Body size and obesity during adulthood, and risk of lympho-hematopoietic cancers: an update of the WCRF-AICR systematic review of published prospective studies

[1]Leila Abar, [1,2]Jakub G Sobiecki, [1]Margarita Cariolou and [1]Neesha Nanu, [1]Ana Rita Vieira, [1]Christophe Stevens, [1]Dagfinn Aune, [3]Darren C Greenwood, [1]Doris SM Chan and [1]Teresa Norat

Affiliations

[1]Department of Epidemiology and Biostatistics, Imperial College, London, United Kingdom (L.A; J.S; M.C; N.N; A.R.V; C.S; D.A; D.C.G; D.S.M.C; T.N)

[2]Medical Research Council Epidemiology Unit, University of Cambridge School of Clinical Medicine, Institute of Metabolic Science, Cambridge Biomedical Campus, Cambridge, United Kingdom

[3]School of Medicine, University of Leeds, Leeds, United Kingdom (D.C.G)

Correspondence

Mrs. Leila Abar, Department of Epidemiology and Biostatistics,

School of Public Health, Imperial College London, St. Mary's Campus, Norfolk Place,

Paddington, London W2 1PG, UK.

Telephone: +44 (0) 20 7594 2786

E-mail: l.abar@imperial.ac.uk

Abstract

Background: To summarise the evidence on the associations between body mass index (BMI) and BMI in early adulthood, height, waist circumference (WC) and waist to hip ratio (WHR), and risk of lympho-hematopoietic cancers.

Method: We conducted a meta-analysis of prospective studies and identified relevant studies published up to December 2017 by searching PubMed. A random effects model was used to calculate dose-response summary relative risks (RRs).

Results: Our findings showed BMI, and BMI in early adulthood (aged 18-21 years) is associated with the risk of Hodgkin's and Non-Hodgkin's lymphoma (HL and NHL), Diffuse Large Beta Cell Lymphoma (DLBCL), Leukaemia including Acute and Chronic Myeloid Lymphoma (AML and CML), and Chronic Lymphocytic Leukaemia (CLL) and Multiple Myeloma. The summary RR per 5 kg/m² increase in BMI were 1.12 (95% CI: 1.05-1.20) for HL, 1.05 (95% CI:1.03-1.08) for NHL, 1.11 (95% CI:1.05-1.16) for DLBCL, 1.06 (95% CI:1.03-1.09) for ML, 1.09 (95% CI:1.03-1.15) for leukaemia, 1.13 (95% CI:1.04-1.24) for AML, 1.13 (95% CI:1.05-1.22) for CML and 1.04 (95% CI:1.00-1.09) for CLL, and were1.12 (95% CI:1.05-1.19) for NHL, 1.22 (95% CI:1.09-1.37) for DLBCL, and 1.19 (95% CI:1.03-1.38) for FL for BMI in early adulthood analysis.Results on mortality showed a 15%, 16% and 17% increased risk of NHL, multiple myeloma and leukaemia, respectively. Greater height increased the risk of NHL by 7%, DLBCL by 10%, FL by 9%, multiple myeloma by 5%, and Leukaemia by 7%. WHR was associated with increased risk of DLBCL by 12%. No association was found between higher WC and risk of multiple myeloma.

Conclusion

Our results revealed that general adiposity in adulthood and early adulthood, and greater height may increase the risk of almost all types of lympho-hematopoietic cancers and this adds to a growing body of evidence linking body fatness to several types of cancers.

Introduction

Overweight and obesity are a global health problem. During the last forty years, the number of obese adults increased from 100 million in 1975 (69 million women, 31 million men) to 671 million in 2016 (390 million women, 281 million men) [1]. Excess weight and obesity have been linked to several chronic diseases including cardiovascular disease [2,3], diabetes [3] and many types of cancersincluding lympho-hematopoietic cancers [4].

The age standardized incidence rates worldwide (per 100 000 inhabitants) were estimated of 1.0 for HL, 6.7 for NHL, 2.1 for multiple myeloma and 5.7 for leukaemia in 2018 [5]. Although, lympho-hematopoietic cancers are not as frequent as other cancers such as lung, breast, colorectal and prostate cancers, it is very important to investigate their association with overweight and obesity, which are the major public health issues. Consequentlyfindings can add to the existing literature about the importance of lifestyle modification specifically weight management in prevention of haematological cancer incidence and mortality [4].

Previous meta-analyses published up to 2014, showed that greater BMI may increase the risk of HL [6], NHL [6], DLBCL [7], myeloma [8] and leukaemia [9]. Since the publication of these meta-analysis, several additional large prospective studies with large number of cases have been published [10-16]. The accumulated evidence has greatly enhanced the investigation of how these modifiable risk factors influence the development of the many different types of lympho-haematopoietic cancers. Moreover, whether BMI in early adulthood (age 18-21 years), height, and abdominal obesity increase the risk of lympho-haematopoietic cancers, has not been summarized in a meta-analysis. Therefore, we conducted a systematic literature review and meta-analysis of prospective studies of BMI, BMI in early adulthood, height, weight, waist circumference and waist to hip ratio, and the risk of lymphoma, myeloma and leukaemia, and their main types to provide an up-to-date and

comprehensive assessment of the existing evidence. We aimed to clarify the strength and shape of dose-response relationship between the general and abdominal adiposity and lympho-haematopoietic cancers and investigate any potential differences by sub-sites, sex, geographical locations, size of cohort, number of cases, years of follow up, exposure assessment methods, and adjustment for potential confounders.

Methods

Search strategy and inclusion criteria

The CUP team at Imperial College London searched in PubMed for studies on anthropometric measures including BMI, BMI in early adulthood (age 18-21), height, weight, waist circumference and waist to hip ratio, and lympho-hematopoietic cancer risk up to December 2017. The specific search criteria and the review protocol can be seen in supplementary materials.

Study selection

Our study selection was restricted to cohort (prospective, retrospective, case–cohort or nested case–control studies) studies which investigated the link between anthropometric measures and lympho-hematopoietic cancer risk and mortality, and reported estimates of the relative risk (RR) (e.g., hazard ratio, risk ratio or odds ratio) and 95% confidence intervals (CIs) for the exposures of interest (BMI, BMI in early adulthood (aged 18-21 years), weight, waist circumference, and waist-to-hip ratio). In case of studies reporting only categorical results, number of cases and denominator data (person-years of follow-up or number of subjects) were required for inclusion in the meta-analysis. If there were multiple publications from the same study, the newest publication which included the largest number of cases was selected.

Data extraction

We extracted the following data from each study: authors, year of publication, country of origin, cancer type, length of study and loss of follow up, sample size, numbers of cases and population at risk/controls, age, sex and other characteristics, anthropometric measures, relative risks and 95% confidence intervals or P-values for each exposure category and adjustment variables. A second reviewer checked at least 10% of the work.

Statistical analysis

We calculated the summary RRs and 95% CIs using random effect models which takes into account heterogeneity between studies[17]. Q and I^2 statistics were used to determine heterogeneity [18], potential sources of which were explored in stratified analyses by sex, geographical location, exposure assessment methods, years of follow-up, number of cases, size of cohort, and adjustments for confounders including alcohol consumption, smoking, and physical activity.

We used RR estimates and CIs for continuous increments directly from the articles if provided, and for studies that only reported categorical data, dose-response associations and 95% CIs were derived using generalized least-squares for trend estimation [19], which required the RRs and CIs associated to at least three categories of anthropometric measures, and number of cases and non-cases or person years of follow up per category to be available. If only the total number of cases or person years was reported in the articles, and the exposure was categorised in quantiles, the distribution of persons or person years was calculated by dividing the total number of persons or person years by the number of quantiles. We used the mean or median values per each anthropometric category if available in the articles, or the midpoint was calculated for studies that only reported a range by category. If the range of the highest or lowest category was open-ended, its width was assumed to be the same as the adjacent category. In case of close-ended lowest and highest categories with category widths substantially greater than those of the middle-categories (e.g. highest category of 35-60 $kg/m^2$of BMI), the Chêne and Thompson [20] method was used to estimate the midpoints. The Hamling's method was used to recalculate the relative risk estimates when the first category was not used as reference [19]. If the results were reported for men and women separately, they were combined using a fixed effects meta-analysis before being pooled with other studies in linear, but not non-linear, analyses.

We assessed small-study effects, such as publication bias, by using funnel plots and Egger's

test [21].

We assessed a potential nonlinear dose-response association between anthropometric measures and risk of lympho-hematopoietic cancers when we had ≥ 3 studies by calculating restricted cubic splines for each study, using three fixed knots at 10^{th}, 50^{th}, and 90^{th} percentiles of distribution of the exposure to account for a wider exposure range while minimising any potential impact from the outliers in the tails, and combined them by using multivariate meta-analysis. In order to be eligible for this procedure, at least three categories of exposure needed to be reported by a given study.

For all analyses, the results of each article with the most comprehensive adjustment for confounders were included. A two-tailed $p<0.05$ was considered statistically significant. Stata version 13.1software (StataCorp, College Station, TX) was used.

Results

Study selection is shown in the flowchart (Figure 1).

Out of 65 publications, 27 studies (37 publications[10-15,22-52]) on blood cancers risk (lymphoma, leukaemia and myeloma) and 68 studies (10 publications including 1 Pooled analysis of 39 cohorts and 1 Pooled analysis of 20 cohort studies[22,46,46,50-53,53,54,54,55,55,56,56,57,57])on blood cancers mortality (lymphoma, leukaemia and myeloma) were included in the dose-response meta-analyses. The characteristics of the included studies are shown in supplementary materials.

BMI and lymphomas risk and mortality

The summary RR per 5 kg/m^2 increase of BMI was 1.12 (95%CI=1.05-1.20, I^2=1.9%, $P_{heterogeneity}$ =0.40) for HL (5 studies[12,36,39,40,58], Figure 2A), 1.05(95%CI: 1.03-1.08, I^2=45%, $P_{heterogeneity}$ =0.02) for NHL (20 studies[10-12,23,24,27-31,33,34,36,39-42,58], Figure 3), 1.11, 95%CI=1.05-1.16, I^2=16%, $P_{heterogeneity}$ =0.29) for DLBCL (18 studies[11,12,24,26,29,30,32,33,36,42,48], supplementary Figure 1), and 1.03 (95%CI=0.98-1.09, I^2=3%, $P_{heterogeneity}$ =0.41) for FL (19 studies [11,12,24,26,29,30,32,33,36,42,48], supplementary Figure 2).

The summary RR per 5 kg/m^2 increase of BMI for NHL mortalitywas1.15 (95%CI=1.10-1.20, I^2=0%, $P_{heterogeneity}$ =0.44, 6 studies [22,45,51,52,56,57]) (Table 1and supplementary Figure 3).

There was no evidence of publication bias in any of the analysis (p-value for Egger's test= 0.24 for HL; 0.12 for NHL (incidence); 0.10 for NHL (mortality) 0.17 for DLBCL;0.37 for FL).

There was evidence of nonlinearity of the association of BMI and HL (p for non-linearity < 0.001). The risk increase was observed in the range of BMI above 32 kg/m^2 (Figure 2B).

However, there was no evidence of non-linearity association between BMI and NHL (p for non-linearity=0.66) (Supplementary Figure 4), DLBCL (p for non-linearity=0.50) (Supplementary Figure 5), and FL (p for non-linearity=0.58) (Supplementary Figure 6). Moreover, there was no evidence of nonlinearity (p for non-linearity=0.66) between BMI and NHL mortality (Supplementary Figure 7).

BMI and multiple myeloma (MM) risk and mortality

The summary RR per 5 kg/m^2 increment of BMI was 1.06 (95%CI=1.03-1.10, I^2=13%, $P_{heterogeneity}$ =0.31, 23 studies [10,12,14,15,26,27,30-32,37,40,43,44,59,60]) for MM risk (Figure 4) and 1.16 (95%CI=1.07-1.25, I^2=20%, $P_{heterogeneity}$ =0.27, 57 studies) for MM mortality (Table 1 and supplementary Figure 8).

There was evidence of publication bias in MM risk analysis (the p-value for Egger's test =0.05) but no evidence of publication bias in MM mortality analysis (p-value for Egger's test = 0.26).

There was no evidence of nonlinearity for the association of BMI and MM risk (p for non-linearity=0.50) (Supplementary Figure 9), and mortality (p for non-linearity=0.33) (Supplementary Figure 10).

BMI and leukaemia risk and mortality

The summary RR per 5 kg/m^2 increment of BMI was 1.09 (95%CI=1.03-1.15, I^2=46%, $P_{heterogeneity}$ =0.05, 12 studies [10,12,13,27,31,34,39,40,47,59,61]) for leukaemia, 1.11(95%CI=1.03-1.21, I^2=43%, $P_{heterogeneity}$ =0.10, 14 studies[12,13,31,47,58,60]) for AML, 1.13 (95%CI=1.05-1.22, I^2=0%, $P_{heterogeneity}$ =0.57, 4 studies[13,16,58,60]) for CML, and 1.04 (95%CI=1.00-1.09, I^2=0%, $P_{heterogeneity}$ =0.65, 7 studies[13,30,31,39,47,58])) for CLL (Figure 5).

The summary RR per 5 kg/m^2 increment of BMI was 1.17 (95%CI=1.05-1.30, I^2=49%, $P_{heterogeneity}$ =0.06, 46 studies [45,46,51,52,54,56,57,62] for leukaemia mortality (Supplementary Figure 11).

There was no evidence of publication bias in any of the analyses (p-value for Egger's test =0.97 for leukaemia; 0.24 for AML; 0.68 for CML; 0.36 for CLL).

There was no statistical evidence of departure from linearity (p-values for non-linearity tests were 0.60 for leukaemia risk; 0.46 leukaemia mortality; 0.68 for AML and 0.32 for CLL (Supplementary Figures 12, 13, 14 and 15, respectively).

BMI in early adulthood (age 18-21 years) and lymphoma risk

The summary RR per 5 kg/m^2 increment of BMI was 1.12 (95%CI=1.05-1.19, I^2=43%, $P_{heterogeneity}$ =0.10) for NHL (7 studies [11,23,24,29,33,42]) (Table 1 and supplementary Figure 16), 1.22 (95%CI=1.09-1.37, I^2=0%, $P_{heterogeneity}$ =0.77) for DLBCL(8 studies [11,24,29,30,33,42,48]) (Table 1 and supplementary Figure 17), and 1.19 (95%CI=1.03-1.38, I^2=2%, $P_{heterogeneity}$ =0.41) for FL (8 studies [11,24,29,30,33,42,48]) (Table 1 and supplementary Figure 18).

There was no evidence of publication bias in most of the analyses (p-value for Egger's test =0.36 for NHL; 0.74 for DLBCL). However, there was an evidence of publication bias in the FL analysis (p-value for Egger's test =0.05). Visual inspection of the funnel plot showed moderate asymmetry, which appeared to be driven by the strong and relatively precise association reported in the NHS study [11].

There was some evidence of nonlinearity of the association of early adulthood BMI and NHL (p for non-linearity=0.05), with steady risk increase within the BMI range of approximately

15-23 kg/m^2, with gradual flattening of the slope with increasing BMI thereafter (Supplementary Figure 19).

There was no evidence of nonlinearity of the association of early adulthood BMI and DLBCL (p for non-linearity=0.83) (Supplementary Figure 20), and FL (p for non-linearity=0.60) (Supplementary Figure 21).

Height

Height and lymphoma risk

The summary RR per per 5 cm increment of height was 1.07 (95%CI=1.05-1.10, I^2=70%, $P_{heterogeneity}$<0.01) for NHL(13 studies[11,12,23-25,28-30,33,42,58,63]) (Table 1 and supplementary Figure 22), 1.10 (95%CI=1.06-1.15, I^2=41%, $P_{heterogeneity}$ 0.09) for DLBCL (10 studies[11,12,24,29,30,32,33,36,42,48]) (Table 1 and supplementary Figure 23), and 1.09 (95%CI=1.06-1.13, I^2=0%, $P_{heterogeneity}$ =0.54) for FL(10 studies[11,12,24,29,30,33,36,42,48]) (Table 1 and supplementary Figure 24).

There was no evidence of publication bias in any of analysis (p-value for Egger's test= 0.57 for NHL; 0.48 for DLBCL; 0.64 for FL).

There was no evidence of nonlinearity of the association between height and NHL (p for non-linearity=0.51) (Supplementary Figure 25), DLBCL (p for non-linearity=0.98) (Supplementary Figure 26), and FL (p for non-linearity=0.29) (Supplementary Figure 27).

Height and multiple myeloma risk

The summary RR per per 5 cm increment of height was 1.05 (95%CI=1.02-1.08, I^2=1%, $P_{heterogeneity}$=0.42, 8 studies [12,15,25,30,32,43,63,64]) (Table 1 and supplementary Figure 28).There was no evidence of publication bias (p-value for Egger's test= 0.64).

There was no evidence of nonlinearity of the association of height and MM (p for non-linearity=0.17) (Supplementary Figure 29).

Height and leukaemia risk

The summary RR per per 5 cm increment of height was 1.07 (95%CI=1.03-1.11, I^2=51%, $P_{heterogeneity}$ =0.06, 7 studies [12,13,25,47,63-65]) (Table 1 and supplementary Figure 30).

There was no evidence of publication bias (p-value for Egger's test= 0.24).

There was no evidence of nonlinearity of the association of height and Leukaemia (p for non-linearity=0.76) (Supplementary Figure 31).

Weight

Weight and lymphoma risk

The summary RR per 5 kg increment of weight was 1.02 (95%CI=0.99-1.06, I^2=70%, $P_{heterogeneity}$=0.01) for NHL (5 studies[24,28,29,33,42]) (Supplementary Figure 32), 1.03 (95%CI=0.98-1.07, I^2=22%, $P_{heterogeneity}$=0.89) for DLBCL (6 studies [24,29,32,33,42,48]) (Supplementary Figure 33), and 1.00 (95%CI=0.96-1.04, I^2=7%, $P_{heterogeneity}$ =0.37) for FL (6 studies [24,29,32,33,42,48]) (Supplementary Figure 34) (Table 1).

There was no evidence of publication bias (the p-value for Egger's test= 0.56 for NHL; 0.89 for DLBCL; 0.40 for FL).

There was no evidence of nonlinearity of the association of weight and NHL (p for non-linearity=0.35) (Supplementary Figure 35), DLBCL (p for non-linearity=0.81) (Supplementary Figure 34), and FL (p for non-linearity=0.45) (Supplementary Figure 37).

Waist circumference

Waist circumference and lymphoma risk

The summary RR per 5 cm increment of waist circumference was 1.06 (95%CI=0.97-1.15, I^2=0%, $P_{heterogeneity}$=0.92, 5 studies [11,24,32,48]) for DLBCL and 1.00 (95%CI=0.92-1.09, I^2=0%, $P_{heterogeneity}$=0.80, 5 studies [11,24,32,48]) for FL (Supplementary Figure 38 and 39).

There were not enough studies to conduct the non-linear analysis.

Waist circumference and multiple myeloma risk

The summary RR per 5 cm increment of waist circumference was 1.01 (95%CI=0.97-1.05, I^2=79.8%, $P_{heterogeneity}$<0.001, three studies [32,43,48]) (Table 1 and supplementary Figure 40).

There were not enough studies to conduct the non-linear analysis.

Waist to hip ratio

Waist to hip ratio and lymphoma risk

The summary RR per 0.1 unit increment of waist to hip ratio was 1.12 (95%CI=1.01-1.26, I^2=0%, $P_{heterogeneity}$ =0.71) for DLBCL (7 studies [11,24,32,36,42,48]) (Supplementary Figure 41), and 0.98 (95%CI=0.86-1.11, I^2=0%, $P_{heterogeneity}$ =0.84) for FL (7 studies [11,24,32,36,42,48]) (Supplementary Figure 42) (Table1).

There was no evidence of publication bias in any of analysis (the p-value for Egger's test= 0.61 for DLBCL; 0.17 for FL).

There was no evidence of nonlinearity of the association of WHR and DLBCL (p for non-linearity = 0.45) (Supplementary Figure 43), and FL (p for non-linearity = 0.75) (Supplementary Figure 44).

Subgroup analyses

The observed associations in the main analysis persisted in most subgroup analyses defined by sex, geographical locations, exposure assessment methods, duration of follow-up, cohort size, number of cases and adjustments for potential confounding factors including alcohol consumption, smoking and physical activity, although the results were not always statistically significant (Table 1 and Supplementary tables). There were no apparent differences between the subgroups that could explain the moderate heterogeneity observed in the analyses of BMI and risk of NHL and AML and leukaemia mortality; BMI in early adulthood and NHL; and height and NHL. For the analysis of BMI and leukaemia, weaker positive associations were observed in the studies in men than studies in women. For the analyses of height and DLBCL and leukaemia, null associations were observed in the studies in men, which were also studies with medium-size of cohort and >20 years of follow-up. Other factors did not appear to explain the observed heterogeneity.

Study quality

In most of the included studies, cases were ascertained via record linkage to cancer and death registries. All the studies were adjusted at least for age and sex, but only some studies were adjusted for confounders including alcohol consumption, smoking and physical activity; and unadjusted studies more often showed statistically significant results on average than adjusted studies. Most of the included studies used self-reported measurements.

Most of the included studies did not report loss to follow up and only few studies reported a follow-up that was almost complete (≤1%) which include 5 studies for BMI [24,28,43,58,61], and height [24,25,28,43,58], 2 studies for weight [24,28], and 1 study [24] for BMI in early adulthood, waist to hip ratio and waist circumference.

Discussion

This study provides the most comprehensive and up-to-date summary estimates of the association between all anthropometry factors including BMI, BMI in early adulthood, height, weight, waist circumference and waist to hip ratio and risk of lympho-hematopoietic cancers including lymphomas, multiple myeloma, and leukaemia.

Higher BMI showed to be associated with increased risk of all included type of lympho-hematopoietic cancers, except for FL, for which no significant association was observed. The observed increased risk ranged from 4% in CLL to 13% in AML and CML, respectively, per 5 kg/m^2. Moreover, higher BMI in early adulthood (age 18-21) showed to increase the risk of NHL, FL and DLBCL cancers by 12%, 19% and 22%, respectively.

Our main findings on BMI, are consistent with previous published meta-analysis which all showed greater BMI is associated with increased risk of HL [6], NHL [6], DLBCL [7], multiple myeloma [8] and leukaemia [9]. However, our meta-analysis included higher number of studies and we did separate analysis for BMI in early adulthood. We also investigated the associations by subgroup analyses, including sex, geographical locations, size of cohort, number of cases, years of follow up, exposure assessment methods, and adjustment for potential confounders for all types of lympho-hematopoietic cancers, providing a more comprehensive estimate of the effects of adiposity in the incidence of lympho-hematopoietic cancers.

The analysis on height also revealed that greater height was associated with increased risk of lymphomas, multiple myeloma and leukaemia, and the increased risks ranged from 5% in multiple myeloma to 10% in DLBCL, respectively.

Our results on abdominal obesity and the risk of lympho-hematopoietic cancers using WHR and waist circumference measures showed an increased risk of DLBCL by12% with higher

WHR, and no association was found between higher waist circumferences and risk of multiple myeloma which could be due to limited number of studies (n=3).

Several risk factors of haematological malignancies have been identified including radiation, chemicals (e.g. benzene for AML [66]), viruses (e.g. Epstein Barr virus for adult HL [67]), HIV infection[68], hepatitis C virus for NHL [69] and some conditions such as autoimmune disease and chronic inflammatory conditions [7,9]. However, less is known about lifestyle factors. There are several potential mechanisms whereby excess body fatness may increase the risk of haematological malignancies [70,71]. Body fatness and obesity leads to changes in circulating levels of adipocytokines, including adiponectin, resistin, and leptin, and these hormones can affect insulin resistance, immunity, and inflammation[7,70-75]. Leptin has pro-inflammatory properties and promotes the growth of some cancer cells, and it stimulates the proliferation of normal haematopoietic cells and circulating monocytes producing pro-inflammatory cytokines [71,75]. Also, obesity may increase the risk of lymphoma by affecting insulin resistance and hyper-insulinemia which leads to increased bio-available insulin-like growth factor-I (IGF-I)[71]. IGF-I is known to act as a growth factor which promotes cell proliferation and inhibits apoptosis through IGF-I receptor-mediated signalling mechanisms in various tissues, including haematopoietic cells [71].

Our meta-analysis has some limitations that should be taken into account when interpreting the results. Moderate proportions of between-study heterogeneity were observed in some analyses and remained largely unexplained by the factors explored in the current study. In some subgroup analyses, the number of studies was too small to allow full exploration of heterogeneity. Uncontrolled confounding maybe an issue, particularly for BMI and AML, where smoking which is linked to body weight [76] has been shown to increase the risk of AML [77]

It is possible that our results could be biased due to the fact that most of studies used self-reported BMI rather than measured, and there is an observed tendency for overweight and obese people to overestimate height and underestimate weight compared to normal weight individuals. However, when we analysed the data according to measured or self-reported anthropometry the results were mostly similar, with confidence intervals overlapping.

Another limitation of the study is that not all studies separated the haematopoietic cancers according to the current WHO classification system. For instance, the most current lymphoid malignancy classification system typically considers CLL to be the same cancer as SLL and as such, CLL/SLL is considered as non-Hodgkin lymphoma. Some of the studies included in the meta-analysis for NHL include CLL and others may also include multiple myeloma. This potential source of heterogeneity could not be addressed. Also, there may be an overlapping of some cancers across groups.

A strength of our study are as follows:(i) inclusion of large studies with prospective design, which reduces the possibility of recall or selection bias (ii) large number of studies with relatively long duration of follow up and large number of cases that increase the statistical power of our analysis, and (iii) the nonlinear analyses which allowed us to examine the shape of the dose–response relationships.

Conclusion

In conclusion, our results revealed that greater BMI in adulthood as well as greater height may increase the risk of lympho-hematopoietic cancers and this adds to a growing body of evidence linking body fatness to several types of cancers.

Acknowledgment: The authors' responsibilities were as follows—L. A., D.S.M.C, J.S, M.C., N.N and A.R.V: performed the updated literature search and the updated data extraction; L. A., and J. G. S: conducted statistical analyses. L.A: wrote the first draft of the original manuscript, had primary responsibility for the final content of the manuscript, and took responsibility for the integrity of data and accuracy of the data analysis; C. S.: was database manager for the project D.A reviewed the manuscripts. C. G.: advised on and contributed to statistical analyses.

T. N. is the principal investigator of the Continuous Update Project at Imperial College. All authors commented on drafts of the paper and approved the final version.

The views expressed in this review are the opinions of the authors. The views may not represent the views of World Cancer Research Fund International/American Institute for Cancer Research and may differ from those in future updates of the evidence related to food, nutrition, physical activity, and cancer risk. The sponsor of this study had no role in the decisions about the analysis or interpretation of the data; or preparation, review, or approval of the manuscript.

Funding: This work was funded by the World Cancer Research Fund network (grant number 2007/SP01) as part of the Continuous Update Project (http://www.wcrf-uk.org/).

Conflict of interest: None of the authors reported a conflict of interest related to the study.

Table 1. Summary of results

	BMI, per 5 kg/m²					BMI in early adulthood (age 18-21 yrs), per 5 kg/m²				
	n	Cases	RR (95% CI)	I^2 (%)	P_h	*n*	Cases	RR (95% CI)	I^2 (%)	P_h
Incidence										
Hodgkin's Lymphoma										
All studies	5	1 776	1.12 (1.05-1.20)	1.9%,	0.40					
Stratified by sex										
Men	2	932	1.00 (0.90-1.10)	0%,	0.34					
Women	2	756	1.23 (1.13-1.34)	0%,	0.49					
Stratified by geographic location										
Europe	3	1688	1.14 (1.02-1.27)	47.9%,	0.15					
North America	1	57	1.08 (0.74-1.57)	-	-					
Asia	1	31	1.31(0.66-2.63)	-	-					
Non-Hodgkin's Lymphoma										
All studies	20	30 898	1.05 (1.03-1.08)	45%,	0.02	7	6 211	1.12 (1.05-1.19)	43%	0.10
Stratified by sex										
Men	7	7 910	1.06 (1.02-1.09)	0%,	0.64	3	2 052	1.09 (0.95-1.27)	76%	0.01
Women	10	12 287	1.04 (1.00-1.09)	62%,	<0.01	5	2 990	1.13 (1.05-1.21)	0%	0.73
Stratified by geographic location										
Europe	7	21 413	1.05 (1.01-1.09)	55%,	0.04					
North America	9	8 940	1.05 (1.01-1.10)	54%,	0.02	7	6 211	1.12 (1.05-1.20)	43%	0.10
Asia	3	545	1.13 (0.97-1.31)	0%,	0.67					
Diffuse Large Beta Cell Lymphoma										
All studies	19	3 109	1.11(1.05-1.16)	16%	0.29	8	1 315	1.22 (1.09-1.37)	0%	0.77
Stratified by sex										
Men	10	410	1.12 (0.93-1.33)	21.7%	0.28	2	211	1.09 (0.78-1.52)	36%	0.21

Women	13	2 082	1.12 (1.07-1.18)	0%	0.61	5	730	1.28 (1.08-1.51)	0%	0.83
Stratified by geographic location										
Europe	10	1 634	1.13 (1.01-1.26)	43%	0.15	1	182	1.26 (0.97-1.62)		
North America	8	1 653	1.08 (1.02-1.15)	0%	0.55	7	1 133	1.21 (1.07-1.38)	0%	0.68
Asia										
Follicular Lymphoma										
All studies	19	2 546	1.03 (0.98-1.09)	3%	0.41	8	858	1.19 (1.03-1.38)	2%	0.41
Stratified by sex										
Men	10	252	1.19 (0.70-2.00)	79.8%	<0.01	2	113	1.11 (0.73-1.68)	0%	0.40
Women	13	1 799	1.03 (0.97-1.09)	0%	0.87	5	528	1.33 (1.11-1.58)	0%	0.60
Stratified by geographic location										
Europe	10	1 325	0.97 (0.91-1.05)	0%	0.44	1	67	0.96 (0.60-1.53)		
North America	8	1 221	1.08 (1.01-1.16)	0%	0.74	7	791	1.22 (1.04-1.43)	3%	0.40
Asia										
Multiple Myeloma										
All studies	23	7 807	1.06 (1.03-1.10)	13%	0.31					
Stratified by sex										
Men	13	1 718	1.08 (1.00-1.17)	18.7%	0.29					
Women	15	2 600	1.06 (1.02-1.11)	0%	0.46					
Stratified by geographic location										
Europe	13	6 175	1.06 (1.02-1.10)	8%	0.37					
North America	7	1 531	1.06 (0.98-1.16)	30.6%	0.18					
Asia	1	101	1.24 (0.77-2.02)							
Leukaemia										
All studies	12	10 054	1.09 (1.03-1.15)	46%	0.05					
Stratified by sex										
Men	4	1 253	1.01 (0.90-1.14)	25.5%,	0.26					
Women	6	2 493	1.14 (1.04-1.25)	47.7%,	0.09					
Stratified by geographic location										
Europe	7	9 275	1.08 (1.02-1.14)	48.6%,	0.08					
North America	3	488	1.10 (0.94-1.29)	51.2%,	0.13					
Asia	2	291	1.27 (0.89-1.82)	64.8%,	0.09					

Acute Myeloid Leukaemia

All studies	7	3 679	1.13 (1.04-1.24)	48%,	0.09
Stratified by sex					
Men	3	1 665	1.07 (1.00-1.15)	0%,	0.75
Women	4	1 948	1.16 (1.03-1.32)	64.6%,	0.04
Stratified by geographic location					
Europe	6	3 607	1.10 (1.03-1.18)	23.6%,	0.26
North America	1	72	1.49 (1.12-1.98)	-	-
Asia	-		-	-	-

Chronic Myeloid Leukaemia

All studies	4	1 252	1.13 (1.05-1.22)	0%,	0.57
Stratified by sex					
Men	3	625	1.12 (0.97-1.29)	14%,	0.31
Women	2	449	1.11 (0.99-1.24)	0%,	0.93
Stratified by geographic location					
Europe	3	1 074	1.12 (1.04-1.22)	0%,	0.44
North America	1	178	1.21 (0.98-1.50)	-	-
Asia	-		-	-	-

Chronic Lymphocytic Leukaemia

All studies	7	3 820	1.04 (1.00-1.09)	0%,	0.65
Stratified by sex					
Men	3	2 196	1.04 (0.97-1.11)	7.7%,	0.34
Women	3	1 331	1.06 (1.00-1.13)	0%,	0.85
Stratified by geographic location					
Europe	6	3 736	1.04 (1.00-1.09)	0%,	0.54
North America	1	84	1.12 (0.84-1.48)	-	-
Asia	-		-	-	-

Height per 5 cm **Weight per 5 kg**

Non-Hodgkin's Lymphoma										
All studies	13	23 771	1.07 (1.05-1.10)	70%	<0.01	5	3 658	1.02 (0.99-1.06)	70%	0.01
Stratified by sex										
Men	5	8 493	1.06 (1.01-1.10)	88%	<0.01	1	460	1.01 (0.95-1.06)		
Women	9	13 194	1.08 (1.06-1.09)	0%	0.65	3	1 755	1.00 (0.98-1.02)	0%	0.65
Stratified by geographic location										
Europe	3	13 194	1.09 (1.06-1.12)	58%	0.09					
North America	9	10 389	1.06 (1.03-1.09)	62%	<0.01	4	3 470	1.02 (0.98-1.06)	76.3%	<0.01
Asia						1		1.06 (0.97-1.16)		
Diffuse Large Beta Cell Lymphoma										
All studies	11	3 202	1.10 (1.06-1.15)	41%	0.09	6	1 225	1.03 (0.98-1.07)	22%	0.89
Stratified by sex										
Men	3	308	0.99 (0.93-1.05)	0%	0.82	2	222	0.97 (0.89-1.06)	0%	0.97
Women	7	2 112	1.13 (1.08-1.17)	0%	0.95	5	789	1.03 (0.98-1.07)	15.7%	0.31
Stratified by geographic location										
Europe	3	1 499	1.13 (1.07-1.20)	18%	0.30	1		1.06 (0.95-1.17)		
North America	8	1 703	1.09 (1.03-1.15)	40%	0.13	5	1 081	1.03 (0.99-1.07)	36.1%	0.18
Asia										
Follicular Lymphoma										
All studies	11	2 443	1.09 (1.06-1.13)	0%	0.54	6	841	1.00 (0.96-1.04)	7%	0.37
Stratified by sex										
Men	3	176	1.13 (0.96-1.34)	45%	0.16	2	104	1.06 (0.91-1.24)	21.4%	0.26
Women	7	1 771	1.12 (1.06-1.18)	9%	0.36	5	575	0.98 (0.91-1.06)	50.5%	0.09
Stratified by geographic location										
Europe	3	1 213	1.13 (1.07-1.20)	0%	0.99	1		0.95 (0.85-1.07)		
North America	8	1 230	1.07 (1.02-1.11)	0%	0.52	5	710	1.01 (0.96-1.05)	14%	0.32
Asia										
Multiple Myeloma										
All studies	8	3 597	1.05 (1.02-1.08)	1%	0.42					

Stratified by sex										
Men	2	713	1.03 (0.98-1.08)	0%	0.33					
Women	7	2 605	1.08 (1.01-1.14)	41%	0.11					
Stratified by geographic location										
Europe	3	2 075	1.06 (1.01-1.10)	0%	0.79					
North America	5	1 481	1.06 (0.99-1.13)	38%	0.17					
Asia										
Leukaemia										
All studies	7	5 177	1.07 (1.03-1.11)	51.2%	0.06					
Stratified by sex										
Men	3	1 778	1.02 (0.99-1.06)	0%	0.77					
Women	7	3 399	1.10 (1.06-1.13)	13%	0.33					
Stratified by geographic location										
Europe	2	2 441	1.10 (1.05-1.16)	22%	0.26					
North America	4	2 194	1.05 (1.00-1.10)	29%	0.24					
Asia										
	Waist circumferences per 5 cm					**Waist to hip ratio per 0.1 unit**				
Diffuse Large Beta Cell Lymphoma										
All studies	5	694	1.06 (0.97-1.15)	0%	0.92	7	967	1.12 (1.01-1.26)	0%	0.71
Stratified by sex										
Men	2	131	1.14 (0.90-1.44)	0%	0.67	2	131	1.33 (1.00-1.77)	0%	0.84
Women	4	563	1.05 (0.96-1.14)	0%	0.92	5	696	1.12 (0.98-1.27)	0%	0.91
Stratified by geographic location										
Europe	1	133	1.16 (0.82-1.65)			1	133	1.02 (0.69-1.50)		
North America	4	561	1.05 (0.97-1.14)	0%	0.89	6	834	1.13 (1.01-1.27)	0%	0.62
Asia										
Follicular Lymphoma										
All studies	5	956	1.00 (0.92-1.09)			7	757	0.98 (0.86-1.11)	0%	0.84
Stratified by sex										
Men	2	509	1.00 (0.76-1.32)	2%	0.31	2	101	0.95 (0.64-1.41)	0%	0.80
Women	4	447	1.00 (0.91-1.10)	0%	0.81	5	539	0.96 (0.83-1.11)	0%	0.76
Stratified by geographic location										
Europe	1	532	0.86 (0.60-1.24)			1	124	0.87 (0.58-1.30)		
North America	4	424	1.01 (0.92-1.11)	0%	0.80	6	633	0.99 (0.87-1.14)	0%	0.80

Asia					
MM					
All studies	3	314	1.01 (0.97-1.05)	79.8%	<0.001

Mortality

BMI per 5 kg/m²

Non-Hodgkin's Lymphoma

All studies	6	3 570	1.15 (1.10-1.20)	0%	0.44
Stratified by sex					
Men	4	1 574	1.21 (0.94-1.56)	50%	0.11
Women	4	1 856	1.06 (0.91-1.24)	66%	0.03
Stratified by geographic location					
Europe	1	726	1.07 (0.96-1.20)		
North America	2	2 513	1.16 (1.11-1.22)	0%	0.46
Asia	3	331	1.18 (0.94-1.50)	22%	0.28

Multiple Myeloma

All studies	57	>2000	1.16 (1.07-1.25)	20%	0.27
Stratified by sex					
Men	15	903	1.12 (1.01-1.23)	0%	0.51
Women	21	1 039	1.13 (1.01-1.28)	38.5%	0.16
Stratified by geographic location					
Europe	1	284	1.25 (1.07-1.45)		
North America	3	678	1.09 (1.01-1.19)	0%	0.39
Asia	32	96	1.40 (0.81-2.42)	42%	0.19

Leukaemia

All studies	46	3 403	1.17 (1.05-1.30)	48.5%	0.06
Stratified by sex					
Men	44	1 899	1.17 (1.01-1.36)	37.5%	0.16

Women	40	1 493	1.13 (0.99-1.29)	55.4%	0.08
Stratified by geographic location					
Europe	2	536	1.06 (0.83-1.36)	54%	0.14
North America	3	2 621	1.21 (0.90-1.61)	74%	0.02
Asia	33	164	1.35 (1.01-1.80)	0%	0.81

Figure 1. Flowchart of study selection.

Figure 2. Dose–response and Non-linear meta-analysis of BMI and risk of HL cancer risk. RR, relative risk; 95% CI, 95% confidence interval. Summary RR calculated by using a random-effects model.

Figure 3. Dose–response meta-analysis of BMI and risk of NHL cancer risk. RR, relative risk; 95% CI, 95% confidence interval. Summary RR calculated by using a random-effects model.

Figure 4. Dose–response meta-analysis of BMI and risk of Multiple Myeloma cancer risk. RR, relative risk; 95% CI, 95% confidence interval. Summary RR calculated by using a random-effects model.

Figure 5. Dose–response meta-analysis of BMI and risk of Leukaemia, AML, CLL and CML cancers risk. RR, relative risk; 95% CI, 95% confidence interval. Summary RR calculated by using a random-effects model.

Reference List

1. Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128.9 million children, adolescents, and adults. Lancet 2017; 390: 2627-42.

2. Wormser D, Kaptoge S, Di AE et al. Separate and combined associations of body-mass index and abdominal adiposity with cardiovascular disease: collaborative analysis of 58 prospective studies. Lancet 2011; 377: 1085-95.

3. Singh GM, Danaei G, Farzadfar F et al. The age-specific quantitative effects of metabolic risk factors on cardiovascular diseases and diabetes: a pooled analysis. PLoS One 2013; 8: e65174.

4. IARC Handbooks of Cancer Prevention Volume 16: Body Fatness. 25-8-2016.

Ref Type: Online Source

5. Ferlay J . Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer. 2018.

Ref Type: Online Source

6. Larsson SC, Wolk A. Body mass index and risk of non-Hodgkin's and Hodgkin's lymphoma: a meta-analysis of prospective studies. Eur J Cancer 2011; 47: 2422-30.

7. Castillo JJ, Ingham RR, Reagan JL et al. Obesity is associated with increased relative risk of diffuse large B-cell lymphoma: a meta-analysis of observational studies. Clin Lymphoma Myeloma Leuk 2014; 14: 122-30.

8. Wallin A, Larsson SC. Body mass index and risk of multiple myeloma: a meta-analysis of prospective studies. Eur J Cancer 2011; 47: 1606-15.

9. Castillo JJ, Reagan JL, Ingham RR et al. Obesity but not overweight increases the incidence and mortality of leukemia in adults: a meta-analysis of prospective cohort studies. Leuk Res 2012; 36: 868-75.

10. Bhaskaran K, Douglas I, Forbes H et al. Body-mass index and risk of 22 specific cancers: a population-based cohort study of 5.24 million UK adults. Lancet 2014; 384: 755-65.

11. Bertrand KA, Giovannucci E, Zhang SM et al. A prospective analysis of body size during childhood, adolescence, and adulthood and risk of non-Hodgkin lymphoma. Cancer Prevention Research 2013; 864-73.

12. Murphy F, Kroll ME, Pirie K et al. Body size in relation to incidence of subtypes of haematological malignancy in the prospective Million Women Study. Br J Cancer 2013; 108: 2390-8.

13. Saberi HF, Romieu I, Gallo V et al. Anthropometric characteristics and risk of lymphoid and myeloid leukemia in the European Prospective Investigation into Cancer and Nutrition (EPIC). Cancer Causes Control 2013; 24: 427-38.

14. Hofmann JN, Moore SC, Lim U et al. Body mass index and physical activity at different ages and risk of multiple myeloma in the NIH-AARP diet and health study. Am J Epidemiol 2013; 177: 776-86.

15. Wang SS, Voutsinas J, Chang ET et al. Anthropometric, behavioral, and female reproductive factors and risk of multiple myeloma: a pooled analysis. Cancer Causes Control 2013; 24: 1279-89.

16. Kabat GC, Wu JW, Moore SC et al. Lifestyle and dietary factors in relation to risk of chronic myeloid leukemia in the NIH-AARP Diet and Health Study. Cancer Epidemiol Biomarkers Prev 2013; 22: 848-54.

17. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986; 7: 177-88.

18. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002; 21: 1539-58.

19. Hamling J, Lee P, Weitkunat R et al. Facilitating meta-analyses by deriving relative effect and precision estimates for alternative comparisons from a set of estimates presented by exposure level or disease category. Stat Med 2008; 27: 954-70.

20. Chene G, Thompson SG. Methods for summarizing the risk associations of quantitative variables in epidemiologic studies in a consistent form. Am J Epidemiol 1996; 144: 610-21.

21. Egger M, Davey SG, Schneider M et al. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997; 315: 629-34.

22. Fujino Y. Anthropometry, development history and mortality in the Japan Collaborative Cohort Study for Evaluation of Cancer (JACC). Asian Pac J Cancer Prev 2007; 8: 105-12.

23. Patel AV, Diver WR, Teras LR et al. Body mass index, height and risk of lymphoid neoplasms in a large United States cohort. Leuk Lymphoma 2013; 54: 1221-7.

24. Kabat GC, Kim MY, Jean WW et al. Anthropometric factors, physical activity, and risk of non-Hodgkin's lymphoma in the Women's Health Initiative. Cancer Epidemiol 2012; 36: 52-9.

25. Kabat GC, Heo M, Kamensky V et al. Adult height in relation to risk of cancer in a cohort of Canadian women. Int J Cancer 2013; 132: 1125-32.

26. Nagel G, Stocks T, Spath D et al. Metabolic factors and blood cancers among 578,000 adults in the metabolic syndrome and cancer project (Me-Can). Ann Hematol 2012; 91: 1519-31.

27. Andreotti G, Hou L, Freeman LEB et al. Body mass index, agricultural pesticide use, and cancer incidence in the Agricultural Health Study cohort. Cancer Causes & Control 2010; 21: 1759-75.

28. Kanda J, Matsuo K, Inoue M et al. Association of anthropometric characteristics with the risk of malignant lymphoma and plasma cell myeloma in a Japanese population: a population-based cohort study. Cancer Epidemiol Biomarkers Prev 2010; 19: 1623-31.

29. Troy JD, Hartge P, Weissfeld JL et al. Associations between anthropometry, cigarette smoking, alcohol consumption, and non-Hodgkin lymphoma in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. Am J Epidemiol 2010; 171: 1270-81.

30. Pylypchuk RD, Schouten LJ, Goldbohm RA et al. Body mass index, height, and risk of lymphatic malignancies: a prospective cohort study. Am J Epidemiol 2009; 170: 297-307.

31. Soderberg KC, Kaprio J, Verkasalo PK et al. Overweight, obesity and risk of haematological malignancies: a cohort study of Swedish and Finnish twins. Eur J Cancer 2009; 45: 1232-8.

32. Britton JA, Khan AE, Rohrmann S et al. Anthropometric characteristics and non-Hodgkin's lymphoma and multiple myeloma risk in the European Prospective Investigation into Cancer and Nutrition (EPIC). Haematologica 2008; 93: 1666-77.

33. Maskarinec G, Erber E, Gill J et al. Overweight and obesity at different times in life as risk factors for non-Hodgkin's lymphoma: the multiethnic cohort. Cancer Epidemiol Biomarkers Prev 2008; 17: 196-203.

34. Song YM, Sung J, Ha M. Obesity and risk of cancer in postmenopausal Korean women. J Clin Oncol 2008; 26: 3395-402.

35. Engeland A, Tretli S, Akslen LA et al. Body size and thyroid cancer in two million Norwegian men and women. British journal of cancer 2006; 95: 366.

36. Lim U, Morton LM, Subar AF et al. Alcohol, smoking, and body size in relation to incident Hodgkin's and non-Hodgkin's lymphoma risk. Am J Epidemiol 2007; 166: 697-708.

37. Birmann BM, Giovannucci E, Rosner B et al. Body mass index, physical activity, and risk of multiple myeloma. Cancer Epidemiol Biomarkers Prev 2007; 16: 1474-8.

38. Fernberg P, Odenbro A, Bellocco R et al. Tobacco use, body mass index and the risk of malignant lymphomas--a nationwide cohort study in Sweden. Int J Cancer 2006; 118: 2298-302.

39. Samanic C, Chow WH, Gridley G et al. Relation of body mass index to cancer risk in 362,552 Swedish men. Cancer Causes & Control 2006; 17: 901-9.

40. Oh SW, Yoon YS, Shin SA. Effects of excess weight on cancer incidences depending on cancer sites and histologic findings among men: Korea National Health Insurance Corporation Study. J Clin Oncol 2005; 23: 4742-54.

41. Rapp K, Schroeder J, Klenk J et al. Obesity and incidence of cancer: a large cohort study of over 145,000 adults in Austria. Br J Cancer 2005; 93: 1062-7.

42. Cerhan JR, Janney CA, Vachon CM et al. Anthropometric characteristics, physical activity, and risk of non-Hodgkin's lymphoma subtypes and B-cell chronic lymphocytic leukemia: a prospective study. Am J Epidemiol 2002; 156: 527-35.

43. Blair CK, Cerhan JR, Folsom AR et al. Anthropometric characteristics and risk of multiple myeloma. Epidemiology 2005; 16: 691-4.

44. Friedman GD, Herrinton LJ. Obesity and multiple myeloma. Cancer Causes Control 1994; 5: 479-83.

45. Hong JS, Yi SW, Yi JJ et al. Body mass index and cancer mortality among Korean older middle-aged men: a prospective cohort study. Medicine 2016; 95.

46. Gray L, Lee IM, Sesso HD et al. Association of body mass index in early adulthood and middle age with future site-specific cancer mortality: the Harvard Alumni Health Study. Ann Oncol 2012; 23: 754-9.

47. Ross JA, Parker E, Blair CK et al. Body mass index and risk of leukemia in older women. Cancer Epidemiol Biomarkers Prev 2004; 13: 1810-3.

48. Lu Y, Prescott J, Sullivan-Halley J et al. Body size, recreational physical activity, and B-cell non-Hodgkin lymphoma risk among women in the California teachers study. Am J Epidemiol 2009; 170: 1231-40.

49. Zhang S, Hunter DJ, Rosner BA et al. Dietary fat and protein in relation to risk of non-Hodgkin's lymphoma among women. J Natl Cancer Inst 1999; 91: 1751-8.

50. Khan MM, Mori M, Sakauchi F et al. Risk factors for multiple myeloma: evidence from the Japan Collaborative Cohort (JACC) study. Asian Pac J Cancer Prev 2006; 7: 575-81.

51. Chu DM, Wahlqvist ML, Lee MS et al. Central obesity predicts non-Hodgkin's lymphoma mortality and overall obesity predicts leukemia mortality in adult Taiwanese. Journal of the American College of Nutrition 2011; 30: 310-9.

52. Calle EE, Rodriguez C, Walker-Thurmond K et al. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. N Engl J Med 2003; 348: 1625-38.

53. Teras LR, Kitahara CM, Birmann BM et al. Body size and multiple myeloma mortality: a pooled analysis of 20 prospective studies. Br J Haematol 2014; 166: 667-76.

54. Parr CL, Batty GD, Lam TH et al. Body-mass index and cancer mortality in the Asia-Pacific Cohort Studies Collaboration: pooled analyses of 424,519 participants. Lancet Oncol 2010; 11: 741-52.

55. Sonderman JS, Bethea TN, Kitahara CM et al. Multiple Myeloma Mortality in Relation to Obesity Among African Americans. J Natl Cancer Inst 2016; 108.

56. Reeves GK, Pirie K, Beral V et al. Cancer incidence and mortality in relation to body mass index in the Million Women Study: cohort study. BMJ 2007; 335: 1134.

57. Chiu BC, Gapstur SM, Greenland P et al. Body mass index, abnormal glucose metabolism, and mortality from hematopoietic cancer. Cancer Epidemiol Biomarkers Prev 2006; 15: 2348-54.

58. Engeland A, Tretli S, Hansen S et al. Height and body mass index and risk of lymphohematopoietic malignancies in two million Norwegian men and women. American journal of epidemiology 2007; 165: 44-52.

59. De Roos AJ, Ulrich CM, Ray RM et al. Intentional weight loss and risk of lymphohematopoietic cancers. Cancer Causes Control 2010; 21: 223-36.

60. Fernberg P, Odenbro A, Bellocco R et al. Tobacco use, body mass index, and the risk of leukemia and multiple myeloma: a nationwide cohort study in Sweden. Cancer Res 2007; 67: 5983-6.

61. Tulinius H, Sigfusson N, Sigvaldason H et al. Risk factors for malignant diseases: a cohort study on a population of 22,946 Icelanders. Cancer Epidemiol Biomarkers Prev 1997; 6: 863-73.

62. Batty GD, Shipley MJ, Jarrett RJ et al. Obesity and overweight in relation to organ-specific cancer mortality in London (UK): findings from the original Whitehall study. Int J Obes (Lond) 2005; 29: 1267-74.

63. Kabat GC, Kim MY, Hollenbeck AR et al. Attained height, sex, and risk of cancer at different anatomic sites in the NIH-AARP diet and health study. Cancer Causes Control 2014; 25: 1697-706.

64. Kabat GC, Anderson ML, Heo M et al. Adult stature and risk of cancer at different anatomic sites in a cohort of postmenopausal women. Cancer Epidemiology and Prevention Biomarkers 2013; 22: 1353-63.

65. Sung J, Song YM, Lawlor DA et al. Height and site-specific cancer risk: a cohort study of a Korean adult population. American journal of epidemiology 2009; 170: 53-64.

66. Loomis D, Guyton KZ, Grosse Y et al. Carcinogenicity of benzene. Lancet Oncol 2017; 18: 1574-5.

67. Vockerodt M, Yap LF, Shannon-Lowe C et al. The Epstein-Barr virus and the pathogenesis of lymphoma. J Pathol 2015; 235: 312-22.

68. Yarchoan R, Uldrick TS. HIV-Associated Cancers and Related Diseases. N Engl J Med 2018; 378: 1029-41.

69. Torres HA, Shigle TL, Hammoudi N et al. The oncologic burden of hepatitis C virus infection: A clinical perspective. CA Cancer J Clin 2017; 67: 411-31.

70. Lichtman MA. Obesity and the risk for a hematological malignancy: leukemia, lymphoma, or myeloma. Oncologist 2010; 15: 1083-101.

71. Dalamaga M, Christodoulatos GS. Adiponectin as a biomarker linking obesity and adiposopathy to hematologic malignancies. Horm Mol Biol Clin Investig 2015; 23: 5-20.

72. Askmyr M, Quach J, Purton LE. Effects of the bone marrow microenvironment on hematopoietic malignancy. Bone 2011; 48: 115-20.

73. Harvey AE, Lashinger LM, Hursting SD. The growing challenge of obesity and cancer: an inflammatory issue. Ann N Y Acad Sci 2011; 1229: 45-52.

74. Meijer K, de VM, Al-Lahham S et al. Human Primary Adipocytes Exhibit Immune Cell Function: Adipocytes Prime Inflammation Independent of Macrophages. PLoS One 2011; 6.

75. Park J, Euhus DM, Scherer PE. Paracrine and endocrine effects of adipose tissue on cancer development and progression. Endocr Rev 2011; 32: 550-70.

76. Chiolero A, Faeh D, Paccaud F et al. Consequences of smoking for body weight, body fat distribution, and insulin resistance. Am J Clin Nutr 2008; 87: 801-9.

77. Colamesta V, D'Aguanno S, Breccia M et al. Do the smoking intensity and duration, the years since quitting, the methodological quality and the year of publication of the studies affect the results of the meta-analysis on cigarette smoking and Acute Myeloid Leukemia (AML) in adults? Crit Rev Oncol Hematol 2016; 99: 376-88.