Original Study

Obesity Is Associated With Increased Relative Risk of Diffuse Large B-Cell Lymphoma: A Meta-Analysis of Observational Studies

Jorge J. Castillo,[1] Randall R. Ingham,[2] John L. Reagan,[2] Michael Furman,[3] Samir Dalia,[4] Joanna Mitri[5]

Abstract

Our study aimed at evaluating the relation, if any, between obesity and diffuse large B-cell lymphoma (DLBCL). We pooled and analyzed data from 16 studies accounting for approximately 7500 cases of DLBCL. We found an approximately 30% increase in the relative risk of DLBCL in obese individuals; this increase was consistent among men and women.

Background: The relation between body mass index (BMI) and incidence of diffuse large B-cell lymphoma (DLBCL) has been suggested, but no systematic review has been undertaken. **Material and Methods:** We performed a literature search through December 2012. Meta-analyses were performed to quantify the relative risk (RR) of DLBCL incidence in overweight and obese persons compared with normal weight individuals using the random-effects model. Subset analyses were performed according to study design, sex, and geographic region. Overweight was defined as a BMI 25 to 29.9 kg/m^2, and obesity was defined as a BMI of 30 kg/m^2. Meta-regression, using an unrestricted maximum likelihood model, was performed to evaluate the linear association between BMI and odds of DLBCL. **Results:** Our study included 6 case-control and 10 cohort studies. The RR of DLBCL in overweight individuals was 1.14 (95% confidence interval [CI], 1.04-1.24; $P = .004$), and in obese individuals, RR was 1.29 (95% CI, 1.16-1.43; $P < .001$). The RR of DLBCL in overweight men and women was 1.22 and 1.27, respectively. In overweight individuals, both prospective and case-control studies showed an RR of 1.13. The RR of DLBCL in obese men and women was 1.40 and 1.34, respectively. In obese individuals, the RR in prospective studies was 1.25 and in case-control studies it was 1.33. Meta-regression analysis showed a 14% increase in DLBCL incidence for each 10 kg/m^2 increase in BMI. **Conclusion:** An increased BMI is associated with higher RR of DLBCL regardless of sex. Also, there seems to be a linear association between BMI and DLBCL incidence.

Clinical Lymphoma, Myeloma & Leukemia, Vol. 14, No. 2, 122-30 © 2014 Elsevier Inc. All rights reserved.
Keywords: Body mass index, Epidemiology, Lymphoma, Meta-analysis, Obesity

Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common non-Hodgkin lymphoma subtype, accounting for approximately 25% to 30% of cases in Western countries.[1,2] Although few specific risk factors for DLBCL have been described—eg, HIV infection and autoimmune conditions among others—a definitive cause cannot be found in the large majority of cases. Hence, it is likely that other more subtle risk factors could be at play.

Overweight and obesity have emerged as risk factors for a variety of malignancies.[3] Based on standard criteria, overweight is defined by a body mass index (BMI) between 25 and 29.9 kg/m^2, whereas obesity is defined as a BMI of $\geq$ 30 kg/m^2.[4] Previous studies evaluating the association between obesity and DLBCL have rendered inconclusive results because some studies have shown a positive association,[5,6] whereas others have shown mixed results.[7,8] As long as the events on the exposed population are rare, the relative

This work was presented in part as an oral presentation at Lymphoma & Myeloma 2012: An International Congress on Hematologic Malignancies; October 25-27, 2012; New York, NY and as a poster presentation at the 54th American Society of Hematology Annual Meeting and Exposition; December 8-11; Atlanta, GA.

[1]Division of Hematologic Malignancies, Dana Farber Cancer Institute, Boston, MA
[2]Division of Hematology and Oncology
[3]Department of Medicine
Rhode Island Hospital, Providence, RI
[4]Division of Hematology and Oncology, Moffitt Cancer Center and Research Institute, Tampa, FL
[5]Service of Endocrinology, Prima CARE, Fall River, MA

Submitted: May 9, 2013; Revised: Oct 1, 2013; Accepted: Oct 21, 2013; Epub: Nov 14, 2013

Address for correspondence: Jorge J. Castillo, MD, M221, 450 Brookline Ave, Boston, MA 02215
Fax: 617-632-4862; e-mail contact: jorgej_castillo@dfci.harvard.edu

2152-2650/$ - see frontmatter
http://dx.doi.org/10.1016/j.clml.2013.10.005

risk (RR) from prospective cohort studies and the odds ratio (OR) from case-control studies are virtually equivalent.[9] Hence, the combination of such studies is statistically sound and could provide additional information about the relation between BMI and DLBCL by increasing the study sample size.

Using a meta-analysis of case-control and cohort studies, the main objective of our study was to evaluate and quantify the association that overweight and obesity could have with the incidence of DLBCL. Additionally, secondary objectives looked to assess the effect that BMI has in the incidence of DLBCL according to study design, sex, and geographic region.

Material and Methods

Literature Search, Data Gathering, and Quality Assessment

A literature search using PubMed, EMBASE, and the Cochrane Database for Systematic Reviews through December 31, 2012 was performed. The key search was *(obesity OR overweight OR "body mass index" OR BMI) AND lymphoma*. Reference lists of each selected study and published meta-analyses were reviewed looking for missing studies. An article was relevant if it contained data from an epidemiologic study reporting on the association between BMI and incidence of DLBCL in adults, regardless of the language in which it was written. If there were multiple publications from the same study, the most recent or relevant (or both) was selected using older publications for methodology. If a publication included data on multiple studies (pooled analysis), data from each separate study was used, whenever possible. Cross- sectional studies, narrative reviews, letters to the editor, and editorials were excluded. Abstracts from scientific conferences were not included.

For case-control studies, we extracted author, year of publication, country or region of origin, sample size, inclusion and exclusion criteria for cases and controls, methods of ascertainment of obesity and DLBCL, the outcome measured (OR) and the variables used for matching, if applicable. For cohort studies, we also extracted the source of the exposed and unexposed cohorts, years of follow-up, the source of expected incidence, the outcome measured (RR), and the variables used for adjustment, if applicable. For the ascertainment of DLBCL, we included studies that classified DLBCL cases based on the World Health Organization (WHO) or the Revised European American Lymphoma (REAL) classification. For missing information, attempts were made to contact the authors of the original studies.

The quality of the studies was assessed using the Newcastle-Ottawa Scale (NOS).[10] Empirically, we assigned scores of 7 to 9 for high-, 4 to 6 for intermediate-, and 1 to 3 for low-quality studies. Literature search (RRI, JJC), study selection (RRI, JJC), data gathering (RRI, JRL, MF, SD), and quality assessment (RRI, JRL, MF, SD) were performed independently. Any discrepancies between reviewers were addressed by a joint reevaluation of the article with the principal investigator. The results of this meta-analysis are presented in accordance with the checklist proposed by the Meta-analysis of Observational Studies group.[11]

Data Analysis

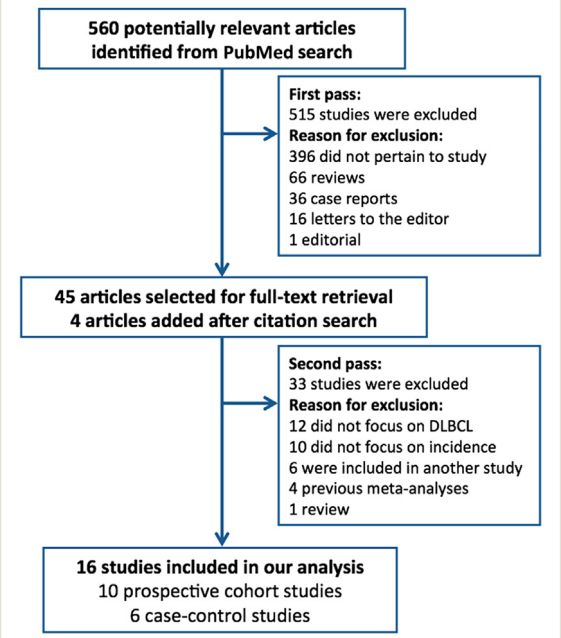
Based on WHO criteria, overweight was defined as a BMI between 25 and 29.9 kg/m^2, and obesity was defined as a BMI of $\geq$ 30 kg/m^2. The primary outcome measured was the maximally adjusted RR with 95% confidence interval (95% CI) of the development of DLBCL in overweight and obese individuals when compared with individuals with normal BMIs, which was defined as $<$ 25 kg/m^2. The random-effects model (DerSimonian-Laird method) was used to estimate the outcome of interest.[12] Heterogeneity was assessed using the I^2 index.[13] I^2 values of 25%, 50%, and 75% are consistent with mild, moderate, and severe heterogeneity, respectively. Publication bias was identified by direct observation of funnel plots[14] and measured by the trim-and-fill method, which estimates the potential effect that nonpublished (imputed) studies might have had on the outcome.[15] The actual RR values are reported throughout the article unless otherwise noted. Meta-regression analysis using the unrestricted maximum likelihood method was used to assess the linear relation between BMI as a continuous variable and the incidence of DLBCL. The value in kilograms per meter squared assigned to each category was the midpoint for closed categories.[16] For open categories, we assumed lowest and highest BMI at 16 and 50 kg/m^2, respectively. Such a BMI range would include at least 95% of the population within the United States.[17] All calculations and graphs were obtained using Comprehensive Meta-Analysis, version 2 (Biostat Inc, Englewood, NJ).

Results

Search Results

Our PubMed search rendered 560 articles, from which we included 16 epidemiologic studies, 6 case-control studies,[8,18-22] and 10 prospective cohort studies.[5,6,23-30] The search flow is shown in Figure 1. Our search on EMBASE and the Cochrane Database

Figure 1 Search Strategy



Abbreviation: DLBCL = diffuse large B-cell lymphoma.

Table 1 Main Characteristics of Cohort Studies Evaluating the Association Between Body Mass Index and the Incidence of DLBCL

Author (Year)	Source Cohort (Region)	Total Cohort (No. Cases)	Follow-Up (Enrollment) (Years)	DLBCL Ascertainment	BMI Ascertainment	Adjustments	NOS
Cerhan (2002)	Iowa Women's Health Study, US	37,931 (137)	13 (1986-1998)	Iowa Cancer Registry	Self-reported	Age	8
Lim (2007)	NIH-AARP Diet and Health Study, US	473,984 (346)	5 (1995-2000)	Cancer Registry Data and Cause of Death Registry	Self-reported	Age, sex, ethnicity, alcohol intake, physical activity	8
Britton (2008)	EPIC cohort, Europe	371,983 (144)	9 (1993-1998)	Population cancer registries or active follow-up	Measured	Age, study center	9
Maskarinec (2008)	Multiethnic cohort, Hawaii and California, US	193,051 (284)	10 (1993-1996)	Hawaii, Los Angeles and California cancer registries	Self-reported	Age, ethnicity, education, alcohol intake	8
Lu (2009)	California Teachers' Study, US	121,216 (155)	11 (1995-2007)	California cancer registry	Self-reported	Age, ethnicity, alcohol intake	7
Pylypchuk (2009)	Netherlands Cohort Study on Diet and Cancer, the Netherlands	120,852 (224)	13 (1986)	Netherlands cancer and pathology registry	Self-reported	Age, sex	8
Troy (2010)	NCI Prostate, Lung, Colorectal, and Ovarian cancer screening trial, US	142,982 (215)	9 (1993-2001)	Self-reported with screening center confirmation	Self-reported	Age, sex, ethnicity, education	7
Kabat (2012)	Womens' Health Initiative Observational Study, US	158,975 (302)	11 (1993-1998)	Self-reported with centralized verification of medical records and pathology reports	Self-reported	Age, alcohol history, smoking history, education, caloric intake, ethnicity	9
Nagel (2012)	Me-Can project, Austria, Norway and Sweden	575,386 (195)	11-13 (1972-2005; variable)	National cancer registries, Austria, Norway, and Sweden	Measured	Age, sex, smoking history	9
Patel (2013)	American Cancer Society Cancer Prevention Study-II Nutrition Cohort, US	152,423 (443)	15 (1992-2007)	Self-reported and confirmed by medical records or linkage with state cancer registries	Self-reported	Age, family history, alcohol history, education, smoking history, physical activity	9

Abbreviations: BMI = body mass index; DLBCL = diffuse large B-cell lymphoma; NCI = National Cancer Institute; PLCO = Prostate, Lung, Colorectal, and Ovarian; NIH-AARP = National Institutes of Health-American Society of Retired Persons; NOS = Newcastle-Ottawa scale.

of Systematic Reviews did not provide additional studies. Case-control studies accounted for 4904 cases and 25,084 controls, whereas prospective cohort studies accounted for 2445 cases identified in a cohort of > 2.3 million individuals. Characteristics of the studies included in our meta-analysis are shown in Tables 1 and 2.

Overweight and DLBCL

Overweight individuals had an RR of 1.14 (95% CI, 1.04-1.24; $P = .004$) for the development of DLBCL when compared with normal weight individuals. The RR in prospective studies was 1.13 (95% CI, 1.02-1.25; $P = .02$) and in case-control studies it was 1.13 (95% CI, 0.98-1.32; $P = .10$). The RR of DLBCL was significantly increased in overweight women (RR, 1.22; 95% CI, 1.07-1.38; $P = .002$) as well as men (RR, 1.27; 95% CI, 1.09-1.47; $P = .002$). RR was significantly increased in American (RR, 1.15; 95% CI, 1.05-1.25; $P = .002$) and Asian (RR, 1.31; 95% CI, 1.10-1.55; $P = .002$) individuals, but not in Europeans (RR; 1.05; 95% CI, 0.84-1.32; $P = .44$). Heterogeneity and publication bias assessments with imputed RRs are shown in Table 3. Forest plots are shown in Figure 2.

Obesity and DLBCL

For obese individuals, the RR of DLBCL was 1.29 (95% CI, 1.16-1.43; $P < .001$) when compared with individuals with normal BMIs. The RR in obese women was 1.33 (95% CI, 1.14-1.56; $P < .001$), and in obese men the RR was 1.25 (95% CI, 1.08-1.45; $P = .003$). The RR in prospective studies was 1.25 (95% CI, 1.08-1.48; $P = .003$) and in case-control studies it was 1.33 (95% CI, 1.14-1.56; $P < .001$). The RR was significantly increased in American (RR, 1.37; 95% CI, 1.23-1.51; $P < .001$) and Asian (RR, 1.36; 95% CI, 1.08-1.70; $P = .008$), but not in European studies (RR 1.08; 95% CI, 0.77-1.51; $P = .65$). Heterogeneity and publication bias assessment with imputed RRs are shown in Table 4. Forest plots are shown in Figure 3.

Meta-Regression

Meta-regression analyses showed a relative OR (rOR) of DLBCL incidence of 1.014 per kg/m^2 of BMI with a significant linear association ($P = .03$) (Fig. 4). Based on our model, the rOR is 1.00 (reference) at a BMI of approximately 20 kg/m^2, and the rOR of DLBCL would increase by 14% per 10 kg/m^2 increase in BMI. Hence, the increase in rOR of DLBCL in individuals with BMIs of 30 and 40 kg/m^2 would be 14% and 28%, respectively. No linear association was found in women ($P = .76$), but there was a trend for an association in men ($P = .07$) (data not shown). A linear association was seen in American individuals ($P = .01$), and there was a trend in Asian individuals ($P = .06$), but no association was identified in European individuals ($P = .46$) (data not shown).

Discussion

In recent years, several epidemiologic studies have looked deeper into the cause of lymphomas. Lymphomas are a very heterogeneous group of diseases characterized by the uncontrolled malignant growth of immature and mature lymphocytes. Given the biological, clinical, pathologic, and genetic heterogeneity associated with the development of lymphomas, it is likely there is an inherent heterogeneity in their cause as well. As support to this paradigm,

Table 2 Main Characteristics of Case-Control Studies Evaluating the Association Between Body Mass Index and the Incidence of DLBCL

Author (Year)	Source Cases (No.)	Source Controls (No.)	Period of Enrollment	DLBCL Ascertainment	BMI Ascertainment	Matching	NOS
Skibola (2004)	San Francisco Bay area, US (510)	Population based (2400)	1988-1995	California Cancer Centers' rapid case ascertainment (97% pathologic confirmation)	Self-reported	Age, sex, residence	8
Pan (2005)	Eight Canadian provinces, Canada (419)	Population based (3106)	1994-1997	National enhanced cancer surveillance system (pathology reports)	Self-reported	Age, sex	8
Morton (2008)	Four SEER registries, US (416)	Population based (1057)	1998-2000	Cancer registries (confirmation by a local pathologist)	Self-reported	Age, sex, race, SEER registry	7
Willett (2008)	Eighteen case-control studies from Asia, Europe and US (3139)	Population based, outpatient clinics, and inpatient services (16,507)	1983-2004	Rapid case ascertainment techniques (100% pathologic confirmation)	Self-reported	Not reported	7
Chen (2011)	Connecticut (245)	Population based (868)	1996-2000	Yale Cancer Center's rapid case ascertainment shared resource (100% pathologic confirmation)	Self-reported	Age	7
Kelly (2012)	Mayo Clinic, Rochester, MN (175)	Clinic based (1146)	2002-2008	Medical records (100% pathologic confirmation)	Self-reported	Age, sex, residence	7

Abbreviations: BMI = body mass index; DLBCL = diffuse large B-cell lymphoma; NOS = Newcastle-Ottawa scale; SEER = Surveillance, Epidemiology and End Results.

Table 3 Outcome Estimates on the Association Between Overweight and DLBCL According to Study Design, Sex, and Geographic Region

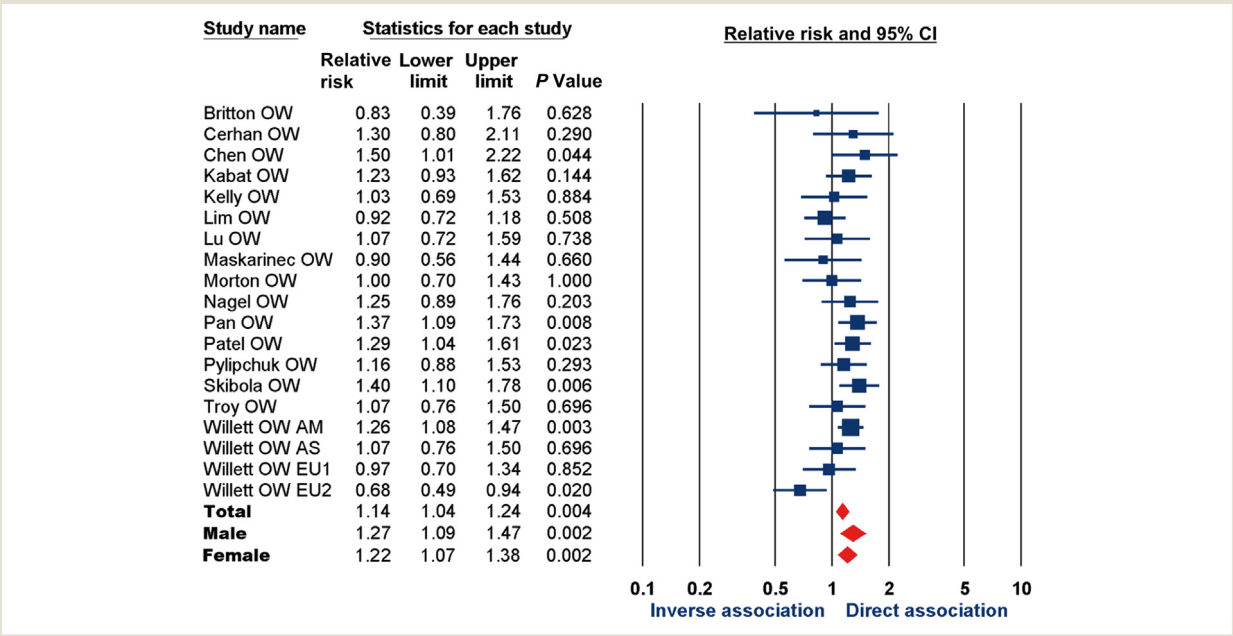
Overweight	No. Studies	RR (95% CI)	*P* Value	I^2 (%)	No. Imputed Studies	Adjusted RR (95% CI)[a]
All Studies	16	1.14 (1.04-1.24)	.004	33	6 — right	1.24 (1.12-1.37)
Study Design						
Case-control	6	1.13 (0.98-1.32)	.10	59	—	—
Cohort	10	1.13 (1.02-1.25)	.02	0	1 — right	1.13 (1.03-1.25)
Sex						
Male	6	1.27 (1.09-1.47)	.002	0	2 — right	1.34 (1.11-1.60)
Female	11	1.22 (1.07-1.38)	.002	0	2 — right	1.23 (1.09-1.39)
Geographic Region						
US	10	1.15 (1.05-1.25)	.002	0	4 — right	1.22 (1.10-1.36)
Asia	3	1.31 (1.10-1.55)	.002	0	—	—
Europe	5	1.05 (0.84-1.32)	.44	64	—	—

Abbreviations: CI = confidence interval; DLBCL = diffuse large B-cell lymphoma; RR = relative risk.
[a]Adjusted for publication bias analysis.

a variety of viral and bacterial infections and chronic inflammatory and autoimmune processes, among other conditions, have been associated with specific types of lymphoma.

Overweight and obesity have emerged as risk factors for a variety of hematologic malignancies.[31-33] Using a meta-analysis of case-control and cohort studies, our study aimed to evaluate the relation between BMI and risk of DLBCL. Based on the results of our meta-analysis, overweight and obese individuals have approximately a 15% and 30% higher risk for the development of DLBCL, respectively, than do individuals with normal BMIs. Overall, the results are consistent when evaluating prospective cohort and case-control studies separately, with mild to moderate heterogeneity. The odds of the incidence of DLBCL appear increased in both men and women. Finally, the risk of DLBCL appears increased in overweight and obese individuals from American and Asian studies. There was no increased risk of DLBCL seen in European studies. Meta-regression analyses showed a linear association between BMI and DLBCL. However, our analysis by sex did not reach statistical

Figure 2 Estimate of the Relative Risk (RR) of the Incidence of Diffuse Large B-Cell Lymphoma (DLBCL) in Overweight Individuals



Abbreviation: CI = confidence interval.

Table 4 Outcome Estimates on the Association Between Obesity and DLBCL According to Study Design, Sex, and Geographic Region

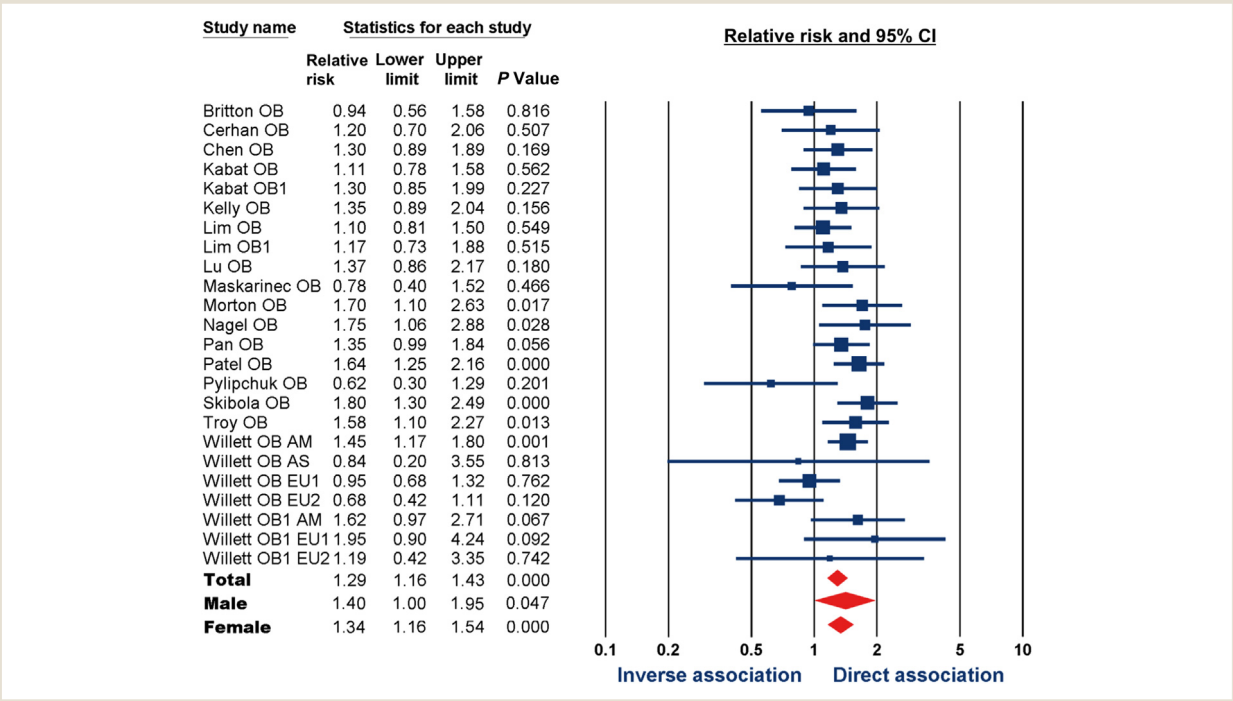
Obesity	No. Studies	RR (95% CI)	*P* Value	I^2 (%)	No. Imputed Studies	Adjusted RR (95% CI)[a]
All Studies	16	1.29 (1.16-1.43)	<.001	32	4 — right	1.36 (1.21-1.53)
Study Design						
Case-control	6	1.33 (1.14-1.56)	<.001	40	—	—
Cohort	10	1.25 (1.08-1.45)	.003	27	2 — right	1.31 (1.12-1.53)
Sex						
Male	6	1.40 (1.00-1.95)	.047	55	—	—
Female	11	1.34 (1.16-1.54)	<.001	0	1 — right	1.36 (1.18-1.57)
Geographic Region						
America	10	1.37 (1.23-1.51)	<.001	0	4 — right	1.48 (1.32-1.66)
Asia	3	1.36 (1.08-1.70)	.008	0	1 — right	1.37 (1.10-1.71)
Europe	5	1.08 (0.77-1.51)	.65	69	1 — right	1.16 (0.84-1.59)

Abbreviations: CI = confidence interval; DLBCL = diffuse large B-cell lymphoma; RR = relative risk.
[a]Adjusted for publication bias analysis.

significance in men or women. There also was a linear association between BMI and DLBCL in American studies but not in Asian or European studies.

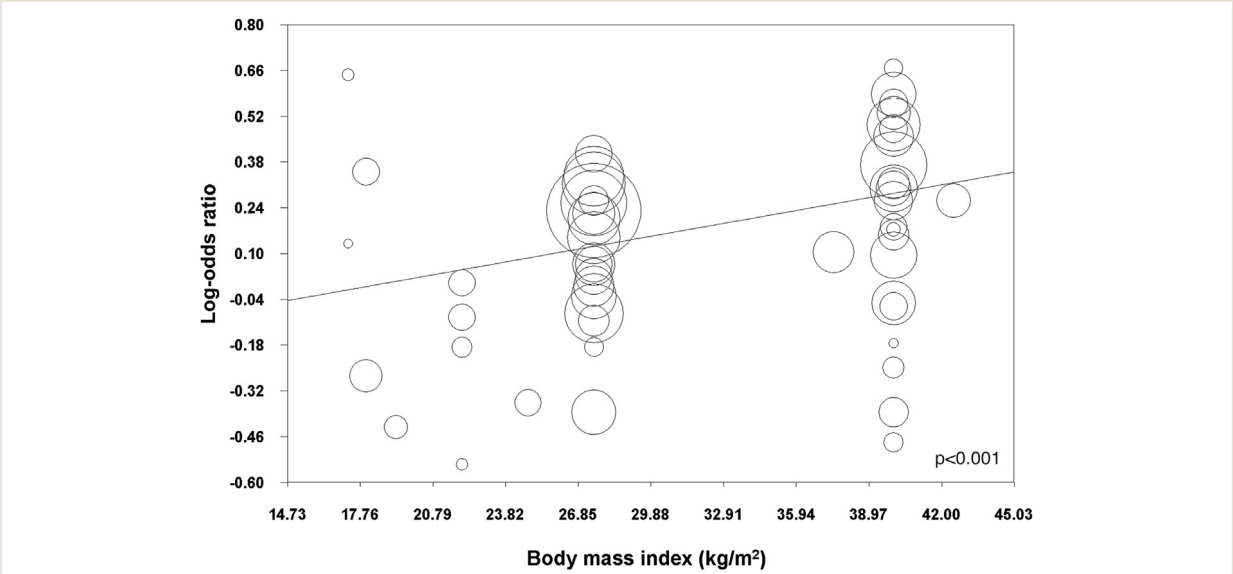
Obesity is a chronic inflammatory condition, which is characterized by an increased production of proinflammatory adipocytokines, hyperinsulinemia, and elevated levels of insulin-like growth factors, which have been associated with abnormalities in hematopoietic cell proliferation, differentiation, and apoptosis.[34,35] There is also evidence that the bone marrow microenvironment plays a key role in the initiation and maintenance of hematologic malignancies.[36] More recently, it has been shown that DLBCL cells lines depend on fatty acids for their survival and that fatty acid metabolism could be a potential therapeutic target for DLBCL.[37,38] Hence, the relationship between obesity and DLBCL is biologically

Figure 3 Estimate of the Relative Risk (RR) of the Incidence of Diffuse Large B-Cell Lymphoma (DLBCL) in Obese Individuals



Abbreviation: CI = confidence interval.

Figure 4 Linear Regression Analysis of the Association of the log-Odds of the Incidence of Diffuse Large B-Cell Lymphoma (DLBCL) and Body Mass Index (BMI) as a Continuous Variable



plausible. However, these are incomplete explanations, and the actual linking mechanisms between obesity and DLBCL remain to be elucidated.

In our study, we found a similar RR of DLBCL in obese men and women (RR, 1.25 and 1.33, respectively). In Surveillance, Epidemiology and End Results (SEER), the age-adjusted incidence of non-Hodgkin lymphoma is higher in men than in women. Between 2000 and 2010, the incidence rate in men has ranged between 23 and 24 cases per 100,000 individuals and in women it has ranged between 16 and 17 cases per 100,000 individuals.[39] Based on the most recent publication from Flegal et al, the prevalence of obesity in women is higher than in men.[17] Men then have lower rates of obesity than do women, but they also have a higher incidence of DLBCL. However, based on our study, obese men have a slightly lower risk of DLBCL than do obese women. One could then hypothesize that there could be a higher predisposition toward the development of DLBCL in obese women, which deserves further research. Such a hypothesis must be taken cautiously, because with any subset analysis any conclusion reached could have been biased based on sample selection or error or from chance alone. In a recent meta-analysis from our group, we identified an increased risk of the incidence of leukemia seen almost exclusively in obese men.[31] Conversely, the risk of myeloma seems to also be increased in both obese men and women.[33] It would be of interest to further investigate sex disparities in the incidence of DLBCL in the context of obesity.

There was a consistent increase in the risk of DLBCL in overweight and obese individuals in Asian and American studies but not in European ones. Current evidence supports differences in the incidence of specific lymphoma subtypes between continents.[2,40,41] However, differences in lymphoma subtype distribution based on overweight and obesity have not been previously reported. The prevalence rate of overweight and obesity in adults varies greatly between continents. In a recent report from the WHO,[42] the prevalence rate of overweight in the United States, Europe, and Asia was reported as $>$ 60%, 40% to 60%, and $<$ 40%, respectively. Similarly, the rates of obesity were $>$ 30%, 10% to 30%, and $<$ 10%, respectively. It was not unexpected that populations from different continents experienced different risks for DLBCL based on obesity. However, the relation between obesity and ethnicity definitely develops within the context of other environmental factors (ie, chemical exposure, viruses, and so on), which might also modify such risk. In a previous meta-analysis, the risk of leukemia seemed to be increased in obese individuals regardless of their ethnicity.[31] However, in another meta-analysis, the risk of myeloma seemed to be increased in European and American individuals but not in the Asian population.[33] Taken together, there are emerging data supporting a degree of variability in the incidence of hematologic malignancies depending on BMI and geographic location.

Our study has several weaknesses. First, most of the studies assessed BMI by self-report; a self-reported BMI lower than the actual BMI could direct our results toward the unity. However, recent epidemiologic studies have shown that self-reported BMI does not differ statistically from measured BMI, as long as the outcome is investigated in population-based settings and not for individual analysis.[43,44] Second, there are several potential confounding behavioral risk factors for the development of DLBCL associated with obesity that were partially accounted for, such as caloric intake, diet, and other lifestyle-related factors. Diabetes, eg, has been associated with an increase in the odds of hematologic malignancies[45]; however, none of the studies included here were adjusted based on diabetes status. Third, it is possible that other

anthropometric characteristics, such as percentage of fat, waist-to-hip ratio, BMI at a specific age, or changes in BMI over time, could also be of importance. Fourth, subgroup and meta-regression analyses could have been affected by small sample size, which could have increased the rate of false-negative results. For example, we were able to identify a linear association between BMI and risk of DLBCL using data from the entire group; however, when evaluating men and women separately, we failed to identify a statistically significant association. Finally, our results could have been affected by ecological bias, in which individual characteristics are inferred based on the characteristics of the group to which the individual belongs but may not necessarily apply to that individual.

Conclusion

Based on the results of our meta-analysis of epidemiologic studies, there seems to be increased risk of DLBCL in overweight and obese individuals. The increased risk of DLBCL is seen in both men and women. However, we identified specific differences according to geographic location. It is important to note that other potential factors associated with obesity, such as diet, exercise, diabetes or prediabetes and metabolic syndrome, among others, might also play a role in the incidence of DLBCL. From a public health perspective, overweight and obesity affect two thirds of the population in the United States. Further research should focus on investigating if by promoting weight loss or preventing overweight and obesity, the incidence of specific cancer subtypes, including DLBCL, could be reduced.

Clinical Practice Points

- Obesity, defined as a BMI > 30 kg/m^2, has been associated with an increased risk for several hematologic malignancies; however, the relation with DLBCL is unclear.
- Our meta-analysis found an increase of approximately 30% in the RR of DLBCL developing in obese individuals when compared with individuals with normal BMIs.
- The RR of DLBCL appears increased in both obese men and women and in American and Asian studies but not in European studies.
- Further studies are needed to evaluate if preventing obesity or promoting weight loss can decrease the incidence of DLBCL.

Acknowledgments

The authors would like to thank Dr Gabriele Nagel at the Institute of Epidemiology and Medical Biometry, Ulm University, Ulm, Germany, for providing information from the Metabolic Syndrome and Cancer Project; Dr Romana Pylypchuk at the Department of Epidemiology, School for Oncology and Developmental Biology, Maastricht University, Maastricht, the Netherlands, for providing information from the Netherlands Cohort Study on Diet and Cancer; and Dr Alpa Patel at the American Cancer Society in Atlanta, Georgia, United States, for providing information on the Cancer Prevention Study-3.

Disclosure

The authors have stated that they have no conflicts of interest.

References

1. Morton LM, Wang SS, Devesa SS, et al. Lymphoma incidence patterns by WHO subtype in the United States, 1992-2001. *Blood* 2006; 107:265-76.
2. Anderson JR, Armitage JO, Weisenburger DD. Epidemiology of the non-Hodgkin's lymphomas: distributions of the major subtypes differ by geographic locations. Non-Hodgkin's Lymphoma Classification Project. *Ann Oncol* 1998; 9: 717-20.
3. Renehan AG, Tyson M, Egger M, et al. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. *Lancet* 2008; 371:569-78.
4. World Health Organization. Obesity and overweight. Fact sheet No. 311. Available at: http://www.who.int/mediacentre/factsheets/fs311/en/index.html. Accessed: January 1, 2013.
5. 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.
6. 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.
7. Chang ET, Hjalgrim H, Smedby KE, et al. Body mass index and risk of malignant lymphoma in Scandinavian men and women. *J Natl Cancer Inst* 2005; 97:210-8.
8. Willett EV, Morton LM, Hartge P, et al. Non-Hodgkin lymphoma and obesity: a pooled analysis from the InterLymph Consortium. *Int J Cancer* 2008; 122: 2062-70.
9. Zhang J, Yu KF. What's the relative risk? A method of correcting the odds ratio in cohort studies of common outcomes. *JAMA* 1998; 280:1690-1.
10. Ottawa Hospital Research Institute. The Newcastle-Ottawa Scale (NOS) for assessing the quality of non-randomised studies in meta-analyses. Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed: January 1, 2013.
11. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis of Observational Studies in Epidemiology (MOOSE) group. *JAMA* 2000; 283:2008-12.
12. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986; 7:177-88.
13. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002; 21:1539-58.
14. Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997; 315:629-34.
15. Duval S, Tweedie R. Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics* 2000; 56:455-63.
16. Greenland S, Longnecker MP. Methods for trend estimation from summarized dose-response data, with applications to meta-analysis. *Am J Epidemiol* 1992; 135: 1301-9.
17. Flegal KM, Carroll MD, Kit BK, et al. Prevalence of obesity and trends in the distribution of body mass index among US adults, 1999-2010. *JAMA* 2012; 307: 491-7.
18. Chen Y, Zheng T, Lan Q, et al. Cytokine polymorphisms in Th1/Th2 pathway genes, body mass index, and risk of non-Hodgkin lymphoma. *Blood* 2011; 117: 585-90.
19. Kelly JL, Fredericksen ZS, Liebow M, et al. The association between early life and adult body mass index and physical activity with risk of non-Hodgkin lymphoma: impact of gender. *Ann Epidemiol* 2012; 22:855-62.
20. Morton LM, Wang SS, Cozen W, et al. Etiologic heterogeneity among non-Hodgkin lymphoma subtypes. *Blood* 2008; 112:5150-60.
21. Pan SY, Mao Y, Ugnat AM. Physical activity, obesity, energy intake, and the risk of non-Hodgkin's lymphoma: a population-based case-control study. *Am J Epidemiol* 2005; 162:1162-73.
22. Skibola CF, Holly EA, Forrest MS, et al. Body mass index, leptin and leptin receptor polymorphisms, and non-Hodgkin lymphoma. *Cancer Epidemiol Biomarkers Prev* 2004; 13:779-86.
23. 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.
24. 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.
25. 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.
26. 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.
27. 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.
28. 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.

29. 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.
30. Kabat GC, Kim MY, Jean-Wactawski W, 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.
31. 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.
32. 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.
33. 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.
34. Gainsford T, Willson TA, Metcalf D, et al. Leptin can induce proliferation, differentiation, and functional activation of hemopoietic cells. *Proc Natl Acad Sci U S A* 1996; 93:14564-8.
35. 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.
36. Askmyr M, Quach J, Purton LE. Effects of the bone marrow microenvironment on hematopoietic malignancy. *Bone* 2011; 48:115-20.
37. Dashnamoorthy R, Lansigan F, Davis WL III, et al. Fatty acid metabolism in diffuse large B-cell lymphoma (DLBCL): interaction with oncogenic cell signaling pathways and the identification of a novel treatment paradigm. *ASH Annual Meeting Abstracts* 2012; 120:abstract 2711.
38. Lansigan F, Davis WL III, Kuemmerle N, et al. Diffuse large B-cell lymphomas utilize endogenous and exogenous fatty acids for cell growth and survival. *ASH Annual Meeting Abstracts* 2012; 120:abstract 1581.
39. Surveillance Epidemiology and End Results. Cancer Statistics. Fast Stats. Available at: http://seer.cancer.gov. Accessed: August 30, 2013.
40. Laurini JA, Perry AM, Boilesen E, et al. Classification of non-Hodgkin lymphoma in Central and South America: a review of 1028 cases. *Blood* 2012; 120:4795-801.
41. Yang QP, Zhang WY, Yu JB, et al. Subtype distribution of lymphomas in Southwest China: analysis of 6,382 cases using WHO classification in a single institution. *Diagn Pathol* 2011; 6:77.
42. World Health Organization. Global Health Observatory (GHO). Available at: http://who.int/gho. Accessed: September 30, 2013.
43. Dekkers JC, van Wier MF, Hendriksen IJ, et al. Accuracy of self-reported body weight, height and waist circumference in a Dutch overweight working population. *BMC Med Res Methodol* 2008; 8:69.
44. Yoong SL, Carey ML, D'Este C, et al. Agreement between self-reported and measured weight and height collected in general practice patients: a prospective study. *BMC Med Res Methodol* 2013; 13:38.
45. Castillo JJ, Mull N, Reagan JL, et al. Increased incidence of non-Hodgkin lymphoma, leukemia, and myeloma in patients with diabetes mellitus type 2: a meta-analysis of observational studies. *Blood* 2012; 119:4845-50.