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Review Article

Overweight, Obesity and Physical activity in relation to Follicular Lymphoma incidence and Mortality: A meta-analysis

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Abstract

Purpose: In the last few years there has been a growing interest in exploring the association between risk factors such as overweight, obesity and physical activity, and incidence of various cancers.

Methods: Meta-analysis was performed to investigate the risk ratio of follicular lymphoma incidence and mortality in overweight and obese individuals, and in individuals with a different physical activity levels using the random-effects model. A literature search through September 2016 was performed. Case-control studies accounted for over 2.100 cases and 12.700 controls, whereas cohort studies accounted for over 2.600 cases in cohort of about 3.000.000 individuals.

Results: In overweight individuals (body mass index between 25 and 29.99 kg/m^2) risk ratio for the development of follicular lymphoma was 1.03 (0.95-1.11; 95% CI; p=0.51) and in obese (body mass index ≥ 30 kg/m^2) it was 1.15 (1.01-1.31; 95% CI; p=0.04) when compared to individuals with normal body mass index (<25 kg/m^2). The risk ratio of specific follicular lymphoma mortality in overweight was 0.59 (0.38-0.91; 95% CI; p=0.02), while in obese patients it was 1.08 (0.68-1.71; 95% CI; p=0.75). In patients with the highest physical activity levels, the risk ratio for follicular lymphoma occurrence was 0.95 (0.75-1.21; 95% CI; p=0.68) when compared to patients that had the lowest physical activity levels.

Conclusions: In summary, our meta-analysis has shown statistically significant direct association between obesity and follicular lymphoma incidence.

Introduction

Follicular lymphoma (FL) is the second most common subtype of non-Hodgkin lymphoma (NHL) in Europe and North America, and accounts for about 20-30 percent of all NHL cases [1]. Although it is known that the risk factors, such as alcohol [2], cytogenetic abnormality [3], immunosuppression, and some autoimmune diseases [4], may influence FL incidence, indubitable risk factor for its occurrence is not yet known.

In the last few years there has been a growing interest in exploring an association between risk factors as obesity (OB) and physical activity (PA), and incidence of various cancers [5, 6]. Obesity, whose prevalence has lately increased in many countries [7], is associated with a chronic state of inflammation. Thus, as the principal source of

inflammatory cytokines, adipose tissue may be linked with the development of cancer [8, 9]. For many malignancies overweight (OW) and OB are noted as risk factors [10, 11]. However, the authors' findings regarding FL are controversial. While some claim that there is an association between these risk factors and FL incidence [12-15], others deny it [16, 17]. Furthermore, current research on reduction of PA associated with OB is focused on their link with various cancers [6]. So far there is no meta-analysis of the association between OW and OB and a relative risk of FL mortality, while the influence of PA on FL incidence emphasized only in one published meta-analysis [18].

The aim of this study was to evaluate the association of OW and OB with FL incidence and mortality, as well as association of PA with FL incidence, using the both cohort and case-control studies. Also, we investigated the influence of OW, OB and PA on FL incidence depending on the type of study, gender and region in which examinees lived.

Methods

Study selection

Using PubMed and searching the reference list of retrieved articles the literature search through September 2016 was performed. The key search were: follicular lymphoma, overweight, obesity, body mass index, meta-analysis, physical activity, mortality. No language restrictions were imposed. Also, references cited in the corresponding articles were incorporated in the search. Both prospective and case-controls studies were included in the meta-analysis. Abstracts of articles, narrative studies, letters to the authors and cross-sectional studies were not included in this meta-analysis.

A study was relevant if it contained data reporting on the association between body mass index (BMI) and incidence and mortality of FL as well as the association between PA and incidence of FL. We identified a total of 39 articles with data that were potentially eligible for inclusion in this meta-analysis, of which 36 were related to FL incidence (31 were included in the analysis of influence of OW and OB, and 9 were included in the analysis of the influence of PA on FL incidence, with 4 studies overlapping, that is containing both topics), while 3 studies, all with a prospective design, was related to FL mortality. A total of 19 studies related to FL incidence were excluded because these articles did not include data on BMI values in relation to FL incidence. From the studies of FL mortality, one was excluded because it lacked data on mortality in relation to BMI. At the end of the identification process there were 17 applicable studies left with the data on FL incidence (14 for analysis of the influence of OW and OB [12-26], and 7 for analysis of the influence of PA, from which 4 were previously included [13,15,17, 25,27-29]) as well as 2 studies with data on association between OW and OB and FL mortality [30,31].

Data analysis

For both cohort and case-control studies, we extracted the following data: authors last names; publication year; study type; source (region); gender and age; case - total cohort or case-control size; time of follow-up; method of BMI determining; type and assessment of PA; the highest and the lowest PA level; adjustments (for cohort studies) or matching (for case-control studies); the risk ratio (RR) and hazard ratio (HR) for cohort studies and the odds ratio (OR) for case-control studies, with 95% confidence interval for all (95% CI).

Statistical analysis

OW was defined as BMI values between 25 and 29.99 kg/m^2 (pre-obese), OB as BMI values over 30 kg/m^2 (obese class I), while the high OB was defined as BMI values over 35 kg/m^2 (obese class II) according to the WHO criteria [32]. Normal BMI (<25 kg/m^2) values were the reference category for all computing related to BMI. For analysis

of the influence of PA, we compared the highest to the lowest PA level. The lowest level was the reference category for all comparisons. For studies with the highest PA level as the reference category, instead of the lowest level, the inverse value was used. If risk estimates for PA were reported for more than one period, the most recent data were used. For studies that reported recreational and occupational activity separately the former was preferred, and if a publication included data on total activity, these data were used. For all analysis, if study reported risk estimates for men and women separately, values for both were analyzed.

The summary RR with 95% CI was computed to assess the risk for FL incidence and mortality in overweight and obese examinees in relation to examinees with normal BMI, or the risk for the development of FL in examinees with the highest versus the lowest PA level. In the analysis of FL incidence (influence of OW and OB, and PA) we performed subgroup analysis depending on the type of study, gender and region in which examinees lived. While analyzing the mortality depending on the BMI index it was calculated as a specific/univariate or nonspecific/multivariate mortality.

DerSimonian-Laird method for the random-effects model was used to compute the outcome of study-specific RR [33]. To assess statistical heterogeneity among studies, the Q and I^2 statistics were used [34]. Heterogeneity was defined as mild (I^2 of 25%), moderate (I^2 of 50%) and severe (I^2 of 75%). Publication bias was noticed on funnel plots and was assessed by using Egger's test [35]. Statistical significance was defined for *p*-value < 0,05. All statistical analyses and graphics were performed with Comprehensive Meta-Analysis (Version 3; Biostat Inc, Englewood, NJ).

Results

For studies observing the influence of OW and OB on FL incidence, a total number of cohort studies were 7 and studies included 1.979 cases in cohort of 2.712.088 individuals; a total number of case-control studies were 7 and these studies included 1959 cases and 11.725 controls.

For studies observing the influence of OW and OB on FL mortality, a total number of cohort studies were 2 and studies included 493 cases in a cohort of over 215.000 individuals.

For studies observing the influence of PA on FL incidence, a total number of cohort studies were 4 (two of which overlapped with previous included 7 cohort studies related to FL incidence) and studies included 490 cases in a cohort of 661.878 individuals; a total number of case control studies was 3 (two of which overlapped with previous included 7 case-control studies related to FL incidence) and these studies included 583 cases and 4.583 controls in tables 1 and 2.

OW and FL incidence and mortality

For overweight examinees RR was 103 (0.95-1.11; 95% CI; p=0.51) for the development of FL when compared to examinees that had a normal BMI. The RR in cohort studies was 1.00 (0.90-1.11; 95% CI; p=0.97) and in case-control studies was 1.06 (0.95-1.19; 95% CI; p=0.31). The RR in men was 1.15 (0.87-1.53; 95% CI; p=0.33), in women was 0.99 (0.88-1.12; 95% CI; p=0.87), while in both men and women the RR was 1.05 (0.94-1.17; 95% CI; p=0.40). Americans had the RR of 1.12 (0.99-1.27; 95% CI; p=0.06), while Europeans had the RR of 0.97 (0.87-1.08; 95% CI; p=0.54). For overweight examinees, the statistically significant RR was 0.59 (0.38-0.91; 95% CI; p=0.02) for specific mortality, while for non-specific was 0.72 (0.46-1.12; 95% CI; p=0.14). There was no statistically significant heterogeneity among studies. There was not statistically significant publication bias (Figure 1 and Table 3).

Table 1: Characteristics of studies observing overweight and obesity in relation to follicular lymphoma incidence or mortality.

Author (Year)	Type of studies	Source (Region)	Gender and age (years)	Case - total cohort (No.-No.) or case-control (No.-No.) size	Enrollment (Years)	BMI determining	Adjustments (cohort)/matching (case-control)
INCIDENCE							
Skibola C.F. (2004) [14]	Case-control	United States	M and W; 21-74	351-2.400	1988-1995.	Self-reported	Age, gender, country of residence
Willett E.V. (2005) [19]	Case-control	Europe	M and W; 18-59	227-911	1998-2001.	Self-reported	Gender, date of birth
Chang E.T. (2005) [16]	Case-control	Europe	M and W; 18-74	582-3.158	1999-2002.	Self-reported	Age, gender
Cerhan J.R. (2005) [17]	Case-control	United States	M and W; 20-74	289-977	1998-2000.	Self-reported	Age, gender, race, study center
Pan S.Y. (2005) [15]	Case-control	Canada	M and W; 20-76	239-3.027	1994-1997.	Self-reported	Age, province, gender, education, smoking, alcohol, chemicals, occupational exposure
Chiu B.C.H. (2007) [20]	Case-control	United States	M and W; 20-75	121-527	1999-2002.	Self-reported	Age, gender
Lim U. (2007) [12]	Cohort	United States	M and W; 50-71	257-473.984	1995-2000.	Self-reported	Age, gender, ethnicity, education, alcohol, smoking, height, physical activity
Britton J.A. (2008) [21]	Cohort	Europe	M and W; 25-70	131-371.983	1993-1998.	Measured	Age, study center
Maskarinec G. (2008) [22]	Cohort	United States	M and W; 45-75	129-193.051	1993-1996.	Self-reported	Age, ethnicity, education, alcohol
Lu Y. (2009) [13]	Cohort	United States	W; 22-84	121-121.216	1995-2007.	Self-reported	Height, age at menarche, long-term strenuous plus moderate physical activity
Troy J.D. (2010) [23]	Cohort	United States	M and W; 55-74	162-142.982	1993-2001.	Self-reported	Age, race/ethnicity, gender, education
Kanda J. (2010) [24]	Case-control	Japan	M and W; 18-80	149-725	1988-2005.	Self-reported	Age, gender
Kabat G.C. (2012) [25]	Cohort	United States	W; 50-79	214-158.975	1993-1998.	Self-reported	Age, alcohol, smoking, caloric intake, education, ethnicity, enrollment in the OS, treatment arm assignment in the clinical trials
Murphy F. (2013) [26]	Cohort	Europe	W; 56.6 (The mean age)	965-1.249.897	1996-2009.	Self-reported	Height, alcohol, smoking, socioeconomic status
MORTALITY							
Leo Q.J.N. (2014) [30]	Cohort	United States	M and W; 45-75	214-215.000	1993-2007.	Self-reported	Age, gender, SEER stage, education, NHL type, therapy, smoking, alcohol, comorbidity, age at diagnosis
Hong F. (2014) [31]	Cohort	United States	M and W; 56 (The median age)	279- Not reported	1998-2003.	Not reported	Age, gender, B-symptom, FLIPI score, treatment

Abbreviations: BMI- Body Mass Index, M- Men, W- Women, SEER - the National Cancer Institute's Surveillance, Epidemiology, and End Results, FLIPI- Follicular Lymphoma International Prognostic Index

Table 2: Characteristics of studies observing physical activity in relation to follicular lymphoma incidence.

Author (Year)	Type of studies	Source (Region)	Gender and age (years)	Case - total cohort (No.-No.) or case-control (No.-No.) size	Enrollment (Years)	Type and assessment of physical activity	The highest vs. the lowest physical activity level	Adjustments (cohort)/ matching (case-control)
Cerhan J.R. (2002) [27]	Cohort	United States	W; 55-69	57-37.931	1986-1998.	Recreational; Self-reported questionnaire	High vs. low (Responses created a level activity score)	Age
Cerhan J.R. (2005)* [17]	Case-control	United States	M and W; 20-74	119-406	1998-2000.	Recreational; Self-administered questions	>1.080 METs/week vs. <30 METs/week	Age, gender, race, study center
Pan S.Y. (2005)* [15]	Case-control	Canada	M and W; 20-76	242-3.106	1994-1997.	Recreational; The questionnaire elicited information	>34.4 MET-h/week vs. <6.3 MET-h/week	Age, province, gender, education, smoking, alcohol, chemicals, occupational exposure
Lu Y. (2009)* [13]	Cohort	United States	W; 22-84	121-121.216	1995-2007.	Recreational; Self-administered baseline questionnaire	≥4 h/week/year vs. 0-0.50 h/week/year	Weight, height, age at menarche, long-term strenuous plus moderate physical activity
V Veldhoven C.M. (2011) [28]	Cohort	Europe	M and W; 57.9±8.3 (mean± SD)	98-343.756	1992-2000.	Total; Self-administered or interview-based questionnaires	Standing and manual/heavy manual work + recreational PA (≥45.75 MET-h/week) vs. Sedentary and unwilling + recreational PA (<14.25 MET-h/week)	Education, smoking, alcohol, hypertension, hyperlipidaemia, diabetes, BMI, weight, height, waist and hip circumference, waist-to-hip ratio
Kabat G.C. (2012)* [29]	Cohort	United States	W; 50-79	214-158.975	1993-1998.	Recreational; Self-administered questionnaires	≥17.5 MET-h/week vs. <1.6 MET-h/week	Age, alcohol, smoking, caloric intake, education, ethnicity, BMI, enrollment in the OS, treatment arm assignment in the clinical trials
Kelly J.L. (2012) [29]	Case-control	United States	M and W; <40 - >70	222-1.071	2002-2008.	Total; Self-dministered risk-factor uestionnaire	>2.701 METs/week vs. <615 METs/week	Age, gender, country of residence

*Previously included studies in Table 1. **Abbreviations**: BMI - Body Mass Index, M- Men, W- Women, PA- Physical Activity, MET- Metabolic Equivalent Task, SD- Standard Deviation

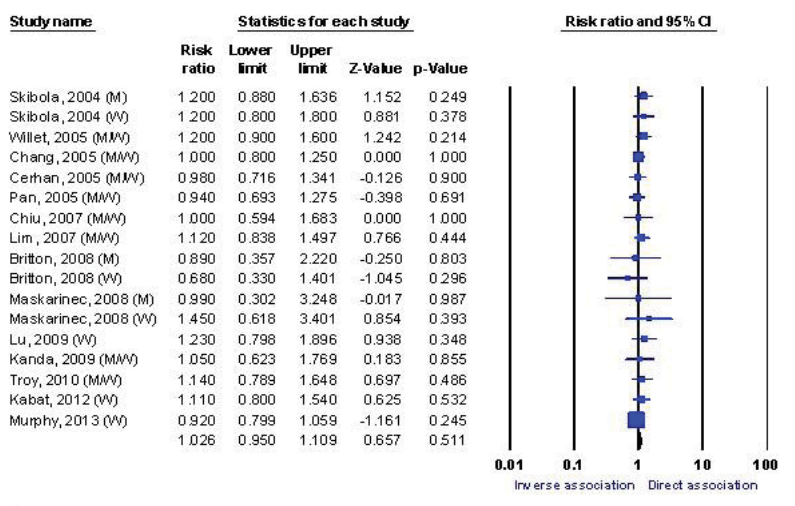

Figure 1: Relative risks of follicular lymphoma incidence associated with overweight. Abbreviations: M – men, W – women, M/W – men and women. Heterogeneity: Q = 9.00, p = 0.91, I^2 = 0%. Publication bias assessed by Egger's test: p = 0.18

Table 3: Relative risks of follicular lymphoma incidence and mortality associated with overweight.

	Studies (No.)	RR (95% CI)	p - Value	Heterogeneity P–Value	Heterogeneity I^2 (%)	Egger's test (p–Value)
INCIDENCE						
All studies	14	1.03 (0.95-1.11)	0.51	0.91	0	0.18
Type of studies						
Cohort	7	1.00 (0.90-1.11)	0.97	0.69	0	0.33
Case-control	7	1.06 (0.95-1.19)	0.31	0.90	0	0.73
Gender						
Men	3	1.15 (0.87-1.53)	0.33	0.80	0	0.26
Women	6	0.99 (0.88-1.12)	0.87	0.40	2.70	0.27
Men and women	8	1.05 (0.94-1.17)	0.40	0.95	0	0.88
Source (Region)						
United States	8	1.12 (0.99-1.27)	0.06	0.99	0	0.63
Europe	4	0.97 (0.87-1.08)	0.54	0.45	0	0.97
MORTALITY						
Specific	2	0.59 (0.38-0.91)	0.02	0.83	0	-
Non-specific	2	0.72 (0.46-1.12)	0.14	0.98	0	-

OB and high OB and FL incidence and mortality

Obese examinees had a significantly increased RR of 1.15 (1.01-1.31; 95% CI; p=0.04) for the development of FL when compared to examinees that had a normal BMI. The RR in cohort studies was 1.14 (0.97-1.34; 95% CI; p=0.13) and in case-control studies was 1.17 (0.92-1.48; 95% CI; p=0.21). The RR in men was 1.42 (0.95-2.12; 95% CI; p=0.09), in women was 1.24 (0.95-1.63; 95% CI; p=0.12), while in both men and women the RR was 1.08 (0.89-1.30; 95% CI; p=0.45). Americans had the RR of 1.25 (1.00-1.58; 95% CI; p=0.06), while Europeans had the RR of 1.03 (0.89-1.18; 95% CI; p=0.72). Obese examinees had the RR of 1.08 (0.68-1.71; 95% CI; p=0.75) for specific mortality and 1.56 for non-specific mortality (0.96-2.55; 95% CI; p=0.08). There was no statistically significant heterogeneity among studies. There was only one statistically significant publication bias Figure 2 and Table 4.

For high obese examinees, an RR was 0.94 (0.72-1.24; 95% CI; p=0.66) for the development of FL when compared to examinees that had a normal weight. The RR in cohort studies was 1.09 (0.74-1.59; 95% CI; p=0.67) and in case-control studies was 0.81 (0.55-1.20; 95% CI; p=0.29). The RR in both men and women was 0.93 (0.68-1.28; 95% CI; p=0.66). There was no statistically significant heterogeneity among studies. There was not statistically significant publication bias Figure 2 and Table 4.

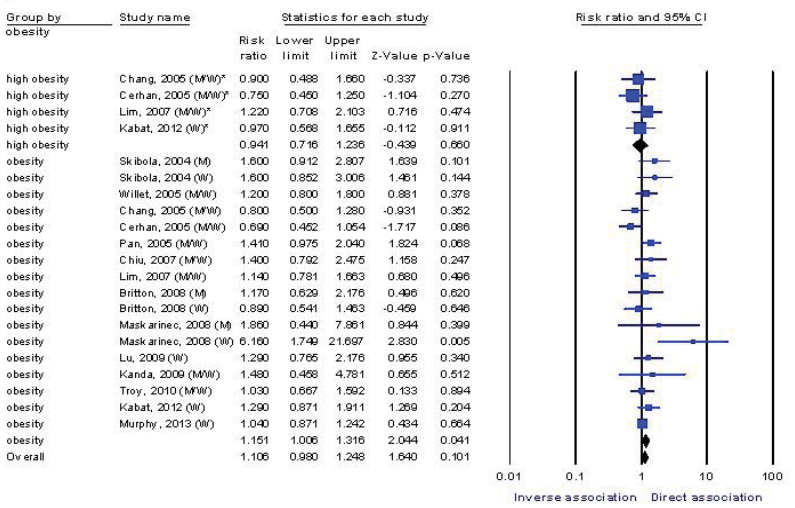

Figure 2: Relative risks of follicular lymphoma incidence associated with obesity and high obesity. Abbreviations: M – men, W – women, M/W – men and women. Heterogeneity for obesity: Q = 22.14, p = 0.14, I^2 = 27.72%; for high obesity: Q = 1.66, p = 0.64, I^2 = 0%; for overall Q = 25.18, p = 0.195, I^2 = 20.58. Publication bias assessed by Egger's test for obesity: p = 0.06; for high obesity: p = 0.76.

Table 4: Relative risks of follicular lymphoma incidence and mortality associated with obesity and high obesity.

	Studies (No.)	RR (95% CI)	P value	Heterogeneity p – Value	Heterogeneity I^2 (%)	Egger's test (p – Value)
INCIDENCE (Obesity)						
All studies	14	1.15 (1.01-1.31)	0.04	0.14	27.72	0.06
Type of studies						
Cohort	7	1.14 (0.97-1.34)	0.13	0.27	19.38	0.06
Case-control	7	1.17 (0.92-1.48)	0.21	0.097	42.17	0.50
Gender						
Men	3	1.42 (0.95-2.12)	0.09	0.71	0	0.77
Women	6	1.24 (0.95-1.63)	0.12	0.061	52.56	0.08
Men and women	8	1.08 (0.89-1.30)	0.45	0.23	24.91	0.85
Source (Region)						
United States	8	1.25 (1.00-1.58)	0.06	0.062	44.53	0.03
Europe	4	1.03 (0.89-1.18)	0.72	0.71	0	0.76
MORTALITY (Obesity)						
Specific	2	1.08 (0.68-1.71)	0.75	0.30	4.87	-
Non-specific	2	1.56 (0.96-2.55)	0.08	0.49	0	-
INCIDENCE (High obesity)						
All studies	4	0.94 (0.72-1.24)	0.66	0.64	0	0.76
Type of studies						
Cohort	2	1.09 (0.74-1.59)	0.67	0.56	0	-
Case-control	2	0.81 (0.55-1.20)	0.29	0.65	0	-
Gender						
Men and women	3	0.93 (0.68-1.28)	0.66	0.44	0	0.83

For both obese and high obese examinees, an RR of FL incidence was 1.11 (0.98-1.25; 95% CI; p=0.10). There was no statistically significant heterogeneity among overall studies (Figure 2).

PA and FL incidence

For examinees with the highest PA level the RR was 0.91 (0.72-1.15; 95% CI; p=0.42) for the development of FL when compared to examinees that had the lowest PA level. The RR in cohort studies was 1.07 (0.81-1.42; 95% CI; p=0.62) and in case-control studies was 0.77 (0.59-1.02; 95% CI; p=0.06). The RR in men was 1.23 (0.51-2.91; 95% CI; p=0.66), in women was 1.02 (0.78-1.32; 95% CI; p=0.89), while in both men and women the statistically significant RR was 0.68 (0.48-0.97; 95% CI; p=0.03).

Americans had the RR of 0.96 (0.77-1.21; 95% CI; p=0.4). There was no statistically significant heterogeneity among studies. There was only one statistically significant publication bias (Figure 3 and Table 5).

Discussion

This research was set with the aim of assessing the importance of BMI and PA for the development of FL. Our meta-analysis of cohort and case-control studies pointed out that overweight individuals did not have increased risk for the development of FL in comparison to individuals with normal weight, while obese individuals had 15% higher risk compared to non-obese. Overweight individuals had a higher risk of FL specific mortality than those with normal weight. However, a note of caution is mandatory since the number of included publication with data on mortality is small. Results of cohort and case-control studies related to the association between BMI and FL incidence did not show statistically significant difference.

In previous meta-analyses the association between BMI and FL incidence was investigated and statistically non-significant positive association between BMI and the relative risk for the development of FL was found. Thus, in a meta-analysis by Larsson and Wolk (2011) relative risk of FL and 5kg/m^2 BMI increase were positively associated (1.03; 0.93 to 1.13; 95% CI), but statistically non-significant [36]. In addition, the second meta-analysis from the same authors (2007) demonstrated statistically non-significant association between obese individuals and the relative risk for the development of FL [37]. However, this meta-analysis did not include data on overweight individuals [37]. However, the findings of the current study do not support the previous research. Moreover, the results of this study indicated that OB individuals had increased risk for the development of FL.

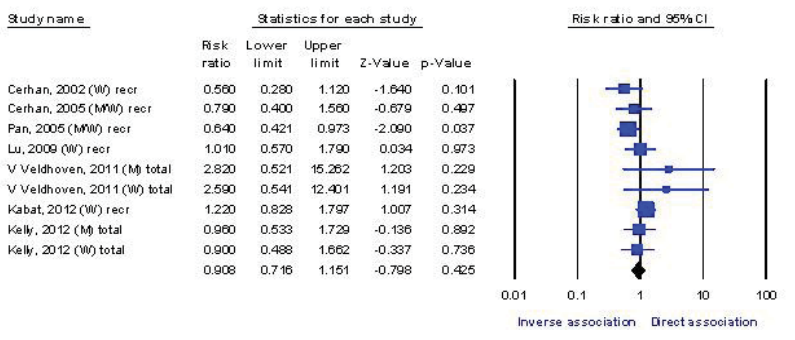

Figure 3: Relative risks of follicular lymphoma incidence associated with physical activity. Abbreviations: M – men, W – women, M/W – men and women. Heterogeneity: Q = 10.57, p = 0.28, I^2 = 24.29%. Publication bias assessed by Egger's test: p = 0.35.

Table 5: Relative risks of follicular lymphoma incidence associated with physical activity.

	Studies (No.)	RR (95% CI)	P value	Heterogeneity P–Value	Heterogeneity I^2 (%)	Egger's test (p–Value)
All studies	7	0.91 (0.72-1.15)	0.42	0.28	24.29	0.35
Type of studies						
Cohort	4	1.07 (0.81-1.42)	0.62	0.18	36.71	0.61
Case-control	3	0.77 (0.59-1.02)	0.06	0.67	0	0.19
Gender						
Men	2	1,23 (0.51-2.91)	0.66	0.24	28.31	-
Women	5	1.02 (0.78-1.32)	0.89	0.27	23.34	0.99
Men and women	2	0.68 (0.48-0.97)	0.03	0.60	0	-
Source (Region)						
United States	5	0.96 (0.77-1.21)	0.74	0.52	0	0.02
Europe	-	-	-	-	-	-

In terms of smaller body fat percentage in men, it may be assumed that the females would be more susceptible for the development of FL. Also, considering that subcutaneous adipose tissue predominate in women, it may be assumed that visceral adipose tissue has a much more essential role for the development of many cancers, including FL [38, 39]. This type of body fat is associated with obesity-related diseases [40], because it is more harmful and inflammatory active than subcutaneous fat which is generally thought to be responsible for OB. However, based on the results of our meta-analysis, there was no increased risk of FL associated with either overweight and obese men or women.

Finally a direct association between OW and OB, and FL incidence is more pronounced among Americans as compared to Europeans. But, none of these differences were statistically significant. For both overweight and obese American individuals, increased risk of FL was formally not significant (p=0.06). These results seem to be consistent with other research which have not found the association between BMI and NHL incidence across strata of geographic region [36]. In the study of Castillo et al. (2014) for both overweight and obese American individuals the RR for the development of diffuse large B-cell lymphoma was significantly increased, but not in Europeans [41]. Although different life habits and harmful effects of the environment may cause the differences between these two groups of individuals, no association was identified in this meta-analysis. In addition, more research on this topic is necessary before the association between geographic area and the risk of FL is more clearly understood.

The prevalence of OB is increasing and is associated with other risk factors such as increased intake of high-fat food and decreased PA [7, 42]. McTiernan [6] proposed that excessive weight and a sedentary lifestyle are linked with about 25% of cancers, and that PA may decrease risk for various cancers by several mechanisms. In this meta-analysis only, for both men and women statistically inverse association of PA with the risk for the development of FL was found. However, this subgroup analysis could have been affected by small sample size. Thus, this finding cannot be extrapolated to all the patients. Thus, the summary risk estimate derived from all studies showed no significant influence of physical activity on the risk of FL. The findings of this study are consistent with the data obtained in other meta-analyses which focused not only to FL but also generally to NHL [18] or NHL and Hodgkin lymphoma [43].

There are numerous studies that were designed to explore the association between OB and cancer [5, 44], but the mechanisms of this causal link are still unclear. Basically the focus is on three hormonal systems that include insulin and insulin-like growth factor (IGF) axis, sex steroids and adipokines. Obesity-related inflammatory cytokines, genetic background, obesity-related hypoxia, and oxidative stress were also noted as possible causes, and more other etiological factors which may have a role in the occurrence and development of cancer [45].

This meta-analysis has some limitations. First, other obesity-related factors, such as change of weight during the time, diet and caloric intake, may also influence the risk for the development of FL. Second, the sample size may be a source of erroneous conclusions. For example, statistically significant inverse association between BMI and FL mortality was found in overweight individuals, while non-significant direct association was presented in obese. Furthermore, these results are not conclusive because of dependence on FL subtype, treatment, comorbidity and SEER stage. Third, determining of BMIs in all included studies was based on the principle of personal declaration. Any discrepancies, such as false weight loss in obese, may have an unquestionable impact on the final results. Fourth, the BMI indicates total body fat (combined subcutaneous adipose tissue and visceral adipose tissue) [45], and therefore it cannot assess what type of body fat has a greater impact - visceral adipose tissue (VAT) or subcutaneous adipose tissue. And finally, all associations either direct when

the effects of excessive weight or OB were analyzed, or inverse when the influence of PA was analyzed, may be influenced by publication bias. In this meta-analysis, there was no evidence of publication bias in most of the studies.

In summary, this meta-analysis of cohort and case-control studies has identified the direct association between obesity and FL incidence. The research has also shown statistically significant association between BMI and FL mortality in overweight individuals as well as association between PA and the risk of FL incidence in both male and female individuals. It could be argued that these last two results could have been affected by small sample size. The current data highlights the importance of obesity for the risk of FL developments. It would be interesting to assess the impact of other risk factors such as insulin and IGF, sex steroids and adipokines involved in the association between OB and malignant lymphomas. Future meta-analyses on the current topic with a larger number of included studies are recommended to confirm these results.

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