	57.4 (53.4–61.2)	73.0 (68.0–77.4)	58.3 (52.9–63.3)	75.3 (68.3–80.9)	56.3 (50.0–62.1)	70.0 (62.1–76.5)
Extranodal MZL	74.7 (67.7–80.3)	87.9 (78.7–93.3)	70.3 (59.6–78.7)	83.6 (68.5–91.9)	78.8 (69.2–85.8)	89.9 (75.7–96.0)
FL	75.6 (72.4–78.5)	86.5 (83.0–89.4)	76.5 (71.6–80.7)	86.8 (81.2–90.9)	74.9 (70.5–78.8)	86.6 (81.5–90.4)
Follicular	75.2 (71.9–78.2)	86.3 (82.6–89.2)	75.8 (70.8–80.1)	86.4 (80.5–90.6)	74.7 (70.2–78.6)	86.5 (81.3–90.4)
Follicular, large cell	88.6 (68.6–96.2)	89.7 (68.0–97.0)	93.4 (61.4–99.0)	93.5 (61.0–99.1)	82.4 (46.0–95.3)	83.3 (45.0–95.9)
Mantle cell	25.0 (18.8–31.6)	31.4 (23.6–39.5)	29.2 (21.5–37.4)	36.8 (26.8–46.8)	16.3 (7.8–27.6)	20.2 (9.5–33.7)
BL	51.0 (40.9–60.2)	52.9 (42.4–62.4)	55.2 (43.3–65.6)	57.7 (45.1–68.4)	39.2 (21.4–56.7)	39.9 (21.7–57.6)
Intermediate DLBCL/CHL ^a	83.1 (61.0–93.3)	84.0 (61.0–94.0)	86.6 (56.2–96.5)	87.1 (55.7–96.8)	76.0 (33.3–93.4)	76.8 (32.7–94.0)
Classical Hodgkin (CHL)	76.5 (73.1–79.6)	82.5 (78.9–85.5)	73.6 (68.7–77.8)	78.7 (73.5–83.0)	80.0 (75.1–84.1)	86.5 (81.0–90.5)
Nodular sclerosis CHL	80.3 (76.5–83.5)	86.0 (82.0–89.2)	75.7 (69.9–80.6)	80.8 (74.5–85.7)	85.0 (79.9–88.9)	91.5 (85.5–95.1)
Mixed cellularity CHL	63.3 (55.3–70.3)	69.3 (60.3–76.7)	65.2 (54.8–73.8)	70.4 (58.7–79.3)	60.8 (47.7–71.7)	65.3 (50.7–76.5)
T-cell	39.5 (33.7–45.2)	45.4 (38.8–51.8)	40.8 (33.0–48.5)	46.8 (37.8–55.4)	37.8 (29.4–46.2)	42.2 (32.7–51.4)
Peripheral—common, unspecified	17.6 (10.3–26.5)	19.7 (11.5–29.5)	20.9 (11.1–32.9)	23.2 (12.2–36.3)	11.7 (3.5–25.3)	12.6 (3.7–27.1)
Angioimmunoblastic	24.2 (12.5–37.9)	26.2 (13.5–40.9)	29.5 (10.3–51.9)	31.0 (10.7–54.1)	23.2 (9.9–39.7)	24.8 (10.5–42.2)
Anaplastic large cell	46.5 (30.5–60.9)	50.8 (33.0–66.2)	40.7 (20.8–59.8)	43.7 (21.9–63.7)	55.1 (30.1–74.4)	57.4 (30.8–77.0)
ALK-negative	17.6 (10.3–26.5)	19.7 (11.5–29.5)	21.5 (3.8–48.6)	23.1 (3.9–51.7)	32.8 (10.2–58.0)	34.2 (10.4–60.1)
ALK-positive	75.0 (46.4–89.8)	75.2 (46.4–90.0)	66.7 (33.8–86.0)	66.8 (33.8–86.1)	—	—
Mycosis fungoides	77.8 (60.1–88.3)	86.6 (61.1–95.8)	77.5 (56.3–89.3)	82.4 (56.9–93.6)	78.0 (35.8–94.2)	82.2 (30.6–96.8)
Primary cutaneous CD30+ LPD	86.0 (69.5–94.0)	88.3 (69.7–95.8)	83.4 (56.7–94.4)	85.4 (55.7–95.8)	88.8 (62.2–97.1)	89.2 (61.7–97.4)
Enteropathy-type	27.2 (11.6–45.6)	28.0 (11.8–46.8)	28.1 (7.5–53.7)	28.8 (7.6–54.7)	23.9 (5.2–50.1)	24.3 (5.3–50.6)

Abbreviations: ALK = anaplastic lymphoma kinase; BL = Burkitt lymphoma; CI = confidence interval; CHL = classical Hodgkin lymphoma; DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; IQR = interquartile range; LPD = lymphoproliferative disorders; MZL = marginal zone lymphoma; NOS = not otherwise specified; OS = overall survival; RS = relative survival.
^aCases classified 2009–2012 only.

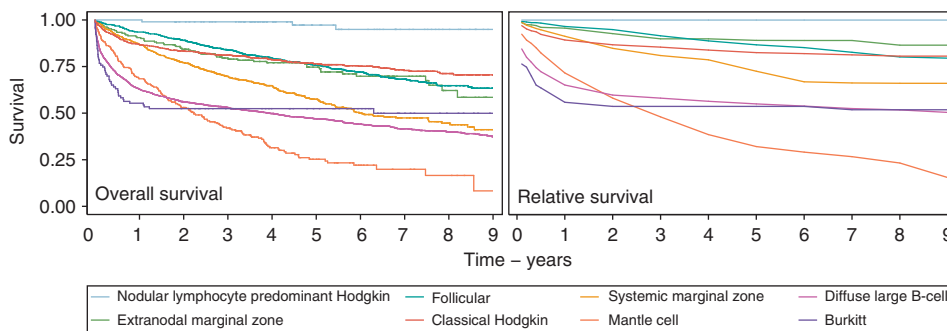


Figure 3. Overall and relative survival by subtype: Haematological Malignancy Research Network (HMRN) 2004–2012.

anaplastic large cell lymphoma (median diagnostic age 35.6 years) which accounted for only 0.3%. Striking differences between males and females in relation to their levels of disease occurrence and ages at diagnosis were observed: males consistently tending to have significantly higher age-standardised incidence rates and to be diagnosed at younger ages, resulting in a doubling of the male/female rate ratio for all lymphomas combined in those diagnosed before 15 years of age. Such strong gender differences have a big impact on prevalence; the combined lymphoma 10-year prevalence

estimate in our dataset being 30 per 100 000 higher in males than in females. That haematological malignancies often occur more frequently in males than females has been noted by others (Morton *et al*, 2006); and in this regard subtypes that fail to exhibit these incidence/age features stand out; follicular lymphoma being the only mature B-cell lymphoma to occur significantly more frequently in women than men and nodular sclerosis classical Hodgkin lymphoma being the only one with a significantly younger diagnostic age in females than males. Likewise, nearly all

Table 4. Lymphoma 3, 5 and 10 year prevalence estimates (95% confidence interval) per 100,000: Haematological Malignancy Research Network (HMRN) 2004–2012

	Prevalence proportion per 100000								
	Total diagnoses			Males			Females		
	3-year	5-year	10-year	3-year	5-year	10-year	3-year	5-year	10-year
All lymphomas	48.0 (45.8–50.3)	72.5 (69.7–75.3)	123.7 (120.0–127.4)	53.6 (50.1–57.0)	81.0 (76.7–85.2)	138.3 (132.7–144.0)	42.8 (39.8–45.8)	64.5 (60.9–68.2)	109.9 (105.1–114.8)
Non-Hodgkin	39.9 (37.9–42.0)	59.9 (57.4–62.5)	100.1 (96.7–103.4)	43.6 (40.5–46.7)	65.5 (61.7–69.3)	109.7 (104.7–114.8)	36.5 (33.7–39.3)	54.7 (51.3–58.1)	91.0 (86.6–95.4)
Hodgkin	8.3 (7.3–9.2)	12.9 (11.7–14.0)	24.0 (22.4–25.6)	10.1 (8.6–11.6)	15.7 (13.9–17.6)	28.8 (26.3–31.3)	6.6 (5.4–7.7)	10.2 (8.7–11.6)	19.4 (17.4–21.4)
B-cell	46.2 (44.0–48.5)	69.9 (67.2–72.6)	119.5 (115.9–123.2)	51.4 (48.1–54.8)	77.7 (73.6–81.9)	133.1 (127.6–138.7)	41.3 (38.4–44.3)	62.5 (58.9–66.1)	106.8 (102.0–111.6)
Diffuse large B-cell	17.6 (16.2–18.9)	25.9 (24.2–27.5)	43.3 (41.1–45.5)	20.0 (17.9–22.1)	28.8 (26.3–31.4)	47.9 (44.5–51.2)	15.3 (13.5–17.0)	23.1 (20.9–25.3)	39.0 (36.1–41.9)
Marginal Zone	10.1 (9.0–11.1)	15.2 (13.9–16.5)	23.8 (22.2–25.4)	11.2 (9.6–12.8)	17.1 (15.1–19.0)	26.7 (24.2–29.2)	9.0 (7.6–10.4)	13.5 (11.8–15.1)	21.1 (18.9–23.2)
Follicular	9.7 (8.7–10.7)	14.8 (13.6–16.1)	25.2 (23.5–26.9)	8.6 (7.2–10.0)	13.6 (11.9–15.4)	24.1 (21.8–26.5)	10.7 (9.2–12.2)	16.0 (14.1–17.8)	26.2 (23.8–28.6)
Mantle cell	1.8 (1.3–2.2)	2.4 (1.9–2.9)	3.3 (2.7–4.0)	2.3 (1.6–3.0)	3.4 (2.5–4.2)	4.7 (3.7–5.8)	1.2 (0.7–1.8)	1.5 (1.0–2.1)	2.0 (1.4–2.7)
Burkitt	0.6 (0.4–0.9)	1.0 (0.7–1.4)	1.8 (1.4–2.3)	1.0 (0.5–1.4)	1.6 (1.0–2.1)	3.0 (2.1–3.8)	0.3 (0.0–0.5)	0.5 (0.2–0.9)	0.8 (0.4–1.2)
Classical Hodgkin	6.9 (6.1–7.8)	11.0 (9.9–12.1)	20.4 (18.9–21.9)	7.9 (6.5–9.2)	12.8 (11.1–14.5)	23.2 (20.9–25.5)	6.1 (5.0–7.2)	9.3 (7.9–10.7)	17.8 (15.9–19.8)
T-cell	1.8 (1.4–2.2)	2.6 (2.1–3.2)	4.3 (3.6–5.0)	2.1 (1.4–2.8)	3.2 (2.4–4.1)	5.2 (4.1–6.3)	1.5 (0.9–2.0)	2.1 (1.4–2.7)	3.4 (2.6–4.3)

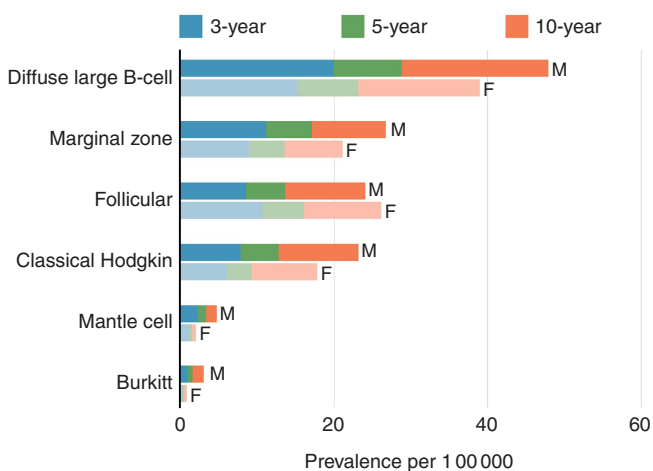


Figure 4. Mature B-cell lymphoma 3, 5, and 10 year prevalence estimates by subtype: Haematological Malignancy Research Network (HMRN) 2004–2012.

T-cell lymphomas occurred at significantly higher levels in males than in females; however, no statistically significant differences between males and females with respect to age at diagnosis were observed. Unfortunately, ethnic differences could not be examined for in the dataset as 95% of the population are Caucasian.

In contrast to the pronounced gender differences seen for lymphoma occurrence and age at diagnosis, no statistically significant survival differences between males and females were detected—either overall or within any of the subtypes. This result is in broad agreement with cancer registry findings from EURO-CARE-4, where close agreement between male and female relative survival estimates in those diagnosed 2000–2002 was also noted (Marcos-Gragera *et al*, 2011). Given the incorporation of male sex into the Hasenclever prognostic score (Hasenclever and Diehl, 1998), it is perhaps worth noting the borderline nature of the overall and relative survival differences for the classical Hodgkin lymphomas. For nodular sclerosis classical Hodgkin lymphoma, the 5-year overall survival estimates for males and females were 75.7 (95% CI 69.9–80.6) and 85.0 (95% CI 79.9–88.9) respectively, and the 5-year relative survival estimates were slightly closer at 80.8 (95% CI 74.5–85.7) and 91.5 (95% CI 85.5–95.1) respectively. Interestingly, mixed cellularity classical Hodgkin lymphoma shows a slight, but again not statistically significant, bias in the other direction, the 5-year relative survival estimates being 70.4 (95% CI 58.7–79.3) and 65.3 (95% CI 50.7–76.5)

respectively. When making such comparisons, it is important to recall that most international prognostic scores are developed using data either from trials or from selected groups of treated patients (International Non-Hodgkin’s Lymphoma Prognostic Factors Project, 1993; Hasenclever and Diehl, 1998; Solal-Céligny *et al*, 2004). In the case of Hodgkin lymphoma, the Hasenclever was based on patients aged 15–65 years who were treated for advanced Hodgkin lymphoma with curative intent before 1992, and for whom outcome was known (Hasenclever and Diehl, 1998).

Taken as whole, survival was generally better for B-cell lymphomas than for T-cell lymphomas, the corresponding 5-year relative survival estimates being 68.8% (95% CI 67.2–70.3) and 45.4% (38.8–51.8) respectively. However, both groups contain a mix of comparatively indolent and aggressive disease forms, some of which are curable and others of which are not. B-cell lymphomas like follicular lymphoma and marginal zone, as well as certain T-cell lymphomas like mycosis fungoides, often follow a remitting/relapsing course that can include long periods without treatment. Reflective of this pattern, the 5-year survival of patients with these comparatively indolent, but currently incurable, subtypes ranges between 75 and 90%. Wider survival variations were, however, evident among the more aggressive lymphomas, several of which tend to be treated with intensive first-line chemotherapy regimens. In this regard, treatment for most of the Hodgkin lymphomas was clearly extremely effective, with 5-year relative survival estimates in excess of 80%. For other potentially curable subtypes, like diffuse large B-cell and Burkitt’s, most deaths occurred within the first year; and although the 5-year relative survival was only 50%, the flattening of the curve after this point implies that the mortality of patients who survive treatment is similar to that of the general population. Currently, outcomes seem less promising for other rarer lymphomas; including mantle cell where the 5-year relative survival of around 30% continued to fall across our 9 years of follow-up, as well as many of the T-cell lymphomas where the common peripheral T-cell and ALK-negative anaplastic large cell both had 5-year relative survival estimates below 20%.

Major strengths of our study include its large well-defined catchment area, completeness of ascertainment and world-class diagnostics. With respect to the latter, all lymphomas were diagnosed and coded using the latest WHO oncology classification by clinical specialists working at a single fully integrated laboratory—the Haematological Malignancy Diagnostic Service (HMDS). As one of the largest integrated haematopathology laboratories in Europe, HMDS has a strong record of national/international leadership in research in lymphoid malignancies, and is cited by the UK’s National Institute for Health and Care

Table 5. Comparison between the age-standardised (European) incidence and prevalence point-estimates for non-Hodgkin and Hodgkin lymphomas derived in this paper from the Haematological Malignancy Research Network (HMRN) and by the International Agency for Research on Cancer's European Union (EUCAN) estimates (<http://eco.iarc.fr/eucan/>)

	Incidence			Prevalence					
	Total	Males	Females	3-year			5-year		
				Total	Males	Females	Total	Males	Females
Non-Hodgkin									
HMRN	14.0	16.6	11.9	39.9	43.6	36.5	59.9	65.5	54.7
EUCAN	14.2	16.8	12.0	39.4	44.5	34.5	58.6	66.4	51.2
Hodgkin									
HMRN	2.8	3.3	2.4	8.3	10.1	6.6	12.9	15.7	10.2
EUCAN	2.5	3.0	2.1	7.0	8.4	5.7	11.2	13.4	9.1

Excellence (NICE) guidance as the model for service delivery (Department of Health, 2007, 2011). This means that, as well as having comprehensive accurate data, our patient cohort does not suffer from the data quality issues commonly faced by non-specialist population-based cancer registries (Sant *et al*, 2010, 2014). Hence, as can be seen from Table 5, although our incidence and prevalence estimates for the traditional groupings of non-Hodgkin lymphoma and Hodgkin lymphoma are reassuringly similar to those calculated for the UK as a whole by the International Agency for Research on Cancer's EUCAN project (<http://eco.iarc.fr/eucan/>) (Ferlay *et al*, 2013; Steliarova-Foucher *et al*, 2014), our B-cell and T-cell age standardised (European) subtype incidence rates tend to be uniformly higher than those estimated by non-specialist European cancer registries (Sant *et al*, 2010). This disparity is partly due to the fact that the range and depth of data used to make the actual diagnosis are difficult for many cancer registries to access systematically (Marcos-Gragera *et al*, 2011), and so lymphomas are often registered using not otherwise specified codes, such as lymphoma not otherwise specified (9590) or non-Hodgkin lymphoma not otherwise specified (9591) (Fritz, 2000). Similar not otherwise specified levels for haematological cancers occur within SEER (Surveillance, Epidemiology, and End Results, <http://seer.cancer.gov/>) registries (Morton *et al*, 2006), where the use of a different standard population (US 2000 census) adds to the difficulty of making comparisons with European populations (Morton *et al*, 2006; Li *et al*, 2015). The US 2000 standard has an older age distribution than the European Standard, so its use results in a general increase; our age-standardised rates (both sexes combined) for diffuse large B-cell and marginal zone lymphomas, for example, increasing from 6.6 and 2.6 per 100 000 (European 2013) to 7.0 and 2.8 per 100 000 (US 2000), respectively.

In addition to affecting measures of disease occurrence, lack of diagnostic specificity at the point of cancer registration also impacts on survival estimates, where external validity may be further reduced by the data exclusions that are frequently applied (Li *et al*, 2014). It is not uncommon, for example, to exclude patients when the date of diagnosis falls on the date of death; this being a marker for registrations based on death certificates only (Rachet *et al*, 2008). In our data, 140 (6.1%) of the 2300 deaths that occurred within 5 years of diagnosis happened on the day of diagnosis, and clearly omission of such deaths would have led to biased estimates. The 5-year relative survival estimates for diffuse large B-cell lymphoma would, for example, have increased by around 3% from 54.8 (95% CI 52.4–57.1) to 57.6 (95% CI 55.1–60.0) had the 101 deaths that occurred on the day of diagnosis been excluded. Comparisons with clinical trials, which by design usually focus on treated patients in specific subgroups, are equally challenging. Hence, in the general patient population, survival estimates for the more aggressive lymphomas like diffuse large B-cell will tend to be lower than those observed in phase III

randomised controlled trials (Cunningham *et al*, 2013); whereas those for the more indolent lymphomas like follicular, which may be actively monitored rather than treated with chemotherapy, will tend to be higher (Press *et al*, 2013).

In summary, our contemporary population-based analyses of incidence, prevalence and survival of lymphomas categorised by WHO subtype provides valuable information for researchers, clinicians and patients. Marked variations by subtype, age and sex were demonstrated; confirming that 'real-world' data are required not only to better inform aetiological hypotheses and plan future health-care services, but also to monitor the impact of therapeutic changes at the population level.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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