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Type 2 diabetes and the risk of non-Hodgkin's lymphoma: a report from two population-based cohort studies in China

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Abstract

Coinciding with the increased incidence of non-Hodgkin's lymphoma (NHL) during the past decades, there has been a significant increase in the prevalence of diabetes mellitus in mainland China. We therefore evaluated whether type 2 diabetes (T2D) is associated with the risk of NHL using data from the Shanghai Men's Health Study (SMHS) and the Shanghai Women's Health Study (SWHS). The SMHS and SWHS are two on-going, prospective, population-based cohorts of more than 130 000 Chinese adults in urban Shanghai. Self-reported diabetes was recorded on the baseline questionnaire and updated in follow-up surveys. Cox regression models with T2D as a time-varying exposure were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) adjusting for covariates. After an average follow-up of 12.9 years for SWHS and 7.4 years for SMHS, 172 NHL cases were identified. Patients with T2D have higher risk of incident NHL with a HR of 2.00(95%CI: 1.32–3.03) compared with non-diabetes. This positive association remained when restricted analysis in untreated diabetes or after excluding NHL cases occurred within 3 year after diabetes onset. No interaction effect in the development of NHL was found between T2D and other potential risk factors. A linear inverse association between T2D duration and risk of NHL in both men and women ($P_{\text{for linearity}} < 0.01$) was found, with a highest risk of incident NHL in the first 5 years after diabetes diagnosis. Our study suggested that T2D might be associated with the increased risk of NHL.

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Keywords

type 2 diabetes; non-Hodgkin's lymphoma; time-varying covariate; cohort study

Introduction

Although the incidence rate of non-Hodgkin's lymphoma (NHL) is lower in China than those in United States, Europe, and other developed countries, it has increased markedly over the past few decades, with an increase of 38.02% in the incidence rate from 1988 to 2002 (Lei *et al.* 2009). However, the etiology of NHL is elusive, which makes difficulties in the prevention for this malignancy.

Coinciding with the increased incidence of NHL, the prevalence of diabetes has risen sharply in China, with age-standardized rates from 2.4% in 1994 (Pan *et al.* 1997) to 9.7% in 2007–2008 (Yang *et al.* 2010), which could parallel a substantial lifestyle transition (Hu, 2011). Different from stable transition in most Western countries, these remarkable changes have taken place within a limited time in mainland China. Although patients with type 2 diabetes (T2D) have been shown to be at high risk for several subsequent cancers including liver (Yang *et al.* 2013; Yang *et al.* 2011) and pancreas (Ben *et al.* 2011), its relationship with NHL is inclusive (Castillo *et al.* 2012). Moreover, to our knowledge, no observational study to date has been focused on mainland Chinese population.

In addition, several research issues relating to the link between diabetes and incidence of NHL still remain unresolved. First, findings from previous studies may have been confounded by unadjusted potential risk factors such as smoking, alcohol drinking, physical activity, and dietary habits (Castillo *et al.* 2012). Second, whether the association between T2D and the risk of NHL is largely attributed to their shared risk factors such as socioeconomic status (SES) and obesity is uncertain. For example, both T2D and NHL are strongly correlated with SES including occupation, family income, education levels, and obesity (Agardh *et al.* 2011; Fisher *et al.* 2004; Larsson *et al.* 2007). Thus, subgroup analysis within subjects who are not obese but have low socioeconomic status would help us to better understand this research issue. Third, results from previous cohort studies would have been underestimated, because almost all studies only considered a single measurement of diabetes at baseline in their analysis, and diabetes newly identified during the follow-up periods were ignored. Fourth, current evidence suggested that diabetes treatments such as history of insulin or metformin use may affect the incidence or mortality of lymphoma and other hematologic malignancies (Fortuny *et al.* 2005; Hjalgrim *et al.* 1997), indicating that future diabetes–cancer association study should consider the effect of anti-diabetic drugs use. Lastly, to our knowledge, no study to date has evaluated the role of diabetes duration in the development of non-Hodgkin's lymphoma.

Therefore, we examined the association among T2D, its duration, and the risk of NHL using data from two ongoing population-based cohorts in mainland China.

Methods

Study population

Participants in this study included 61 491 men in the Shanghai Men's Health Study (SMHS) and 74 941 women in the Shanghai Women's Health Study (SWHS). Details of the study design, scientific rationale, and baseline characteristics of the subjects have been described elsewhere (Villegas *et al.* 2007; Zheng *et al.* 2005). Briefly, the SWHS was initiated in 1997 and completed in 2000 as a population-based cohort of 81 170 female residents of Shanghai aged 40–70 years old, with an overall participation rate of 92.7%; the SMHS was a prospective cohort study including 83 125 men aged 40–74 years old with no history of cancer that enrolled in 2002 and finished in 2006, with an overall participation rate of 74.1%. Participants were interviewed in person by validated questionnaires to obtain information about demographic characteristics, lifestyle and dietary habits, medical history, family history of cancer, and other exposures. Anthropometric measurements, including current weight, height, and circumferences of the waist and hip were also taken at baseline. Informed consent has been obtained from each participant after full interpretation of the purpose and nature of all procedures used.

The following participants were excluded from the current analysis if they had a history of cancer at baseline (none for men, 1598 women); were diagnosed with diabetes before age 20 to reduce possible bias from including patients with probable type 1 diabetes (3 men, 3 women); died of cancers of unknown origin or lack of information on diagnosis date (137 men and 138 women); had missing values for any of covariates of interest (1389 men and 75 women); and were diagnosed with NHL and other hematologic malignancies before the diagnosis of diabetes (0 men and 1 woman). After exclusions, a total of 59 971 men and 73 126 women remained in the final analysis.

Diabetes assessment

Self-reported diabetes was recorded on the baseline questionnaires (2002–2006 for the SMHS and 1997–2000 for the SWHS), and updated in each of the subsequent follow-up questionnaires (2004–2008 for the SMHS, and 2000–2002, 2002–2004 and 2004–2007 for the SWHS). Participants were asked whether they had ever been diagnosed with diabetes by their physicians (yes/no) and if yes, the age at diagnosis was recorded. From the beginning with the 2004–2008 follow-up questionnaires for men and 2000–2002 follow-up questionnaires for women, and for all subsequent surveys, the question was modified, and participants were additionally asked in what year and month and in which hospital their diabetes had been diagnosed since the most recent survey. There was no information about a history of insulin or other hypoglycemic agents use in baseline questionnaires, but these were collected in each follow-up survey (i.e. 2004–2008 for the SMHS, and 2002–2004 and 2004–2007 for the SWHS).

In this analysis, the T2D cases identified both in baseline questionnaires and follow-up questionnaires were all considered and were modeled as a time varying exposure. The procedures for identification of diabetes cases have been published previously (Yang *et al.* 2013; Yang *et al.* 2014). Briefly, a case of T2D was defined as a subject who reported

having been diagnosed with T2D by physician(s) during baseline and follow-up surveys and met at least one of the following self-reported items: 1) fasting plasma glucose concentration ≥ 7 mmol/L, or oral glucose tolerance test (OGTT) performed in the doctor's office with a value ≥ 11.1 mmol/L at least on two separate occasions; and 2) use of insulin or other hypoglycemic agents. Participants were classified as untreated diabetes if the patients with T2D reported having not used insulin or other hypoglycemic agents.

Follow up and ascertainment of cases

The subjects were followed up through home visits every 2 to 3 years to update exposure information and to ascertain new diagnosis of cancers. In SMHS, the first follow up interview was carried out from 2004–2008 with a response rate of 97.6%. In SWHS, the first, second and third follow ups were carried out from 2000–2002, 2002–2004 and 2004–2007 with corresponding response rates of 99.8%, 98.7% and 96.7%, respectively.

The incident NHL cases were defined as a primary tumor with an International Classification of Diseases (ICD)-9 codes of 200 and 202; and were identified through annual record linkage to the Shanghai Cancer Registry and Shanghai Municipal Registry of Vital Statistics. All possible cancer cases were further confirmed through review of medical charts by a panel of clinical and/or pathological experts. Outcome data through December 31, 2011 for both men and women were used for the present analysis. We were unable to evaluate the risks of other hematologic malignancies including leukemia, myeloma, and Hodgkin's disease given limited number of cancer cases identified in the two cohorts.

Statistical analysis

Cox proportional hazards regression models with age as time scale (Cologne *et al.* 2012) were modeled to calculate age-adjusted and multivariate-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for the associations of T2D (yes/no) and T2D duration (0y–, 5y–, 10y) with the risks of incident NHL. T2D (yes/no) was modeled as a time-varying variable in the analysis, meaning that information on type 2 diabetes reported in questionnaire n , was used to prospectively categorize participants for the periods between completion of questionnaires n and $n + 1$, and the risk person-years was assigned to the corresponding groups, the corresponding method was described elsewhere in detail (Yang *et al.* 2013). Risk estimates from men (SMHS) and women (SWHS) were combined using a random-effect meta-analytic approach, allowing for a between-study heterogeneity (DerSimonian *et al.* 1986).

Confounders or covariates were selected on the basis of their potential to confound or modify the association of NHL with T2D, and were modeled using baseline values. The covariates included in the multivariate-adjusted models were age (<50y, 50y–, 60y), birth cohort (1920s, 1930s, 1940s, 1950s, 1960s), education levels (elementary school, middle school, high school, >high school), income levels (low, low to middle, middle to high, high), body mass index (BMI; <18.5, 18.5–, 24–, 28, according to Chinese standard) (Zhou *et al.* 2002), occupation [housewife (women only), manual, clerical, and professional], smoking status (never smoking, ever smoking, current smoking), ever drinking (yes/no), family history of cancer (yes/no), total energy intake (kJ/day, quartiles), fruit intake (g/day,

quartiles), vegetable intake (g/day, quartiles), total physical activity [PA; standard metabolic equivalents (METs) as MET-hr/day in quartiles; 1 MET-hr=15 minutes of moderate intensity activity], hormone replacement therapy (HRT; yes/no for women only), and menopausal status (pre-/post-menopausal for women only).

In sensitivity analysis, allowing for the possible influence by diabetes treatments in the overall analysis, a separate analysis was conducted to evaluate the associations for untreated diabetes. To examine the potential reverse causality bias, we repeated analysis after excluding outcome with less than 3 years of follow-up since diabetes diagnosis. We restricted analysis within subjects who are not obese or overweight (BMI < 24) and have middle or low levels of education (illiteracy or elementary school or middle school or high school) and income (less than ¥2000 per person per month for men and less than ¥20000 per family per year for women), to check whether the link between T2D and the risk of NHL is largely due to their shared risk factors: SES and obesity.

Potential interactions of diabetes with age, income, education, occupation, fruit and vegetable consumptions, alcohol drinking, physical activity, menopausal status (women only), and smoking were also examined, by comparing the fit of models with and without a cross-product interaction term through a likelihood ratio test. In checking of the proportional hazard assumption by creating the product term of diabetes and a logarithm of time in the model, no violation of proportionality was found.

All data analyses were performed with R 3.3.1 (R Development Core Team, R Foundation for Statistical Computing, Vienna, Austria) and SAS 9.2 (SAS Institute, Cary, NC) software, and a two-sided *P* value of 0.05 was considered statistically significant.

Results

The baseline characteristics according to diabetes status are shown in Table 1. A total of 10 902 cases of T2D were identified at baseline and in follow-up periods from the two cohorts. Compared to men and women free of diabetes, patients with T2D tend to be older and have greater BMI, higher intake of total energy, and fruit and vegetable, but have less alcohol drinking at baseline. In SWHS, the diabetic and non-diabetic groups had similar rate for HRT use, but with higher proportion of post-menopausal women in diabetic group.

After an average follow-up of 12.9 years among SWHS and 7.4 years among SMHS, incident NHL cases were detected in 62 men and 110 women. As shown in Table 2, patients with T2D have higher risk of incident NHL with a HR of 2.00 (95%CI: 1.32–3.03) compared with non-diabetes, after adjusted for age, birth cohorts, education levels, income, BMI, occupation, ever smoking, alcohol drinking, family history of cancer, total energy intake, fruit intake, vegetable intake, total physical activity, hormone replacement therapy (women only) and menopausal status (women only). The risks were suggestively higher in men (HR=2.20, 95%CI: 1.10–4.40) than those in women (HR=1.89, 95%CI: 1.12–3.19), but without statistical significance for such a difference (*P* for interaction = 0.73). This positive association between T2D and NHL persisted when restricted analysis in untreated diabetes or after excluding NHL cases occurred within 3 year after the onset of diabetes. Compared

to overall analysis, the risk estimates for NHL were similar but with wider CIs when we repeated analysis within subjects who are not obese or overweight and have middle or low levels of education and income among men (HR= 2.14, 95%CI: 0.46–10.07) and women (HR=1.94, 95%CI:1.13–10.85). No synergistic interaction in the development of NHL was found between T2D and age, smoking status, education, income, menopausal status (Supplemental Table S1), and other factors (data not shown).

The diabetes duration-response analysis showed a linear inverse association between T2D duration and risk of NHL in both men and women ($P_{\text{for linearity}} < 0.01$). We found a highest risk of incident NHL in the first 5 years after diabetes diagnosis with HRs of 2.82 (95%CI=1.42–5.57) and 60.78 (95% CI=14.37–257.21) for men and women, respectively, and the risk was diminishing with the prolonged diabetes duration (data not shown).

Discussion

Findings from the present study suggested an increased incidence of non-Hodgkin lymphoma in patients with type 2 diabetes among Chinese men and women. Such a positive association remained in several sensitivity analyses that accounted for the potential reverse causality bias, diabetes therapy, and their shared risk factors (SES and obesity). The highest risk of incident NHL was showed to be in the first 5 years after diabetes diagnosis, and diminished with the prolonged diabetes duration.

The adjusted HR for developing NHL in patients with diabetes in this analysis is 2.00, which is higher than the risk observed among 3 previous meta-analyses (Castillo *et al.* 2012; Chao *et al.* 2008; Mitri *et al.* 2008). In a meta-analysis of 5 prospective cohort and 11 case-control studies, Mitri and colleagues found a 19% increased risk of incident NHL in patients with T2D (Mitri *et al.* 2008). In their updated meta-analysis with 13 cohort and 13 case-control studies in 2012 (Castillo *et al.* 2012), they observed a similar result (HR=1.22).

Consistently, the HR for NHL in a meta-analysis that included 10 case-control and 3 prospective cohort studies through November 2007 (Chao *et al.* 2008) was found to be 1.28 (95%CI: 1.07–1.53). The discrepancy in the results from our study and recent meta-analyses could be partly explained by a number of unadjusted covariates among previous studies. For example, only few studies adjusted for smoking and alcohol drinking (Jee *et al.* 2005; Khan *et al.* 2008; Khan *et al.* 2006) in the models; only 4 studies adjusted for BMI (Erber *et al.* 2009; Khan *et al.* 2008; Khan *et al.* 2006; Rousseau *et al.* 2006); no studies has accounted for the potential influence by physical activity, or dietary habits. In this analysis, we adjusted for a number of covariates in the models including age, birth cohorts, SES (education, income, and occupation), BMI, smoking, alcohol drinking, family history of cancer, total energy intake, fruit and vegetable intake, physical activity, HRT (women only) and menopausal status (women only).

In sensitivity analysis, we found a positive association between NHL and T2D within participants who were not obese or overweight and have middle or low levels of education and income, thus ruling out a possibility that the observed T2D-NHL association is due to their co-risk factors: obesity (Larsson *et al.* 2007; Vazquez *et al.* 2007) and SES (Agardh *et al.* 2011; Fisher *et al.* 2004). The positive association persisted and remained significant

when examining the link between diabetes without any insulin or other hypoglycemic agents use and risk of NHL, which may strength the association.

To our knowledge, this is the first cohort study investigating the association between the diabetes duration and NHL risk, and found the linear inverse association for both men and women with a highest risk of incident NHL in the first 5 years after diabetes diagnosis, which may add evidence for the insulin–cancer hypothesis (Giovannucci, 2003) that hyperinsulinemia other than hyperglycemia is more likely to be a primary mediator for this association. Because of a reduced level of plasma insulin by beta-cells in the pancreas compared to their earlier stage of diabetes, it is reasonable to observe an inverse association between diabetes duration and cancer development if it is true that hyperinsulinemia plays a key role in the association (Yang *et al.* 2013); whereas if hyperglycemia is largely responsible for such an association, the duration-response function could be positive linear with higher risk in patients with longer duration.

We also noted that risk estimate for incident NHL within 5 years after T2D diagnosis was much higher in women (HR = 60.78) than those in men (HR = 2.82). Such an inconsistency may be partly explained by over-detection bias observed only among SWHS. Because newly diagnosed diabetes is more likely to be diagnosed with cancer given increased detections around the time of diabetes diagnosis, especially in the first 3 months following the diabetes index date (Johnson *et al.* 2011), thus results from diabetes-cancer association studies could have been over-estimated. In current analysis, we found a higher incidence rate of NHL in the first year after the date of diabetes diagnosis compared with those without diabetes, irrespective of the different time intervals of follow-up in SWHS (data not shown), suggesting a potential over-detection bias existing in SWHS. Unlike SWHS, results from SMHS seemed to be not affected by over-detection bias given a lower incidence rate of outcomes in the diabetic group within the first year following the diabetes index date (data not shown). In order to evaluate the potential effect for over-detection bias, sensitivity analysis that excluded NHL cases occurred within the first 3 years after diabetes onset was performed and yielded similar result (HR = 1.85) compared with the overall analysis (HR = 1.89) among women in present study. However, this approach is infeasible when we test the diabetes duration-response function if short duration of T2D is associated with the increased risk of NHL, i.e. insulin–cancer hypothesis (Giovannucci, 2003) could be true. Thus, this research issue should be addressed in future studies.

Our study has several strengths, including the population-based cohort design with large sample size, high follow-up rates (over 96% for in-person home visits), and the use of repeated measures of diabetes status which accounted for the variation of diabetes status during the follow-up period. In addition, taking into account the diabetes treatment may strength the association, because few studies suggested that diabetes therapy such as insulin shots or metformin use may affect the incidence of NHL or leukemia (Fortuny *et al.* 2005; Hjalgrim *et al.* 1997), whereas the information on diabetes treatment is derived from self-reported questionnaire and therefore the misclassification bias cannot be ruled out.

Our study also has several limitations. The biggest limitation is that our exposure data including diabetes and its duration is self-reported, which may led to misclassification of

exposure because many patients with T2D did not know they had the disease (Li *et al.* 2012). Such a misclassification of dichotomous exposure could be nondifferential, resulting in an underestimation of the observed association. The second limitation is that our results could have been accidental and the play of chance could not be ruled out, given a limited number of outcomes in patients with T2D, especially among subgroup and T2D duration analyses where only few cases (1–5) presented in most strata (Supplemental Table S1), which led to a wide range of confidence interval. Third, as acknowledged above, results from SWHS could have been influenced by over-detection bias.

Conclusion

In summary, findings from our study suggested a positive association between T2D and NHL after adjustment for a number of potential confounders. Given a limited number of cases included in the analysis, future studies with large sample size and long-term follow-up that fully accounted for diabetes treatments, the validity of exposure data, and the potential confounders are needed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Baseline characteristics by type 2 diabetes status in the Shanghai Men's Health Study (2002–2006) and the Shanghai Women's Health Study (1997–2000)^a

	Men		Women	
	Non-diabetes	Type 2 diabetes	Non-diabetes	Type 2 diabetes
Number of participants	55,358	4613	66,837	6289
Age at baseline (year)	54.9(9.6)	60.5(9.5)	51.9(8.9)	58.5(8.3)
Income (%) ^b				
Low	12.87	9.32	15.58	21.44
Low to middle	77.45	80.73	38.09	39.90
Middle to high	8.93	9.27	28.46	24.33
High	0.76	0.68	17.87	14.33
Education levels (%)				
Illiteracy or elementary school	6.29	11.34	19.28	43.19
Middle school	33.51	33.62	37.95	29.24
High school	36.69	29.48	28.85	18.43
Graduate school/college	23.51	25.56	13.92	9.14
Occupation (%)				
Housewife	-	-	0.34	0.64
Professional	25.77	31.93	28.98	22.77
Clerical	21.92	22.54	20.81	20.32
Manual worker	52.30	45.52	49.87	56.27
BMI (kg/m ²)	23.6(3.1)	24.6(3.0)	23.8(3.3)	26.1(3.8)
Smoking status (%) ^c				
Never smokers	29.68	38.16	97.41	95.26
Former smokers	10.29	17.33	-	-
Current smokers	60.03	44.51	2.59	4.74
Physical activity (MET hours/week)	59.5(34.0)	60.9(35.8)	107.0(45.3)	102.5(43.3)
Ever alcohol consumption (%)	33.80	29.05	2.29	1.86
Total energy intake (kJ/day)	8029.8(2029.1)	7482.0(1930.5)	7033.8(1680.9)	6843.6(1840.6)
Fruit and vegetable intake (g/day)	496.4(260.9)	471.5(265.4)	567.6(291.6)	493.4(292.2)
Family history of cancer (%)	28.26	29.98	26.48	26.60
Post-menopausal (%)	-	-	46.26	76.56
HRT use (%)	-	-	2.07	2.10

Aberrations: BMI, body mass index; MET, standard metabolic equivalents.

^a Continuous variables are presented as the mean (the SD).

^b Low: less than ¥500 per person per month for men and less than ¥1000 per family per year for women; low to middle: ¥500–1999 per person per month for men and ¥10 000–19 999 per family per year for women; middle to high: ¥2000–3999 per person per month for men and ¥20 000–29 999 per family per year for women; high: ¥4000 and above per person per month for men and ¥30000 and above per family per year for women.

^c Due to the small number of smokers among women, the number of current and former smokers was combined.

Table 2

HRs (95% CI) from Cox regression models relating diabetes and incidence of non-Hodgkin's lymphoma in the Shanghai Men's Health Study (2002–2006) and the Shanghai Women's Health Study (1997–2000)

	Non-diabetes		Type 2 diabetes		Multi-adjusted HR(95%CI) ^c
	NHL cases	Person- years	NHL cases	Person- years	
Men and women	140	1,273,465	32	110,765	2.00(1.32–3.03)
Men					
Overall cohort	51	408,000	11	32,928	2.20(1.10–4.40)
After exclusion ^a	37	407,979	9	32,926	2.41(1.11–5.24)
Untreated diabetes ^b	51	408,000	2	3635	4.60(1.10–19.15)
Women					
Overall cohort	89	865,465	21	77,837	1.89(1.12–3.19)
After exclusion ^a	71	865,438	18	77,832	1.85(1.05–3.28)
Untreated diabetes ^b	89	865,465	20	70,584	1.90(1.11–3.25)

Abberrations: CI, confidence interval; NHL, non-Hodgkin's lymphoma; HR, hazard ratio

^a Analysis after excluding non-Hodgkin's lymphoma cases occurred within the first 3 years after diabetes onset;

^b Participants were classified as untreated diabetes if the patients with T2D reported having not used insulin or other hypoglycemic agents.

^c The adjusted covariates included age, birth cohorts, education, income, body mass index, occupation, ever smoking, alcohol drinking, family history of cancer, total energy intake, fruit intake, vegetable intake, total physical activity, hormone replacement therapy (women only) and menopausal status (women only).