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Age-related heterogeneity of Burkitt lymphoma

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Keywords

EBV; malaria; NHL; molecular pathogenesis

The study reported by Havelange, *et al* (2016) on genetic differences between paediatric and adult Burkitt lymphoma (BL) among 24 BL cases in France provides molecular evidence of age-related heterogeneity in BL. They found that younger onset cases were more likely to have more 13q amplifications and 7q gains, and that exclusive 5q copy number-loss of heterozygosity (CN-LOH) were more likely among younger cases, whereas 18q21 CN-LOH were more likely among adults. All adult cases had *ID3* mutations compared to 42% of the paediatric cases. The uneven age distributions at diagnosis by genomic expression suggests that the aging process impacts the biology of BL. The authors, however, do not mention several epidemiological studies that also hinted at heterogeneity of BL by ageatdiagnosis (Guech-Ongey, *et al* 2010, Mbulaiteye, *et al* 2010, Mbulaiteye, *et al* 2012, Mbulaiteye, *et al* 2014). We observed three age-specific incidence rate peaks near ages 10, 40 and 70 years (Mbulaiteye, *et al* 2010) in a study of 3058 BL cases from US National Cancer Institute's Surveillance Epidemiology and End Results (SEER 1973–2005) database (www.seer.cancer.gov). Similar patterns were observed in a separate dataset of 3403 BL cases obtained from the International Agency for Research on Cancer from different geographical areas of four continents, excluding Africa and the US (1978–2002) (Mbulaiteye, *et al* 2012). Age-period-cohort (APC) models, used in both studies to control for calendar period (e.g., screening) and birth cohort effects (e.g., risk factor exposures), confirmed these patterns. Moreover, age-related heterogeneity was also present in acquired immunodeficiency syndrome (AIDS)-related BL (Guech-Ongey, *et al* 2010). Trimodal incidence patterns remained apparent in our updated analysis of 5611 BL cases from the recent SEER data release (SEER 18 databases, evidenced by incidence peaks around age 4–11 years, 40–47 years and 72–79 years and incidence valleys around 20–27 years and 60–67 years (Figure 1A). Interestingly, paediatric and adult peaks similar to those observed in the much larger SEER Database were apparent in the age distribution of the 24 BL cases reported by Havelange *at al.*, (2016), which were diagnosed after careful morphological diagnosis, (Figure 1B).

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More than 50 years ago, it was suggested that multimodal age distributions at diagnosis of Hodgkin lymphoma provided empiric epidemiological evidence for biological or aetiological heterogeneity in a disease that was otherwise considered to be a homogenous biological entity (Macmahon 1957). Today, age-related heterogeneity has been documented for many other cancers, including lymphoblastic leukaemia, kidney and renal pelvis cancer, breast cancer and brain cancer (Ries and Devesa 2006) and is usually an early justification to search for molecular evidence of biological heterogeneity. However, the notion that BL might be biologically heterogeneous is controversial because it is considered to be an isomorphic disease characterized by hallmark genetic abnormalities involving chromosomal translocation of *MYC* into the vicinity of immunoglobulin genes (Jaffe, *et al* 1999). Accordingly, BL is assigned one code (9867) under both the International Classification of Diseases for Oncology (ICD-O-3) (Jaffe, *et al* 1999) and the 2008 World Health Organization (WHO) classification of lymphomas and hematological malignancies (Leoncini, *et al* 2008). Although morphological variation in BL was known to occur and variant BL cases were labelled as atypical or non-classical BL, those cases still were recorded under the one ICDO-3 code, reflecting the consensus that BL is isomorphic. In 2008, cases previously considered as variant BL were re-assigned to a new category called B-cell lymphoma, unclassifiable (BCL-U), with features intermediate between BL and diffuse large B-cell lymphoma (Leoncini, *et al* 2008). Interestingly, BL also is known to vary clinically and epidemiologically with distinct labels, such as sporadic or endemic BL, based on geographical/incidence patterns, or immunodeficiency-associated BL, based on antecedent immunosuppression, but without modifiers in the ICD-O-3 code. Similarly, age has been known to be an important factor in BL, particularly with respect to treatment response and survival, which vary according to the age of diagnosis, but these effects are usually dismissed as an artifact of diagnostic misclassification of BL among adults or the elderly. The study by Havelange et al., (2016), which used the current WHO classification of lymphoma and included sporadic BL, suggests age-related heterogeneity in sporadic BL in cases where concern about diagnostic misclassification of BCL-U as BL is less of a concern. Clearly, larger series will be needed to confirm and extend these results. However, the preliminary conclusion about age-related heterogeneity from this study agrees with ours arrived at after epidemiological analysis of sporadic and AIDS-related BL (Mbulaiteye, *et al* 2014). These conclusions are also supported by findings from our recent epidemiological study of younger (18–49 years) and adult BL (50+ years) in the International Lymphoma Epidemiology Consortium (InterLymph) (Mbulaiteye, *et al* 2014). Specifically, we found that BL in younger participants was inversely associated with a history of allergy, and a significant positive association with a history of eczema alone and working in a cleaning occupation. Conversely, in older participants BL was associated with a history of hepatitis C virus seropositivity (Mbulaiteye, *et al* 2014). While the small series of BL studied by Havelange *at al.*, (2016) provides molecular evidence consistent with the idea of age-related heterogeneity in BL, it is unclear from their data whether endemic BL also is heterogeneous because they did not include endemic BL. Although endemic BL is considered mostly a paediatric disease, adult BL cases have been reported (Morrow 1985) suggesting that endemic BL might be heteregoenous by age as well. Confirmation that BL is heterogeneous in all settings may not be inconsistent with the definition of BL as an isomorphic condition, however, it could pave the way for developing finer classification of endemic, sporadic and

AIDS-related BL into molecular variants with unimodal (or homogenous) age distributions-at-diagnosis. The development of a finer classification of BL, based on molecular data, could facilitate the identification of BL variants with similar age distributions in cases from different geographical areas and it could simplify comparative studies diagnosis about aetiology, treatment and survival of BL in different settings.

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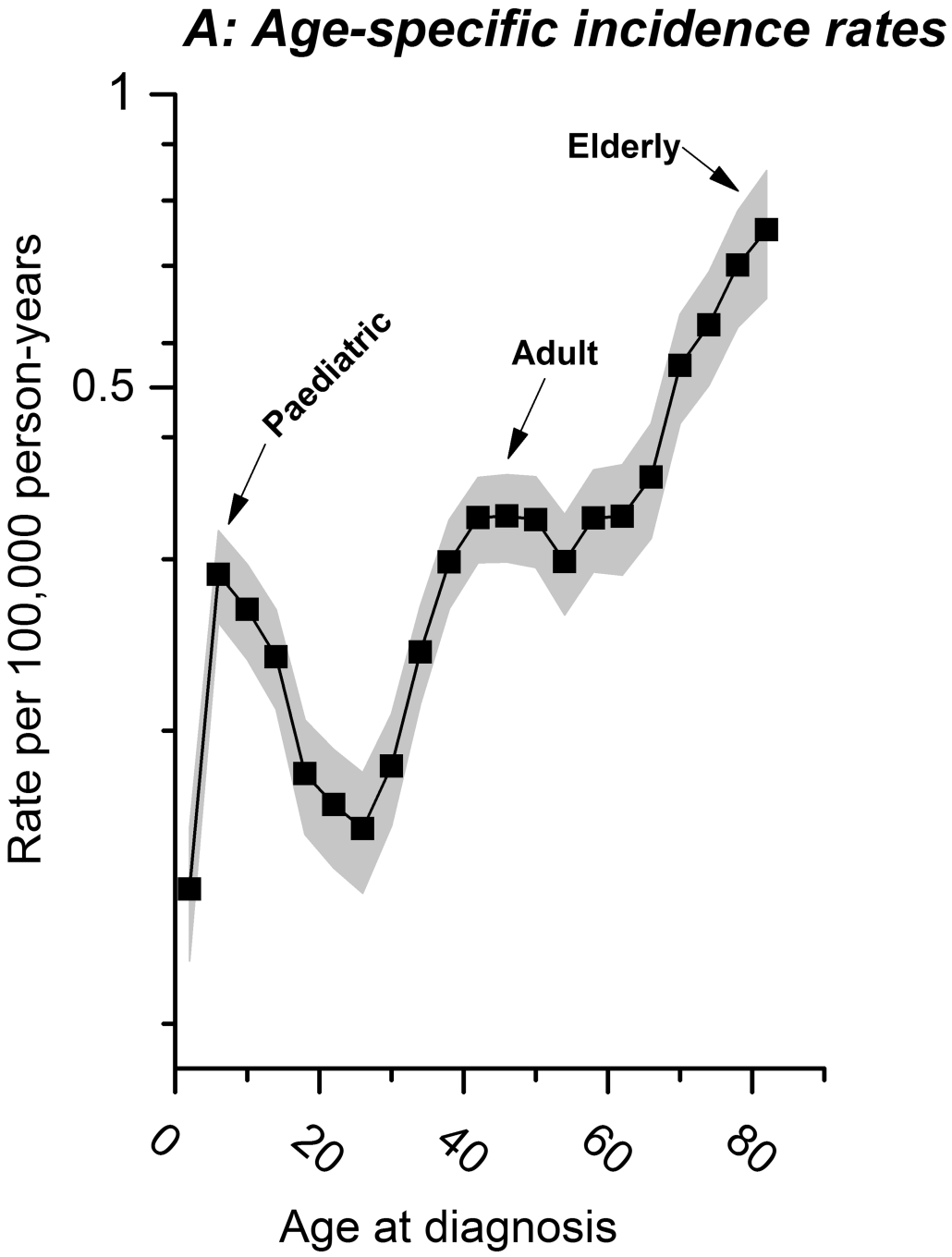

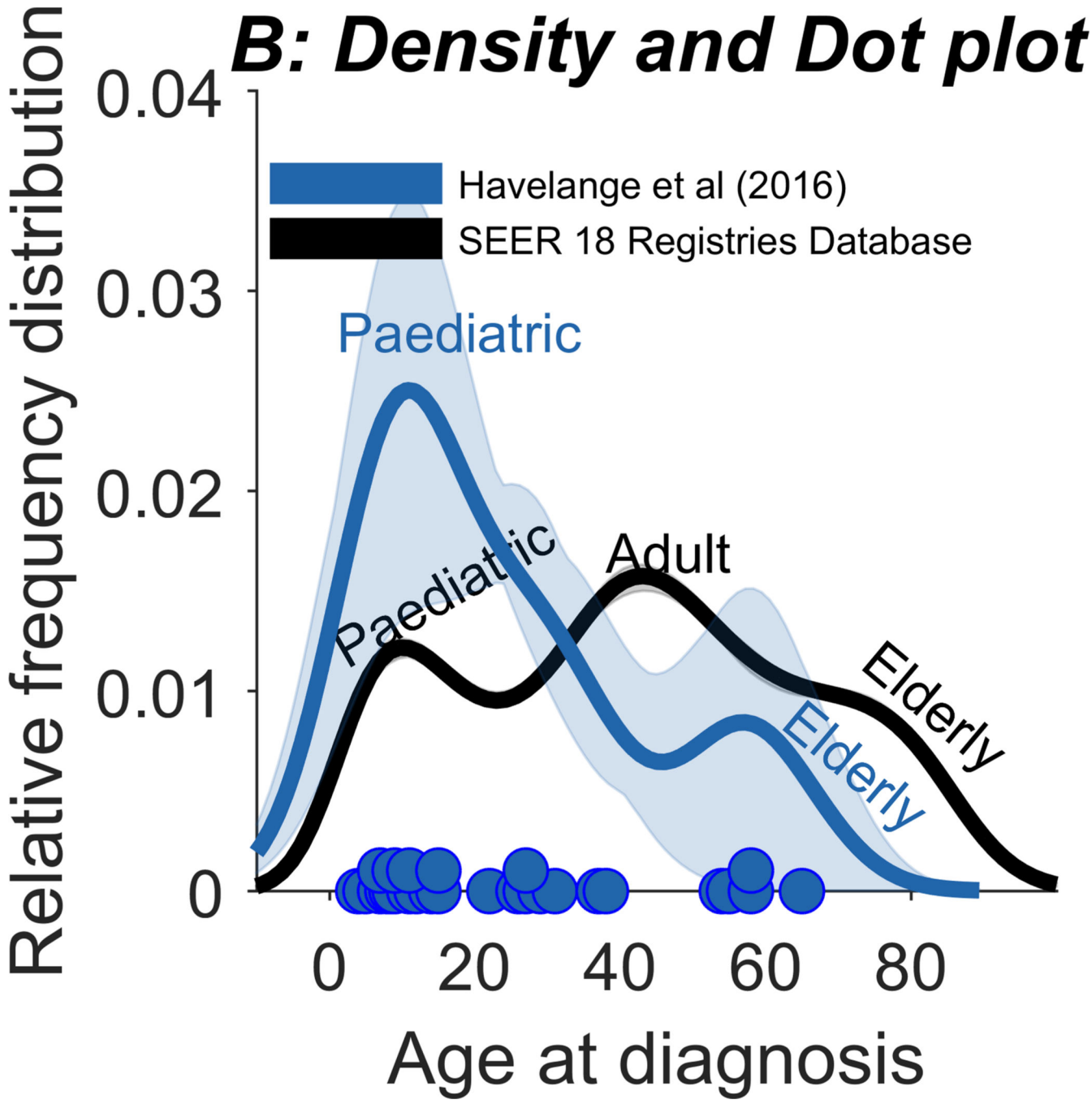

Figure 1.

A: Age-specific incidence rates for Burkitt lymphoma (BL) in the National Cancer Institute Surveillance Epidemiology and End Results 18 Registries Database (SEER 18, 1973–2012) B: Smoothed age distributions-at-diagnosis (Density plot) and dot plot for SEER 18, 1973–2012 (n = 5611) and Havelange *et al* (2016) (n = 24). The shaded area around the density line plots represents 95% confidence bands. The blue dots along the x-axis represent the actual age at diagnosis for the 24 cases reported by Havelange *et al* (2016). Despite the

bimodal appearance of the Havelange density plot, the dot plot suggests a trimodal clustering similar to the SEER 18 density plot.