

# Differences in incidence and trends of haematological malignancies in Japan and the United States

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## Summary

The incidence of a malignant disease reflects the genetic and cumulative exposure to the environment of a population. Therefore, evaluation of the incidence and trends of a disease in different populations may provide insights into its aetiology and pathogenesis. To evaluate the incidence of haematological malignancies according to specific subtypes, we used population-based registry data in Japan ( $N = 125\,148$ ) and the United States (US;  $N = 172\,925$ ) from 1993 to 2008. The age-adjusted incidence of haematological malignancies in Japan was approximately one-half that in the US but has been increasing significantly, whereas no significant change was seen in the US [annual percent change (95% C confidence interval): Japan, +2.4% (1.7, 3.1); US, +0.1% (-0.1, 0.2)]. Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL) showed the largest differences in incidence, with the most remarkable differences observed for chronic lymphocytic leukaemia, HL-nodular sclerosis, mycosis fungoides and cutaneous T-cell lymphoma. HL and NHL are increasing substantially in Japan but not in the US, suggesting that environmental exposures, such as Westernization of the life style may be causing this increase. Differences in the incidence and trends for specific subtypes also showed a marked contrast across subtypes, which, in turn, may provide significant new insights into disease aetiology in the future.

**Keywords:** incidence, trend, haematological malignancies, surveillance epidemiology and end results, Japan.

The incidence of a malignant disease in a certain population reflects the genetic and cumulative exposure to the environment of that population. Evaluation of the incidence and secular trends of a disease in various populations may, therefore, be helpful in providing insights into the aetiology and pathogenesis of that disease (Parkin, 2006; Morton *et al*, 2008). Trends in cancer incidence are reported by the International Agency for Research on Cancer (IARC) of the World Health Organization (WHO) (Ferlay *et al*, 2010). Although these data are useful in comparing the incidence of

cancers between countries, statistics for haematological malignancies are estimated by general categories such as 'leukaemia,' which includes all leukaemic diseases (Ferlay *et al*, 2010). The haematological malignancies are a collection of heterogeneous disease entities with diverse epidemiological features, and their classification has evolved dramatically into highly-specific disease subtypes (Swerdlow *et al*, 2008). Although detailed epidemiological data for these disease subtypes are available from Western countries (Morton *et al*, 2006; Sant *et al*, 2010; Dores *et al*, 2012), and several

studies have evaluated the incidence of haematological malignancies among Asians living in the US (Carreon *et al*, 2008; Yamamoto & Goodman, 2008; Clarke *et al*, 2011), no population-based data from Asia is currently available. This lack of data severely hampers efforts to evaluate the differences in incidence and trends for each disease subtype among different populations.

One major purpose of a specialized registry code, such as the International Classification of Diseases – Oncology (ICD-O), is to collect epidemiological data on well-defined disease entities. Comparison of the incidence of haematological malignancies across countries and over time has been complicated by changes in disease classification systems. However, the most recent ICD-O-3 classification, published in 2000, is closely linked to the WHO classification of haematological malignancies (Jaffe *et al*, 2001; Swerdlow *et al*, 2008), and this has enabled the comparison of various disease entities encoded by ICD-O-3 between different population-based registries. The present study aimed to evaluate the differences in incidence and time trends of various haematological malignancies in Japan and the United States (US).

## Material and methods

### Populations

We used population-based cancer registry data from Japan and the US. The Japanese data came from of 16 prefectures (Fig S1) included in the Monitoring of Cancer Incidence in Japan (MCIJ) project (Matsuda *et al*, 2013), and the US data came from the Surveillance Epidemiology and End Results (SEER) nine database including nine registries (Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Seattle-Puget Sound, and Utah) (<http://www.seer.cancer.gov/>, <http://www.seer.cancer.gov/popdata/>). The period covered in this analysis is 1993–2008, and the population covered is 33.1% of Japan (includes both metropolitan and rural areas) and 9.4% of the US. Our analysis was begun in 1993 because this was the point at which the Japanese cancer registries began to achieve an acceptable degree of organization, and underwent significant expansion thereafter.

### Disease coding

In the Japanese cancer registry system, incidence data are collected according to the ICD-O criteria. ICD-O-3 codes have been used since 2002 and all diseases coded by ICD-O-2 before 2002 have been re-coded in ICD-O-3. ICD-O-3 coding has been used since 2001 by SEER and all cases in ICD-O-2 have also been re-coded. As myeloproliferative neoplasms (MPN) and myelodysplastic syndromes (MDS) were not considered as malignant diseases in ICD-O-2, we excluded these diseases from this study. The ICD-O-3 code assignment for each disease is summarized in Table I.

**Table I.** Disease coding of haematological malignancies.

Disease	ICD-O-3 code
Leukaemia	9800–9948
Acute myeloid leukaemia (AML)	9840, 9861, 9866, 9867, 9871–9874, 9895–9897, 9910, 9920
Acute lymphoblastic leukaemia (ALL)	9826, 9835–9837
Chronic myelogenous leukaemia (CML)	9863, 9875, 9876
Malignant lymphoma (ML)	9590–9729
Hodgkin lymphoma (HL)	9650–9667
Nodular sclerosis (HL-NS)	9663–9667
Mixed cellularity (HL-MC)	9652
Non-Hodgkin lymphoma (NHL)	9670–9729, 9591, 9823
Diffuse large B-cell lymphoma (DLBCL)	9680, 9684
Follicular lymphoma (FL)	9690–9698
Chronic lymphocytic leukaemia/small lymphocytic lymphoma (CLL/SLL)	9823, 9670
Mantle cell lymphoma (MCL)	9673
Burkitt lymphoma (BL)	9687
Marginal zone B-cell lymphoma (MZBCL)	9699
Mycosis fungoides (MF)	9700
Peripheral T-cell lymphoma-NOS (PTCL-NOS)	9702, 9675
Angioimmunoblastic T-cell lymphoma (AITL)	9705
Cutaneous T-cell lymphoma (CTCL)	9709
Anaplastic large T/null-cell lymphoma (ALCL)	9714
NK/T-cell lymphoma, nasal type (NKTCL)	9719
Adult T-cell leukaemia/lymphoma (ATLL)	9827
Non-Hodgkin lymphoma-NOS (NHL-NOS)	9591, 9675, 9684
Multiple myeloma (MM)	9731–9734

ICD-O, International Classification of Diseases – Oncology; NOS, not otherwise specified.

### Statistical methods

Rates of sex-specific disease incidence and 95% confidence intervals (CI) were estimated and standardized by age-adjustment according to the world standard population (Bray *et al*, 2002). Incidence rates for Japan were additionally age-adjusted to the 1985 Japanese population, and those for the US were age-adjusted to the 2000 US population. Incidence rates were calculated for newly-diagnosed cases of each disease per 100 000 person-years. We calculated incidence rate ratios (IRR; US/Japan with 95% CI) for 2008 to compare incidence rates in the latest year between Japan and the US. We also calculated the annual percent change using Joinpoint regression analysis and estimated the annual percent change (APC), as well as the significance of the trend as described in detail elsewhere (Kim *et al*, 2000). Standard error of the age-standardized rates was estimated for each year. All computations were

performed with STATA version 11 (STATA Corporation, College Station, TX, USA), except for the Joinpoint regression analysis for which we used the Joinpoint Regression Program version 3.3 (US National Cancer Institute, Bethesda, MD, USA). For Joinpoint regression analysis, two-sided *P* values <0.05 were considered statistically significant.

## Results

### Major classification

The data for Japan included 125 148 cases and the data from SEER included 172 925 cases. Overall age-standardized incidence rates for all haematological malignancies per 100 000 in 2008 were 18.0 for males and 12.2 for females in Japan, and 34.9 for males and 23.6 for females in the US. The age-standardized incidence rates of males and females combined for acute myeloid leukaemia (AML), acute lymphoblastic leukaemia (ALL), chronic myeloid leukaemia (CML), Hodgkin lymphoma (HL), non-Hodgkin lymphoma (NHL), and

multiple myeloma (MM) from 1993 to 2008 are shown in Fig 1. The crude numbers for incidence and the sex-specific, age-standardized incidence rates of these diseases, which are the basis for Fig 1, are shown in Tables S1–S4. The age-adjusted incidences of AML, ALL, CML, HL, NHL, and MM per 100 000 in 2008 were 2.5, 1.7, 0.9, 2.7, 15.7 and 3.8 in the US and 1.9, 1.1, 0.5, 0.5, 5.9 and 1.5 in Japan, respectively. The most frequent haematological malignancy in both countries is NHL, which consists of 39.6% of all haematological malignancies in Japan and 54.5% in the US. The lowest incidence was seen for CML, at only 3.4% of all haematological malignancies in Japan and 3.0% in the US. The IRR between Japan and the US for each disease is shown in Table II. In total, there are twice as many haematological malignancies per 100 000 in the US than Japan. The difference in the incidence is substantial for HL, NHL and MM (2.5- to 5-fold), whereas the leukaemias (AML, ALL and CML) have a more similar incidence. The trends in incidence during this period, as estimated by Joinpoint regression analysis, are also shown in Table II. The total number of

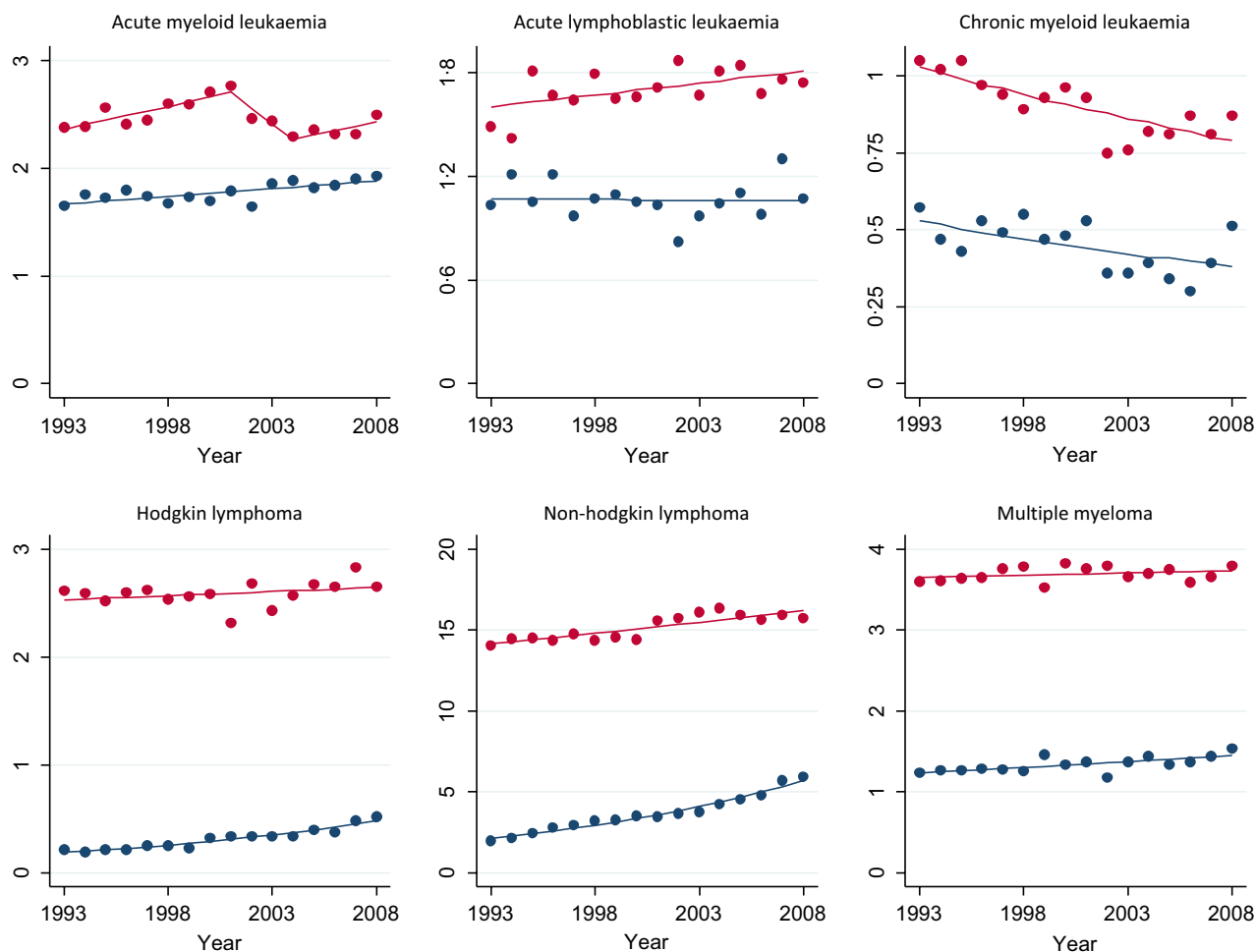


Fig 1. Incidence and trends for haematological malignancies from 1993 to 2008 in Japan and the US. Data for the US are shown in red and Japan in blue. Circles indicate the observed age-standardized incidence rates of males and females combined, and lines indicate the age-standardized incidence rates estimated by Joinpoint regression analysis. Axis indicates the annual incidence /100 000.

**Table II.** Trends in age-standardized incidence rates and incidence rate ratios for 2008, for haematological malignancies in the United States and Japan.

Disease	Trend		Trend		IRR in 2008 (US/Japan) IRR (95% CI)
	Year	APC (95% CI)	Year	APC (95% CI)	
	United States		Japan		
All haematological malignancies	1993–2008	0.1 (−0.1, 0.2)	1993–2008	2.4 (1.7, 3.1)*	1.94 (1.87–2.00)
Acute myeloid leukaemia (AML)	1993–2001	1.7 (0.6, 2.8)*	1993–2008	0.8 (0.4, 1.2)*	1.30 (1.28–1.32)
	2001–04	−5.7 (−14.2, 3.8)			
	2004–08	1.7 (−1.3, 4.7)			
Acute lymphoblastic leukaemia (ALL)	1993–2008	0.8 (0.1, 1.5)*	1993–2008	−0.0 (−1.3, 1.2)	1.63 (1.60–1.65)
Chronic myeloid leukaemia (CML)	1993–2008	−1.7 (−2.5, −1.0)*	1993–2008	−2.2 (−4.0, −0.4)*	1.71 (1.69–1.72)
All malignant lymphoma	1993–2008	0.2 (−0.0, 0.4)	1993–2008	3.2 (2.7, 3.8)*	2.25 (2.21–2.30)
Hodgkin lymphoma (HL)	1993–2008	0.3 (−0.2, 0.8)	1993–2008	6.5 (5.4, 7.7)*	5.10 (5.08–5.12)
Non-Hodgkin lymphoma (NHL)	1993–2008	0.9 (0.6, 1.2)*	1993–2008	6.8 (6.1, 7.6)*	2.65 (2.61–2.70)
Multiple myeloma (MM)	1993–2008	0.1 (−0.1, 0.4)	1993–2008	1.1 (0.4, 1.7)*	2.48 (2.46–2.50)

APC, annual percent change (age-standardized to the world population); CI, confidence interval; IRR, incidence rate ratio.

\*APC is statistically significantly different from zero (two-sided  $P < 0.05$ , calculated using the  $t$ -test.)

haematological malignancies was found to have increased significantly in Japan, whereas no obvious change was seen in the US [APC (95% CI) in Japan, +2.4% (1.7 to 3.1); US, +0.1% (−0.1 to 0.2)]. By subtype, AML and the lymphoid malignancies (HL, NHL and MM) have increased significantly in Japan [APC (95% CI) for HL, +6.5% (5.4–7.7); NHL, +6.8% (6.1–7.6); MM: +1.1% (0.4–1.7)], but only a slight increase was seen for NHL in the US [APC (95% CI) for NHL, +0.9% (0.6–2)]. In contrast, ALL has increased significantly in the US but shown no change in Japan. Interestingly, the incidence of CML has decreased during this period in both countries [APC (95% CI) in Japan, −2.2% (−4.0 to −0.4); US, −1.7% (−2.5 to −1.0)].

### Malignant lymphoma

As HL and NHL consist of diverse entities, we evaluated these diseases further to determine which subtypes contributed to the large IRRs between the two countries. For HL, the dominant subtypes of nodular sclerosis (HL-NS) and mixed cellularity (HL-MC) were evaluated. For NHL, we evaluated the subtypes for which we had enough cases to calculate the trend. Table III shows the distribution of lymphoma subtypes diagnosed in the last 5 years (2003–2008, excluding cases coded as lymphoma, not otherwise specified). Due to the skewed distribution of human T-lymphotropic virus-1 carriers, the proportion of lymphoma subtypes in Japan differs significantly between areas endemic for Adult T-cell leukaemia/lymphoma (ATLL) (Kyushu) and non-endemic areas (Honshu) (Table III). The most common subtype in the US was diffuse large B-cell lymphoma (DLBCL, 27.9%) followed by chronic lymphocytic leukaemia/small lymphocytic leukaemia (CLL/SLL, 24.1%) and follicular lymphoma (FL, 15.1%). The most common subtype in Japan was DLBCL (45.3%) followed by FL (13.5%) and ATLL

**Table III.** Proportion of malignant lymphoma diagnosed in 2003–08 in the US and Japan.

Subtype	US (%)	Japan (%)	Honshu (%)	Kyushu (%)
HL	11.6	5.9	7.4	3.4
DLBCL	27.9	45.3	46.2	27.3
FL	15.1	13.5	13.8	7.7
CLL/SLL	24.1	3.2	4.6	4.6
BL	1.5	1.3	1.9	0.7
MCL	3.0	2.0	1.9	1.3
MZBCL	6.8	7.2	6.1	5.4
PTCL-NOS	1.7	4.1	4.0	3.8
MF	2.2	1.0	1.2	0.9
CTCL	1.0	0.4	0.5	0.7
ALCL	1.0	1.1	1.0	1.2
AITL	0.5	2.0	1.7	1.7
NKTCL	0.2	1.2	1.0	0.5
ATLL	0.2	8.3	5.5	36.8
Others	3.6	3.8	3.8	3.9

HL, Hodgkin lymphoma; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; CLL/SLL, chronic lymphocytic leukaemia/small lymphocytic lymphoma; BL, Burkitt lymphoma; MCL, mantle cell lymphoma; MZBCL, marginal zone B-cell lymphoma; PTCL-NOS, peripheral T-cell lymphoma, not otherwise specified; MF, mycosis fungoides; CTCL, cutaneous T-cell lymphoma; ALCL, anaplastic large T/null-cell lymphoma; AITL, angioimmunoblastic T-cell lymphoma; NKTCL, NK/T-cell lymphoma; ATLL, adult T-cell leukaemia/lymphoma.

(8.3%). DLBCL was the most common subtype in both countries, but differed significantly by proportion. The largest difference in proportion between the US and Japan was seen in CLL/SLL (Japan, 3.2%; US, 24.1%). Consistent with previous results (Anderson *et al*, 1998), the proportion of T-cell lymphoma (TCL, excluding ATLL) was higher in Japan than the US (Japan, 9.8%; US, 6.6%), and this was

even more profound when ATLL is included in TCL (Japan, 18.1%; US, 6.8%).

The age-standardized incidence rates of the various subtypes of HL and NHL are shown in Fig 2. The crude numbers for incidence and sex-specific, age-standardized incidence rates are shown in Tables S5–S8. The age-adjusted incidences of HL-NS, HL-MC, DLBCL, FL, CLL/SLL, mantle cell lymphoma (MCL), Burkitt lymphoma (BL), marginal zone B-cell lymphoma (MZBCL), mycosis fungoides (MF), peripheral T-cell lymphoma not otherwise specified (PTCL-NOS), angioimmunoblastic T-cell lymphoma (AITL), cutaneous T-cell lymphoma (CTCL), anaplastic large T/null-cell lymphoma (ALCL), Natural killer/T-cell lymphoma, nasal type (NKTCL) and ATLL per 100 000 in 2008 were 1.5, 0.2, 4.5, 2.6, 3.5, 0.5, 0.4, 1.2, 0.4, 0.3, 0.1, 0.2, 0.2, 0.04 and 0.02 in the US and 0.2, 0.1, 2.5, 1.1, 0.2, 0.1, 0.1, 0.5, 0.1, 0.3, 0.1, 0.02, 0.1, 0.1 and 0.3 in Japan, respectively. The IRRs between Japan and the US for each of the various subtypes are summarized in Table IV. Most of the subtypes had a higher incidence in the US than in Japan, with the highest IRR seen for CLL/SLL (IRR: 21.0), followed by MF (IRR: 8.1), HL-NS (IRR: 6.8) and CTCL (IRR: 6.4). Some subtypes of TCL, such as ATLL and NKTCL, had a higher incidence in Japan, but the most common subtypes of TCL, PTCL-NOS and AITL, showed similar incidence rates in the two countries. The trends in incidence during this period are summarized in Table IV. With regard to Japan, all subtypes except CLL/SLL, CTCL and ATLL showed a substantial increase during this period. In the US, several NHL subtypes, such as FL, BL, MCL, MZBCL, PTCL-NOS, AITL and NKTCL, also showed a significant increase, whereas HL-MC showed a significant decrease (Fig 2, Table IV).

## Discussion

Although some studies have evaluated the incidence of haematological malignancies in Asians living in the US (Carreon *et al*, 2008; Yamamoto & Goodman, 2008; Clarke *et al*, 2011), they were conducted with relatively small numbers of cases and the incidence of disease in Asians may reflect their lifestyle in the US. In this study, we evaluated the incidence of haematological malignancies in Japanese using population-based data, and show the differences in incidence of haematological malignancies and trends between Japan and the US. Consistent with previous reports, the incidence varies greatly between diseases, with CML showing the lowest incidence and NHL showing the highest incidence in both Japan and the US (Morton *et al*, 2006, 2007; Sant *et al*, 2010). As shown in Fig 1, the incidence of all major diseases was higher in the US. Furthermore, the incidence of lymphoid malignancies, such as HL, NHL and MM, showed impressive differences between the US and Japan, whereas the differences in AML, ALL, and CML were smaller.

This significant difference in the incidences of malignant lymphoma (ML) is partially explained by the difference in

the prevalence of the human immunodeficiency virus (HIV) between countries. Although the prevalence of HIV in the US is low among the general population (0.4% in 2008) (Centers for Disease Control and Prevention (CDC), 2011), HIV significantly increases the risk of NHL and HL (NHL: 77-fold, HL: 11-fold) (Grulich *et al*, 2007). The prevalence rate of HIV in Japan is extremely low, i.e., around 0.01–0.02%, indicating that there is a large difference in the incidence of HIV-related ML between countries.

Among the subtypes of ML, CLL/SLL, MF, HL-NS, CTCL and ATLL showed the largest differences in incidence, which is consistent with previous studies except for the new findings for CTCL (Carreon *et al*, 2008; Clarke *et al*, 2011). In these previous studies, Asians living in the US showed a significantly lower incidence of CLL/SLL and HL-NS than US whites, which points to the importance of genetic background in defining the risk of disease. Clarke *et al* (2011) also showed significantly higher incidence rates of CLL/SLL and HL-NS in US-born Asians compared to foreign-born Asians, which suggests that environmental risk factors also exist for Asians who emigrate to the US. However, the magnitude of these two factors (genetic and environmental) and their contribution to the differences in incidence between populations may vary across the subtypes (Morton *et al*, 2008). For example, the effect of HIV is more profound in the incidence of DLBCL, BL and central nervous system lymphoma (Engels *et al*, 2006). Although we cannot accurately compare the incidence rates in our study to those of previous studies (Morton *et al*, 2006; Carreon *et al*, 2008) because previous studies were not standardized to the world standard population, we can speculate that environmental factors have less effect on the risk of HL-NS than CLL/SLL because the incidence of HL-NS in Asians in the US is more similar to the incidence in Japanese in our study. MF and CTCL are more prevalent among African Americans (Morton *et al*, 2006; Imam *et al*, 2013), suggesting genetic susceptibility in their population. Our findings and those of previous studies strongly suggest that there is aetiological heterogeneity among these diseases and that not only environmental factors, but also genetic background, are important in defining the risk of disease. Considering the differences in incidence in different places and among different populations would be important when investigating the aetiology of these diseases and subtypes.

Not surprisingly, for the major subtypes of nodal T-cell lymphoma, such as PTCL-NOS and AITL, the incidence was similar in Japan and the US. As Japan has significantly fewer cases of B-cell lymphoma and more cases of ATLL, the proportion of TCL is much higher in Japan than in the US (Fig 2; Japan, 18.2%; US, 6.4%). Historically, such information gave the impression that the incidence of TCL is also higher in Asia, but the more accurate incidence calculated using the population-based registry data suggests that this is incorrect, as previously described (Morton *et al*, 2006). NKTCL and ATLL are the only two diseases in Japan with a

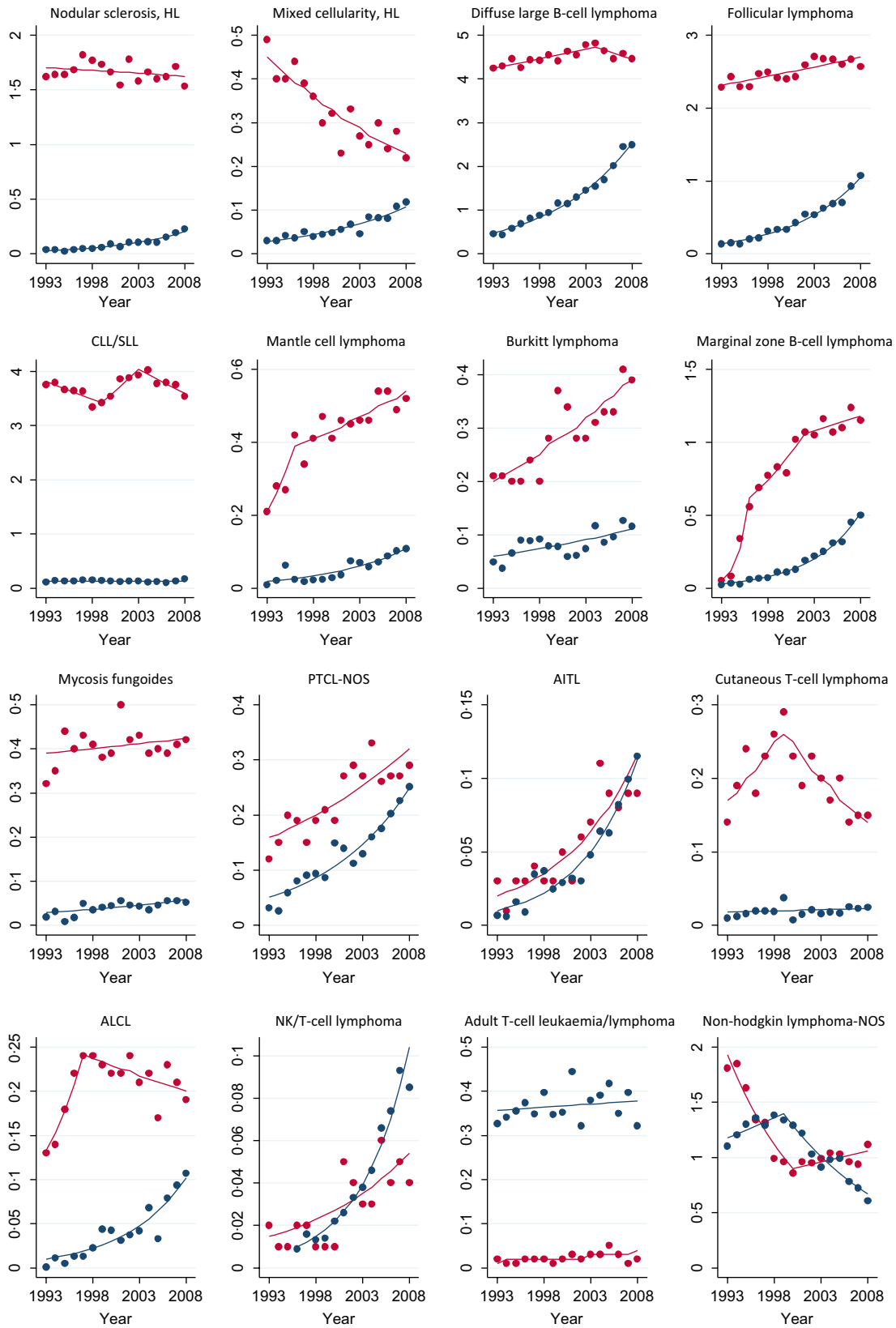


Fig 2. Incidence and trends for malignant lymphoma from 1993 to 2008 in Japan and the US. Data for the US are shown in red and Japan in blue. Circles indicate the observed age-standardized incidence rates of males and females combined, and lines indicate the age-standardized incidence rates estimated by Joinpoint regression analysis. Axis indicates the annual incidence /100 000.

**Table IV.** Trends in age-standardized incidence rates and incidence rate ratio for 2008, for lymphoid malignancies in the United States and Japan.

Disease	Trend			Trend			IRR in 2008 (US/Japan) IRR (95% CI)
	Year	APC (95% CI)	Year	APC (95% CI)	Year	APC (95% CI)	
	United States			Japan			
Hodgkin lymphoma; nodular sclerosis (NS)	1993–2008	-0.3 (-0.9, 0.3)	1993–2008	14.2 (11.8, 16.6)*	1993–2008	6.77 (6.75–6.79)	
Hodgkin lymphoma; mixed cellularity (MC)	1993–2008	-4.4 (-5.7, -3.1)*	1993–2008	9.3 (7.0, 11.7)*	1993–2008	1.85 (1.84–1.86)	
Diffuse large B-cell lymphoma (DLBCL)	1993–2004	1.0 (0.6, 1.4)*	1993–2008	11.8 (10.9, 12.7)*	1993–2008	1.79 (1.76–1.81)	
	2004–08	-1.5 (-3.3, 0.3)					
Follicular lymphoma (FL)	1996–2008	1.0 (0.6, 1.4)*	1993–2008	14.4 (13.2, 15.6)*	1993–2008	2.40 (2.39–2.42)	
Chronic lymphocytic leukaemia/small lymphocytic lymphoma (CLL/SLL)	1993–99	-1.8 (-3.2, -0.3)*	1993–2008	0.2 (-1.5, 2.0)	1993–2008	20.95 (20.93–20.96)	
	1999–2003	4.2 (-0.0, 8.6)					
	2003–08	-2.3 (-3.9, -0.6)*					
Mantle cell lymphoma (MCL)	1993–96	22.2 (2.1, 46.3)*	1993–2008	12.3 (8.0, 16.8)*	1993–2008	4.81 (4.81–4.82)	
	1996–2008	2.7 (1.3, 4.2)*					
Burkitt lymphoma (BL)	1993–2008	4.5 (2.8, 6.2)*	1993–2008	10.1 (4.8, 15.6)*	1993–2008	3.36 (3.35–3.37)	
Marginal zone B-cell lymphoma (MZBCL)	1993–96	128.4 (54.3, 237.9)*	1993–2008	20.8 (18.9, 22.8)*	1993–2008	2.56 (2.55–2.57)	
	1996–2002	9.4 (3.0, 16.3)*					
	2002–08	1.8 (-1.8, 5.7)					
Mycosis fungoides (MF)	1993–2008	0.6 (-0.6, 1.7)	1993–2008	4.9 (2.0, 7.9)*	1993–2008	8.08 (8.07–8.08)	
Peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS)	1993–2008	4.8 (2.9, 6.7)*	1993–2008	11.2 (8.7, 13.8)*	1993–2008	1.15 (1.14–1.16)	
Angioimmunoblastic T-cell lymphoma (AITL)	1993–2008	12.6 (7.9, 17.5)*	1993–2008	17.6 (14.3, 21.0)*	1993–2008	0.80 (0.79–0.80)	
Cutaneous T-cell lymphoma (CTCL)	1993–99	7.3 (-0.1, 15.3)	1993–2008	1.6 (-2.3, 5.7)	1993–2008	6.42 (6.41–6.42)	
	1999–2008	-6.6 (-10.0, -3.1)*					
Anaplastic large T/null-cell lymphoma (ALCL)	1993–97	16.6 (5.9, 28.4)*	1993–2008	16.5 (11.7, 21.5)*	1993–2008	1.78 (1.77–1.78)	
	1997–2008	-1.7 (-3.4, -0.0) *					
NK/T-cell lymphoma, nasal type (NKTCL)	1993–2008	9.1 (4.7, 13.6)*	1996–2008	21.4 (17.9, 25.1)*	1996–2008	0.52 (0.51–0.52)	
Adult T-cell leukaemia/lymphoma (ATLL)	1993–2008	6.2 (1.5, 11.1)*	1993–2008	0.4 (-0.8, 1.6)	1993–2008	0.07 (0.07–0.08)	

APC, annual percent change (age-standardized to the world population); CI, confidence interval; IRR, incidence rate ratio. \*APC is statistically significantly different from zero (two-sided  $P < 0.05$ , calculated using the  $t$ -test.)

higher incidence than in the US. Among a total of 167 patients diagnosed with NKTCL in this period in the US, 112 patients (67%) were white, 40 (24%) were Asian and 15 (9%) were other races. Given that Asians account for only 5% of the US population, it seems that Asians are more prone to develop this disease. ATLL and NKTCL are both associated with viral infections and numerous studies have reported associations between polymorphisms in immune-related genes and risk of NHL (Purdue *et al*, 2009; Skibola *et al*, 2010; Wang *et al*, 2010; Hosgood *et al*, 2011; Lan *et al*, 2011). There seems to be a difference in the immune response to Epstein-Barr virus among Japanese (Kimura, 2006), and it would be interesting to evaluate polymorphisms in immune-related genes to better understand this phenomenon. Unfortunately, however, there is little data evaluating these associations in Asians and this should be investigated in the future.

As well as the differences in incidence, trends in incidence also differ significantly between Japan and the US. Among all haematological malignancies, the differences in the trend for HL and NHL were more striking than for other diseases. ML showed a substantial increase in Japan but there was little change in incidence in the US, as described in a recent study (Shiels *et al*, 2013). The trend of NHL in the US has been affected by HIV, with increases through the early-2000s and subsequent decline after the introduction of highly-active anti-retroviral therapy (HAART) (Shiels *et al*, 2013). Shiels *et al* (2013) showed that the incidence of NHL has plateaued over the last several years in the HIV-uninfected population. Although we found a gradual increase in the incidence of NHL in the US, this difference in trend could be explained by the difference in the study population and period, and a similar trend was also seen in DLBCL in our study. The increasing trend in ML in Japan may be explained by changes in lifestyle and dietary habits to some extent. According to previous studies, vegetable, fish and alcohol intake have been shown to reduce the risk of NHL, whereas meat and fat intake and obesity are thought to increase the risk (Morton *et al*, 2005; Lim *et al*, 2007; Skibola, 2007; Kanda *et al*, 2010a,b). According to the Ministry of Health, Labour and Welfare and Ministry of Agriculture, Forestry and Fisheries in Japan, vegetable, fish and alcohol intake are constantly decreasing, whereas meat and fat intake and the proportion of people with obesity are constantly increasing (<http://www.mhlw.go.jp/>, <http://www.maff.go.jp/>). Although this Westernization in lifestyle has probably increased the incidence of NHL in Japan, there are almost certainly other risk factors that have not been identified. All TCLs, except ALCL, MF and CTCL in the US, and CTCL and ATLL in Japan, are significantly increasing in the two countries. Little is known about the risk factors for TCL and this should be investigated. Comparing the differences in trends and the exposures across countries would be useful to identify new risk factors. When we consider conducting such studies, standardization of exposure information is essential. International

epidemiological consortiums, such as the International Lymphoma Epidemiology Consortium (InterLymph) can play a substantial role in these efforts. The availability of comprehensive data through such consortiums to evaluate genetic information, environmental exposures and lifestyles will facilitate new studies on the aetiology of these diseases.

Interestingly, decreasing trends were seen for CML in both countries, and for HL-MC in the US. Previous studies have suggested an inverse association between socioeconomic status and the risk of HL-MC (McNally *et al*, 2003), and a positive association with an immunosuppressed status, such as HIV infection, and HL-MC (Glaser *et al*, 2003; Clifford *et al*, 2005). Although the effect of HAART on the incidence of HL remains controversial (Clifford *et al*, 2005), the decrease in the incidence of HL-MC may be related to improvements in public health and socioeconomic status, as well as treatment for HIV, in the US. With regard to CML, aside from the possibility that this decreasing trend is real, several other possibilities warrant discussion (Chihara *et al*, 2012). Most important might be a change in disease definition and classification. A more stringent requirement for the *BCR/ABL1* translocation was introduced in the WHO classification during the study period (Jaffe *et al*, 2001). Also, there was no code for MPN in ICD-O-2, and MPNs other than CML may have been misdiagnosed as CML in the pre-ICD-O-3 era. The trend in the incidence of other MPNs cannot be estimated properly, which hampers the confirmation of this hypothesis.

Several limitations should be considered. One is the problem of diagnostic accuracy and introduction of new diagnostic criteria. Figure 2 shows a marked increase in the incidence of MCL, MZBCL and ALCL in the early 1990s. These changes are probably due to improvements in the diagnosis of these lymphomas, as described in a recent study (Shiels *et al*, 2013). When a significant development changes a disease definition, the incidence will change significantly in registry data, as shown in Table III. Another problem is the 'not otherwise specified' (NOS) cases of ML in registry data. The registry data of Japan includes more NHL-NOS and ML-NOS cases than the US data (Japan, 22.1%; US, 9.6%). Given that these cases would allocate to more specific subtypes, the incidence of specific subtypes in Japan tends to be underestimated. Clarke *et al* (2006) evaluated the diagnosis of unclassifiable ML in the SEER database and compared the results with a review of pathology reports. They were able to provide a more accurate diagnosis to the unclassified cases after pathology review and found that the unclassifiable cases tended to be minor subtypes, such as BL, TCL and NKTCL, and were less likely to be major subtypes, such as DLBCL or FL. On this basis, the incidence of minor subtypes is probably underestimated in Japan as the proportion of NOS cases in Japan is over two-fold higher than in the US. The number of NOS cases was higher in the past in both countries (Fig 2). Because of this, the marked increase in trends of specific lymphoma subtypes in Japan and the US (Table IV)



should be interpreted with caution, as this might be partially due to the impact of improvements in diagnosis and coding of registry data. The striking increase in TCLs, such as PTCL-NOS, AITL and NKTCL, in Japan and the US could be a real increase, but should be interpreted with caution given the possibility of a change in diagnostic accuracy of TCL. Centralized review of past cases by haematopathologists would improve the quality of this data, but is unrealistic in population-based registry data. Nevertheless, our results are worthwhile in evaluating the differences in incidence and proportion of diseases between Asia and the US, and in providing clues toward an understanding of aetiology.

In conclusion, this is the first large study to evaluate the incidence of haematological malignancies in Asians using population-based data, and we identified some marked differences in disease incidence and trends between Japan and the US. The incidence of haematological malignancies is lower in Japan than the US, but is still increasing significantly, especially for ML. Aetiological heterogeneity is suggested for these diseases, and epidemiological study by disease subtypes, considering differences in genetics and exposures, will be helpful in understanding tumourigenesis. Improvement in the quality of cancer registries, including information on exposure and genetics across countries, will enable the evaluation of data worldwide and, in turn, provide significant new insights into disease trends and aetiologies in the future.

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## Authorship

T.M., A.S., and T.S. prepared MCIJ data for analysis. M.K., and T.S. played an administrative role in conduct of the study. D.D.W., S.N. and A.K. gave advice on pathological and clinical aspects. D.C., H.I. and K.M. analyzed data. D.C., D.D.W, L.M.M and K.M. wrote draft of the paper and all authors reviewed and finalized the paper.

## Disclosures of conflict of interest

The authors declare no conflict of interest.

## Supporting Information

Additional Supporting Information may be found in the online version of this article:

**Table S1.** Incidence of hematologic malignancies in the United States: Male.

**Table S2.** Incidence of hematologic malignancies in the United States: Female.

**Table S3.** Incidence of hematologic malignancies in Japan: Male.

**Table S4.** Incidence of hematologic malignancies in Japan: Female.

**Table S5.** Incidence of lymphoid malignancies in the United States: Male.

**Table S6.** Incidence of lymphoid malignancies in the United States: Female.

**Table S7.** Incidence of lymphoid malignancies in Japan: Male.

**Table S8.** Incidence of lymphoid malignancies in Japan: Female.

**Fig S1.** The prefectures included in this study in Japan.

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