Increased risk of melanoma in patients with chronic lymphocytic leukaemia: systematic review and meta-analysis of cohort studies

Catherine M. Olsen[a], Steven W. Lane[a,b] and Adèle C. Green[a,c,d]

An increased risk of melanoma has been variously reported in patients with chronic lymphocytic leukaemia (CLL), analogous with other immunosuppressed populations. To fully assess this association, we performed a systematic review and meta-analysis of available evidence from observational cohort studies. All such longitudinal studies of patients diagnosed with CLL that enabled quantitative assessment of the risk of melanoma compared with the general population were eligible. We identified seven studies from a search of all published literature to July 2014 in Medline, Embase and ISI science citation index databases. Data were pooled using a random-effects model. There was an almost four-fold increase in the risk of melanoma in patients with CLL compared with the general population (pooled standardized incidence ratio 3.88 [95% confidence interval (CI) 2.08–7.22]), although significant heterogeneity was evident among studies ($I^2 = 96.0\%$, $P_{het} < 0.001$). The risk of melanoma was higher for men with CLL (3.41; 95% CI 1.49–7.80) than women (2.61; 95% CI 1.13–6.01). CLL patients are at high risk of developing melanoma and the magnitude of the risk is higher than that found in other immunosuppressed populations. Our findings suggest that patients with CLL, as they are also at a higher risk of developing the more common skin cancers, would benefit from regular skin examinations. *Melanoma Res* **26:188–194**

Melanoma Research 2016, **26**:188–194

Keywords: chronic lymphocytic leukaemia, melanoma, risk

[a]QIMR Berghofer Medical Research Institute, [b]Faculty of Medicine and Biomedical Sciences, University of Queensland, Brisbane, Queensland, Australia, [c]Institute of Inflammation and Repair, University of Manchester and [d]Cancer Research UK Manchester Institute, Manchester, UK

Correspondence to Catherine M. Olsen, BSc (Hons I), PhD, MPH, QIMR Berghofer Medical Research Institute, 300 Herston Road, Herston, Queensland 4006, Australia
Tel: + 61 7 3362 0224; fax: + 61 7 3845 3502;
e-mail: catherine.olsen@qimrberghofer.edu.au

Received 26 April 2015 **Accepted** 6 November 2015

Introduction

Melanoma is considered an immunogenic cancer, and populations with compromised immunity such as patients with solid organ transplants or those with HIV/AIDS are at increased risk [1,2]. Immunosuppression is also a characteristic of chronic lymphocytic leukaemia (CLL) [3], a malignancy belonging to the non-Hodgkin's lymphoma (NHL) group, and the most common leukaemia in adults [4]. Systemic therapy for CLL further impairs the immune response in these patients and although advances in treatment have improved response rates [5], this has been at the notable expense of prolonged, profound immunosuppression [6].

Increased risks of a range of second cancers among patients with CLL have been reported [4], and have been variously attributed to genetic susceptibility, treatment-related effects and shared risk factors, such as immunodeficiency. Although an increased risk of melanoma has been reported in patients with CLL, the magnitude of the melanoma risk has yet to be reliably quantified as to date no systematic review of all relevant literature nor meta-analysis of the association has been carried out. A meta-analysis assessing the risk of melanoma in NHL patients reported a pooled relative risk of 1.85 [95% confidence interval (CI) 1.54–2.23] [7], but this analysis excluded CLL patients, who are more likely to present with immune disturbances in comparison with other chronic lymphoproliferative disorders [8]. Given that CLL remains an incurable disease outside allogeneic stem cell transplantation [9] and survivors are living longer with advances in treatment, it is important to confirm the risk of melanoma in CLL patients so that they can benefit from regular screening of the skin, especially as these patients are also at high risk of developing keratinocyte skin cancers [10]. Understanding the association may also help to elucidate the role of shared aetiological factors. This systematic review and meta-analysis aimed to estimate the risk of melanoma in CLL patients compared with the risk of melanoma in the general population on the basis of all currently available evidence.

Methods

The systematic review and meta-analysis was performed in accordance with the Meta-analysis of Observational Studies in Epidemiology guidelines for reviews of observational Studies (MOOSE) [11] and we followed the PRISMA statement [12] to guide the reporting.

Literature search

Eligible studies up to July 2014 were identified by searching the Medline 1950 (US National Library of

 DOI: 10.1097/CMR.0000000000000219

Medicine, Bethesda, Maryland, USA) database using PubMed software as the search interface; Embase 1966 database (Elsevier Science, Amsterdam, Holland) using the Embase search interface; and the ISI Science Citation Index using the ISI Web of Science search interface. We used the following medical subject headings terms or text words (both the US and UK spellings): melanoma, cancer, neoplasms, chronic lymphocytic leukaemia, CLL, leukaemia, non-Hodgkin's lymphoma, NHL, aetiology, cohort. The search was not limited to studies published in English. Relevant identified studies and review articles were included as citation search terms in the ISI Science Citation Index (1990 to the present) to identify subsequent studies that had referenced them. The abstracts of all identified studies were reviewed to exclude those that were clearly not relevant. The full texts of the remaining articles were read to determine whether they fulfilled the study inclusion criteria. Eligible studies were also identified by hand-searching the reference lists of retrieved articles.

Inclusion and exclusion criteria

We included all studies that were based on cohorts of patients diagnosed with CLL that enabled quantitative assessment of the risk of melanoma in CLL patients compared with the general population. Any discrepancies between investigators on inclusion of a study were resolved by joint evaluation of the manuscript. When multiple reports were published on the same population or subpopulation, we included in the meta-analysis the results from the longest follow-up or the most comprehensive data.

Data extraction and quality assessment

Two investigators independently abstracted data from identified studies using a standardized data abstraction form, with inconsistencies resolved by consensus. The following information was recorded for each study: study design, location, years of data collection, source and definition of cohort, number of cases, person-year duration of follow-up, age of study population, variables used for statistical adjustment, point estimates [relative risk, hazard ratio, or standardized incidence ratio (SIR)] and 95% CI. We evaluated the quality of primary studies using the Newcastle–Ottawa Scale [13], a validated technique for assessing the quality of observational studies.

Data synthesis and analysis

To pool individual study estimates for the risk of melanoma in CLL patients, we used the method of DerSimonian and Laird [14] using a random-effects model. Statistical heterogeneity among studies was assessed using the Q-statistic [15] (significance level at $P < 0.10$), and inconsistencies were quantified using the I^2-statistic [16]. We carried out a sensitivity analysis by excluding one study at a time and calculated the pooled relative risk for the remaining studies to evaluate whether the results could have been affected markedly by a single study. Subgroup analyses were carried out according to geographic region and sex. Finally, publication bias was evaluated through visual inspection of a funnel plot and using Begg's and Egger's tests [17,18]. All statistical analyses were carried out using Stata, version 10 (Stata Corporation, College Station, Texas, USA).

Results

Search

Details of the selection process for the eligible studies are shown in Fig. 1. A total of nine eligible studies were identified [19–27], three of which reported on overlapping populations [22,23,27] from Denmark, and one of three being restricted to a high-risk subgroup of CLL patients with a family history of cancer [23]. For these three studies, we therefore included only the most recent and comprehensive report [22], leaving a total of seven eligible studies.

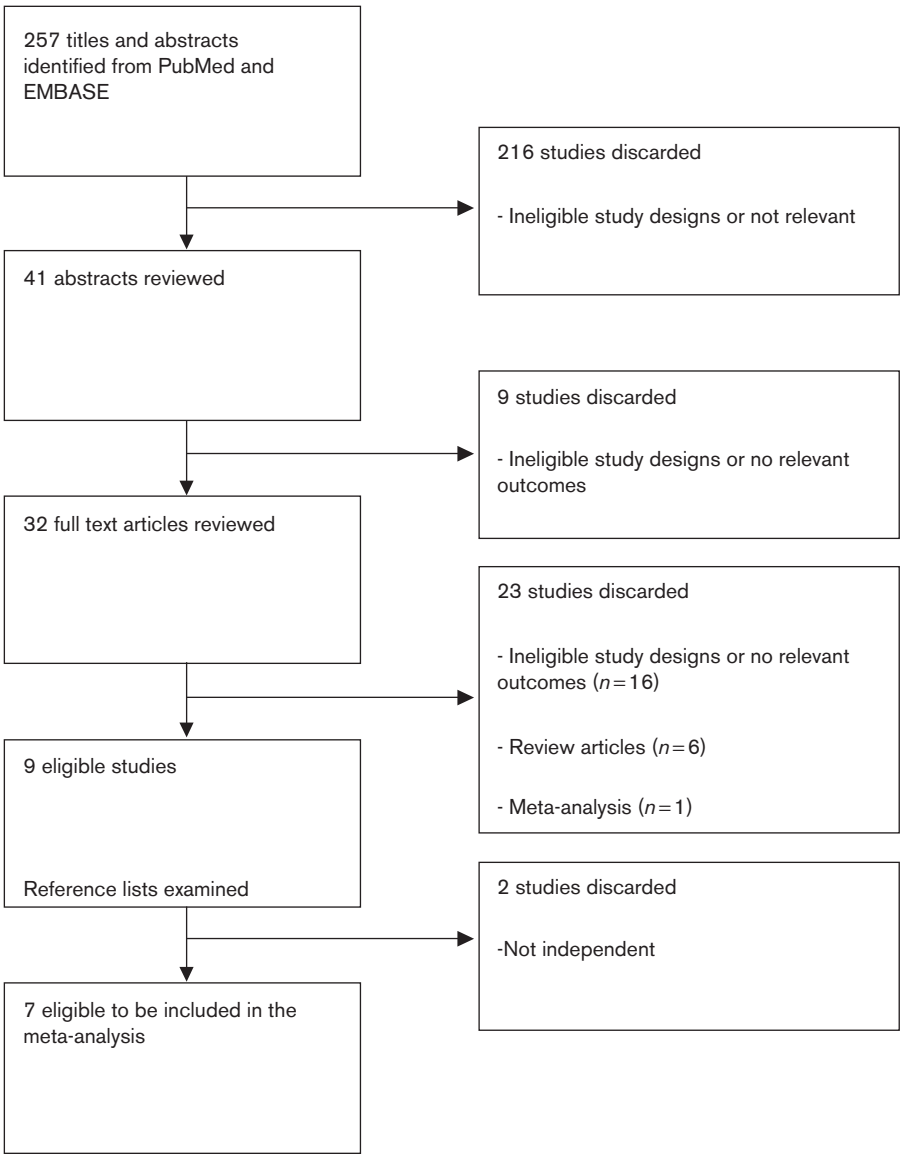
Characteristics of included studies

The main characteristics of the studies included are listed in Table 1. The majority of the studies were of cutaneous melanoma. Studies were published between 1978 and 2011. Four of the studies were carried out in North America [20,21,25,26] and one each in Australia [19], Denmark [22] and Scotland [24]. With the exception of one study that reported on a clinical cohort from a single medical centre [21], all studies were national cancer registry linkage studies and melanoma diagnoses were ascertained through cancer registries for all seven studies. Two studies included patients diagnosed with small lymphocytic lymphoma (SLL) in their cohorts [20,21]. We included these studies as CLL and SLL are considered phenotypic variants on the same disease spectrum by many authors [28], including the WHO classification of tumours of haematopoietic and lymphoid tissues [29]. Moreover, there are few data describing the extent of immune dysfunction between patients with CLL versus SLL. The mean or the median follow-up time for the cohorts ranged from 3.4 to 6.3 years. All studies had accounted for age, sex and time period in their calculations. One study had additionally adjusted for ethnicity [20] (88% white), another reported that 100% of the study population was white [26] and no information on ethnicity was reported by the remaining five studies. With the exception of one study [24], all studies reported a statistically significant increased risk of melanoma.

Quality assessment

One study scored 8 out of a possible score of 9 using the Newcastle–Ottawa quality assessment scale for cohort studies [20]; the remaining studies scored 7 points.

Fig. 1



Flow chart of literature search for studies on the association between CLL and melanoma. CLL, chronic lymphocytic leukaemia.

Outcome

The pooled SIR (pSIR) for studies reporting on risk of melanoma in CLL patients compared with the general population was 3.88 (95% CI 2.08–7.22), with evidence of significant heterogeneity ($I^2 = 96.0\%$, $P_{het} < 0.001$) (Fig. 2). All seven studies reported an increased risk that was statistically significant in all except one study [24]; the heterogeneity thus reflected differences in the size of the effect rather than the direction of the effect. In sensitivity analyses excluding each study in turn, the summary estimate ranged from 3.30 (95% CI 2.09–5.22) with the omission of Royle *et al.* [19] to 4.51 (95% CI 2.62–7.75) with the omission of Morton *et al.* [20]. There was no evidence of publication bias (Begg $P = 0.764$; Egger $P_{het} = 0.358$).

The pSIR was higher for the four studies carried out in the USA (3.68; 95% CI 1.98–6.87; $I^2 = 90.1\%$, $P_{het} \leq 0.001$) than for the two European studies (2.42; 95% CI 1.66–3.51; $I^2 = 0.0\%$, $P_{het} = 0.97$), whereas the single Australian study reported the highest SIR of all (7.74; 95% CI 6.86–8.73). On the basis of the four studies that presented SIRs stratified by sex [19,20,24,25], the pSIR was higher for men (3.41; 95% CI 1.49–7.80; $I^2 = 96.7\%$, $P_{het} < 0.001$) than women (2.61; 95% CI 1.13–6.01; $I^2 = 91.1\%$, $P_{het} < 0.001$). Several studies also

Table 1 Characteristics of the seven studies included in the meta-analysis of risk of melanoma in CLL patients

References	Location	Study period	Cohort description	Cohort (male) [*n* (%)]	Cases (*n*) type	Study type	Comparison population (measure of effect)	Mean or median cohort diagnosis age (follow-up)
Royle *et al.* [19]	Australia	1983–2005	CLL primary diagnosis	13 580 (59)	272 100% cutaneous	Record linkage from state data	Australian population (SIR)	Median: 69 (4.3)
Morton *et al.* [20]	USA, 11 cancer registries	1992–2006	CLL/SLL diagnosis	15 915 (58)	82 100% cutaneous	Record linkage	US population (SIR)	Mean: 67.2 (4.3)
Tsimberidou *et al.* [21]	USA, University of Texas Anderson Cancer Research Centre	1985–2005	CLL/SLL presentation	2028 (61)	19 NS	Clinical cohort	US population (SIR)	Median: 58 (6.3)
Schöllkopf *et al.* [22]	Denmark	1943–2003	CLL diagnosis	12 373 (61)	27 100% cutaneous	National record linkage	Danish population (SIR)	Median: 70 (mean: 3.8)
McKenna *et al.* [24]	Scotland	1975–1997	CLL index case	4016 (59)	6 100% cutaneous	National record linkage	Scottish population (SIR)	Median: 72.2 (NR)
Travis *et al.* [25]	USA, 9 cancer registries	1973–1988	CLL first primary cancer	9456 (58)	28 75% cutaneous 25% ocular	Record linkage	US population (O/E)	Mean: 70 (4.2)
Greene *et al.* [26]	USA, End Results Program NCI (100 hospitals)	1935–1971	CLL initial cancer	4869 (64)	9 NS	Record linkage	US population (SIR)	Mean: NR (3.4)

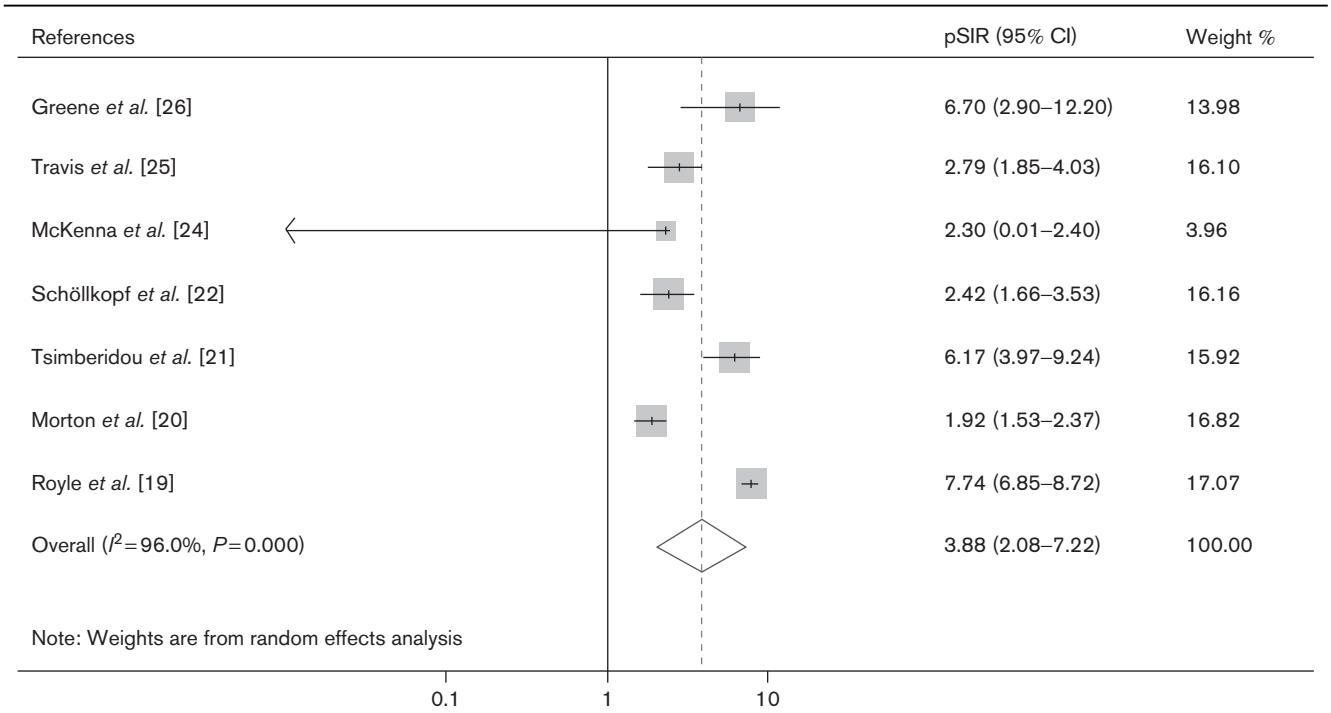
CLL, chronic lymphocytic leukaemia; NR, not reported; NS, not specified; O/E, observed/expected; SIR, standardized incidence ratio; SLL, small lymphocytic lymphoma.

presented SIRs stratified by age at diagnosis [19,20,24] and time from diagnosis of CLL [19,20,24], although because there was heterogeneity in the categorization of time periods/age-groups, estimation of combined estimates of melanoma risk by age group was not possible. A sensitivity analysis excluding one study that included ocular melanoma [25] and two studies that did not specify melanoma type [21,26] resulted in a pSIR of 3.21 (95% CI 1.20–8.60).

Discussion

We have examined all available evidence from observational studies reporting on the risk of melanoma in CLL patients and show that they have an almost four-fold increased risk compared with the general population. Cases were predominantly cutaneous and when we excluded studies where the site was mixed or unclear, risk was still increased by over three-fold. A similar but smaller increase in melanoma risk is also observed in other immunosuppressed populations including organ transplant recipients [1] (pSIR 2.3) and patients with HIV/AIDS (pSIR 1.5) [2] as well as in patients with NHL (pSIR 1.9) [7], but CLL (along with NHL more broadly [30–33]) is unusual because of a bidirectional relationship observed with melanoma [27,34]. Not only are CLL patients at increased risk of subsequent melanoma, but patients diagnosed with melanoma are at increased risk of subsequent CLL, suggesting the existence of shared risk factors. Risk factors for melanoma are well understood, namely sun-sensitive pigmentary phenotype and excessive exposure to ultraviolet radiation, but the aetiology of CLL remains to be fully elucidated [35,36]. Although several lines of evidence support a strong inherited genetic component [37], the role of potentially carcinogenic environmental factors such as ionizing radiation [38,39], pesticides and other chemicals [36,39,40] is less clear, with considerable heterogeneity in the published literature. Evidence on the association of CLL/NHL with exposure to UV radiation is contradictory [36,41]. There is some evidence of a genetic component in the common pathogenesis of CLL and melanoma. Genome-wide association studies have identified germline mutations in genes in the TERT-CLPTM1L region, associated with telomerase activity, in both melanoma [42] and CLL [43]. Also associated with telomerase activity, loss-of-function mutations in POT1 have been found in familial melanoma [42] and have been found to be somatically mutated in CLL (3.5% of all CLL and 9% with an aggressive CLL subtype) [44]. Genome-wide association studies have also reported mutations in CASP8, involved in apoptosis, associated with melanoma [45] but less consistently with CLL [37]. Finally, long-term immunosuppression is a risk factor for both cancers [46], and is likely to be the strongest common underlying factor that explains the association.

Fig. 2



Forest plot of the association between CLL and melanoma compared with the general population. Each line represents an individual study result with the width of the horizontal line indicating 95% CI, the position of the box representing the point estimate and the size of the box being proportional to the weight of the study. CI, confidence interval; CLL, chronic lymphocytic leukaemia; pSIR, pooled standardized incidence ratio.

The increased risk of melanoma in CLL patients is most likely explained by the state of immunosuppression inhibiting the antitumour response. The immune defects associated with the disease are complex and include decreased immunoglobulin synthesis as well as changes in the innate immune system including defects in complement activation, depressed cellular immunity and impaired phagocytosis [47]. Treatment of CLL can further impair the immune response, although currently, there is no evidence of an association between treatment with alkylating agents or nucleoside analogues and risk of melanoma [48,49], suggesting that treatment-related immunosuppression does not increase risk. The higher risk of melanoma found in CLL patients compared with other immunosuppressed populations [1,2] most likely reflects the more severe and prolonged degree of immunosuppression among the former.

All studies included in our meta-analysis received a high-quality score using the Newcastle–Ottawa quality assessment scale for cohort studies [13]. There were some limitations in our meta-analysis. Our analyses may have been subject to publication bias because we did not search for unpublished studies, abstracts or the grey literature; however, inclusion of only results from peer-reviewed studies provided greater assurance of the quality of those data we did include. The mean/median follow-up time for studies included in the meta-analysis ranged from 3.4 to 6.3 years, which may not have sufficiently covered the latent period for melanoma development, leading to a potential underestimation of the association. Limited control of confounding may also have influenced the results as the studies included did not have information on key melanoma risk factors including sun exposure, which has been inconsistently associated with the broader group of NHL [41] and also has an effect on immune function [50]. Similarly, five of the seven studies included did not specify the ethnic composition of the populations included. CLL is common in individuals of European descent, but is rare in Asians [51]; this is also true of melanoma, however, and thus lack of information on ethnicity is unlikely to have influenced the observed association.

Finally, although all studies included reported an increased risk, we observed significant heterogeneity in the magnitude of the effect. This heterogeneity was not explained by geographical variation, and we could not examine the effects of baseline differences in clinical parameters as these were mostly not reported. Studies included in our analysis were based on patients recruited over an extended time period (1935–2006), during which there have been considerable changes in treatment regimens [5].

Although CLL treatment advances have led to impressive benefits in terms of overall survival, this has been at the cost of substantial long-term immunosuppression [6].

The increased longevity of patients with CLL means that, on average, they are now at risk of melanoma for longer periods. It is unknown whether CLL patients diagnosed with melanoma are at greater risk of disease recurrence, but melanoma survival is worse in patients with CLL than in patients without CLL [52]. Given the heterogeneous clinical profile of CLL patients [53], collection of detailed clinical information on disease stage and treatment in future large prospective studies would aid better understanding of the strong association between CLL and melanoma that we have shown.

In summary, patients diagnosed with CLL are a high-risk population for the development of melanoma and as they are also at a higher risk of developing the more common types of skin cancer [10,34,54], these patients would benefit from routine skin examinations as well as counselling to avoid excessive sun exposure.

Acknowledgements

The authors thank Lani Knight for assistance with data extraction.

This study was supported by special purpose donations for melanoma research to the QIMR Berghofer Medical Research Institute.

Conflicts of interest

There are no conflicts of interest.

References

1 Grulich AE, van Leeuwen MT, Falster MO, Vajdic CM. Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis. *Lancet* 2007; **370**:59–67.
2 Olsen CM, Knight LL, Green AC. Risk of melanoma in people with HIV/AIDS in the pre- and post-HAART eras: a systematic review and meta-analysis of cohort studies. *PLoS One* 2014; **9**:e95096.
3 Vanhaelen CP, Fisher RI. Increased sensitivity of T cells to regulation by normal suppressor cells persists in long-term survivors with Hodgkin's disease. *Am J Med* 1982; **72**:385–390.
4 Chiorazzi N, Rai KR, Ferrarini M. Chronic lymphocytic leukemia. *N Engl J Med* 2005; **352**:804–815.
5 Hallek M, Fischer K, Fingerle-Rowson G, Fink AM, Busch R, Mayer J, *et al.* Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukaemia: a randomised, open-label, phase 3 trial. *Lancet* 2010; **376**:1164–1174.
6 Wadhwa PD, Morrison VA. Infectious complications of chronic lymphocytic leukemia. *Semin Oncol* 2006; **33**:240–249.
7 Pirani M, Marcheselli R, Marcheselli L, Bari A, Federico M, Sacchi S. Risk for second malignancies in non-Hodgkin's lymphoma survivors: a meta-analysis. *Ann Oncol* 2011; **22**:1845–1858.
8 Hodgson K, Ferrer G, Montserrat E, Moreno C. Chronic lymphocytic leukemia and autoimmunity: a systematic review. *Haematologica* 2011; **96**:752–761.
9 Herishanu Y, Katz BZ, Lipsky A, Wiestner A. Biology of chronic lymphocytic leukemia in different microenvironments: clinical and therapeutic implications. *Hematol Oncol Clin North Am* 2013; **27**:173–206.
10 Onajin O, Brewer JD. Skin cancer in patients with chronic lymphocytic leukemia and non-Hodgkin lymphoma. *Clin Adv Hematol Oncol* 2012; **10**:571–576.
11 Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, *et al.* Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA* 2000; **283**:2008–2012.
12 Moher D, Liberati A, Tetzlaff J, Altman DG, Moher D, Liberati A, *et al.* PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol* 2009; **62**:1006–1012.
13 Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, *et al.* The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Available at: *http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp*.
14 DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986; **7**:177–188.
15 Hardy RJ, Thompson SG. Detecting and describing heterogeneity in meta-analysis. *Stat Med* 1998; **17**:841–856.
16 Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002; **21**:1539–1558.
17 Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994; **50**:1088–1101.
18 Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997; **315**:629–634.
19 Royle JA, Baade PD, Joske D, Girschik J, Fritschi L. Second cancer incidence and cancer mortality among chronic lymphocytic leukaemia patients: a population-based study. *Br J Cancer* 2011; **105**:1076–1081.
20 Morton LM, Curtis RE, Linet MS, Bluhm EC, Tucker MA, Caporaso N, *et al.* Second malignancy risks after non-Hodgkin's lymphoma and chronic lymphocytic leukemia: differences by lymphoma subtype. *J Clin Oncol* 2010; **28**:4935–4944.
21 Tsimberidou AM, Wen S, McLaughlin P, O'Brien S, Wierda WG, Lerner S, *et al.* Other malignancies in chronic lymphocytic leukemia/small lymphocytic lymphoma. *J Clin Oncol* 2009; **27**:904–910.
22 Schöllkopf C, Rosendahl D, Rostgaard K, Pipper C, Hjalgrim H. Risk of second cancer after chronic lymphocytic leukemia. *Int J Cancer* 2007; **121**:151–156.
23 Landgren O, Pfeiffer RM, Stewart L, Gridley G, Mellemkjaer L, Hemminki K, *et al.* Risk of second malignant neoplasms among lymphoma patients with a family history of cancer. *Int J Cancer* 2007; **120**:1099–1102.
24 McKenna DB, Stockton D, Brewster DH, Doherty VR. Evidence for an association between cutaneous malignant melanoma and lymphoid malignancy: a population-based retrospective cohort study in Scotland. *Br J Cancer* 2003; **88**:74–78.
25 Travis LB, Curtis RE, Hankey BF, Fraumeni JF Jr. Second cancers in patients with chronic lymphocytic leukemia. *J Natl Cancer Inst* 1992; **84**:1422–1427.
26 Greene MH, Hoover RN, Fraumeni JF Jr. Subsequent cancer in patients with chronic lymphocytic leukemia – a possible immunologic mechanism. *J Natl Cancer Inst* 1978; **61**:337–340.
27 Adami J, Frisch M, Yuen J, Glimelius B, Melbye M. Evidence of an association between non-Hodgkin's lymphoma and skin cancer. *BMJ* 1995; **310**:1491–1495.
28 Santos FP, O'Brien S. Small lymphocytic lymphoma and chronic lymphocytic leukemia: are they the same disease? *Cancer J* 2012; **18**:396–403.
29 Campo E, Swerdlow SH, Harris NL, Pileri S, Stein H, Jaffe ES. The 2008 WHO classification of lymphoid neoplasms and beyond: evolving concepts and practical applications. *Blood* 2011; **117**:5019–5032.
30 Yang GB, Barnholtz-Sloan JS, Chen Y, Bordeaux JS. Risk and survival of cutaneous melanoma diagnosed subsequent to a previous cancer. *Arch Dermatol* 2011; **147**:1395–1402.
31 Hemminki K, Lenner P, Sundquist J, Bermejo JL. Risk of subsequent solid tumors after non-Hodgkin's lymphoma: effect of diagnostic age and time since diagnosis. *J Clin Oncol* 2008; **26**:1850–1857.
32 Lens MB, Newton-Bishop JA. An association between cutaneous melanoma and non-Hodgkin's lymphoma: pooled analysis of published data with a review. *Ann Oncol* 2005; **16**:460–465.
33 Caini S, Boniol M, Botteri E, Tosti G, Bazolli B, Russell-Edu W, *et al.* The risk of developing a second primary cancer in melanoma patients: a comprehensive review of the literature and meta-analysis. *J Dermatol Sci* 2014; **75**:3–9.
34 Levi F, Randimbison L, Te VC, La Vecchia C. Non-Hodgkin's lymphomas, chronic lymphocytic leukaemias and skin cancers. *Br J Cancer* 1996; **74**:1847–1850.
35 Vardi A, Agathangelidis A, Sutton LA, Ghia P, Rosenquist R, Stamatopoulos K. Immunogenetic studies of chronic lymphocytic leukemia: revelations and speculations about ontogeny and clinical evolution. *Cancer Res* 2014; **74**:4211–4216.
36 Slager SL, Benavente Y, Blair A, Vermeulen R, Cerhan JR, Costantini AS, *et al.* Medical history, lifestyle, family history, and occupational risk factors for chronic lymphocytic leukemia/small lymphocytic lymphoma: the InterLymph Non-Hodgkin Lymphoma Subtypes Project. *J Natl Cancer Inst Monogr* 2014; **2014**:41–51.
37 Slager SL, Caporaso NE, de Sanjose S, Goldin LR. Genetic susceptibility to chronic lymphocytic leukemia. *Semin Hematol* 2013; **50**:296–302.

38 Bizzozero OJ Jr., Johnson KG, Ciocco A, Kawasaki S, Toyoda S. Radiation-related leukemia in Hiroshima and Nagasaki 1946–1964 II. *Ann Intern Med* 1967; **66**:522–530.

39 Zablotska LB, Bazyka D, Lubin JH, Gudzenko N, Little MP, Hatch M, *et al*. Radiation and the risk of chronic lymphocytic and other leukemias among chornobyl cleanup workers. *Environ Health Perspect* 2013; **121**:59–65.

40 Malone KE, Koepsell TD, Daling JR, Weiss NS, Morris PD, Taylor JW, *et al*. Chronic lymphocytic leukemia in relation to chemical exposures. *Am J Epidemiol* 1989; **130**:1152–1158.

41 Armstrong BK, Kricker A. Sun exposure and non-Hodgkin lymphoma. *Cancer Epidemiol Biomarkers Prev* 2007; **16**:396–400.

42 Aoude LG, Wadt KA, Pritchard AL, Hayward NK. Genetics of familial melanoma: 20 years after CDKN2A. *Pigment Cell Melanoma Res* 2015; **28**:148–160.

43 Speedy HE, Di Bernardo MC, Sava GP, Dyer MJ, Holroyd A, Wang Y, *et al*. A genome-wide association study identifies multiple susceptibility loci for chronic lymphocytic leukemia. *Nat Genet* 2014; **46**:56–60.

44 Ramsay AJ, Quesada V, Foronda M, Conde L, Martínez-Trillos A, Villamor N, *et al*. POT1 mutations cause telomere dysfunction in chronic lymphocytic leukemia. *Nat Genet* 2013; **45**:526–530.

45 Law MH, Bishop DT, Lee JE, Brossard M, Martin NG, Moses EK, *et al*. Genome-wide meta-analysis identifies five new susceptibility loci for cutaneous malignant melanoma. *Nat Genet* 2015; **47**:987–995.

46 Mueller N. Overview of the epidemiology of malignancy in immune deficiency. *J Acquir Immune Defic Syndr* 1999; **21** (Suppl 1):S5–S10.

47 Ravandi F, O'Brien S. Immune defects in patients with chronic lymphocytic leukemia. *Cancer Immunol Immunother* 2006; **55**:197–209.

48 Cheson BD, Vena DA, Barrett J, Freidlin B. Second malignancies as a consequence of nucleoside analog therapy for chronic lymphoid leukemias. *J Clin Oncol* 1999; **17**:2454–2460.

49 Robak T, Blonski JZ, Gora-Tybor J, Kasznicki M, Konopka L, Ceglarek B, *et al*. Second malignancies and Richter's syndrome in patients with chronic lymphocytic leukaemia treated with cladribine. *Eur J Cancer* 2004; **40**:383–389.

50 Schwarz T. The dark and the sunny sides of UVR-induced immunosuppression: photoimmunology revisited. *J Invest Dermatol* 2010; **130**:49–54.

51 Yang SM, Li JY, Gale RP, Huang XJ. The mystery of chronic lymphocytic leukemia (CLL): why is it absent in Asians and what does this tell us about etiology, pathogenesis and biology? *Blood Rev* 2015; **29**:205–213.

52 Brewer JD, Shanafelt TD, Otley CC, Roenigk RK, Cerhan JR, Kay NE, *et al*. Chronic lymphocytic leukemia is associated with decreased survival of patients with malignant melanoma and Merkel cell carcinoma in a SEER population-based study. *J Clin Oncol* 2012; **30**:843–849.

53 Lad DP, Malhotra P, Varma S. Chronic lymphocytic leukemia: inception to cure: are we there? *Indian J Hematol Blood Transfus* 2013; **29**:1–10.

54 Brewer JD, Shanafelt TD, Khezri F, Sosa Seda IM, Zubair AS, Baum CL, *et al*. Increased incidence and recurrence rates of nonmelanoma skin cancer in patients with non-Hodgkin lymphoma: a Rochester Epidemiology Project population-based study in Minnesota. *J Am Acad Dermatol* 2015; **72**:302–309.