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Follicular lymphoma polygenic risk score is associated with increased disease risk but improved overall survival among women in a population based case-control in Los Angeles County California

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Abstract

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Credit Statement

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Authorship Contribution

SSW, CRC, WC, and LB conceived of the study; CZ, JYS, DDW, JL, YCD, SLN conducted data collection and data analysis; all contributed to data interpretation and manuscript preparation.

Declaration of Interests

The authors declare that they have no conflict of interests.

Introduction: Although clinical prognostic indicators exist for follicular lymphoma(FL), patient outcomes remain heterogeneous.

Material and Methods: We evaluated the association between survival and a polygenic risk score(PRS) composed of five previously identified FL susceptibility loci(rs12195582, rs13254990, rs17749561, rs4245081, rs4938573) among women who participated in a case-control study of non-Hodgkin lymphoma in Los Angeles County between 2004-2008. Risk associations were estimated through logistic regression, calculating the odds ratios(OR) and 95% confidence intervals(95% CI). Survival was estimated under a Cox proportional hazards model and hazard ratios(HR) and 95% CI were calculated.

Results: Among 437 non-Hispanic White controls and 100 non-Hispanic White FL patients, we confirmed a 2.6-fold increased risk of FL associated with the highest PRS tertile (95% CI:1.35-4.86). After accounting for clinical indicators, the PRS was associated with improved overall survival in non-Hispanic women (HR:0.31; 95% CI:0.10-0.96).

Conclusion: PRS was associated with increased risk of FL, but improved overall survival.

Keywords

Non-Hodgkin lymphoma; epidemiology; genetics; survival

1. Introduction

Follicular lymphoma (FL) is the second most common type of non-Hodgkin lymphoma (NHL)[1]. Prognostic indictors for FL include the International Prognostic Index (FLIPI) and various genetic changes (e.g., *TP53 mutation*) found in FL which aims to identify high-risk patients with poor survival [2-4]. However, heterogeneity in FL patient outcomes after diagnosis still remains [2, 4-8]. Several large genome wide association studies (GWAS) have now been conducted among Caucasian populations and have identified and validated several susceptibility loci associated with FL risk [9, 10]. Here, we evaluate the potential association between these FL risk loci and outcomes in a population of FL cases diagnosed in Los Angeles County.

2. Material and Methods

2.1 Study Population

Our study population comprised FL cases that consented to participate in a population-based case-control study of women diagnosed with primary B-cell non-Hodgkin lymphoma (NHL) in Los Angeles County. Study methods have previously been published [11]. Briefly, cases were identified through rapid case ascertainment (RCA) by the Los Angeles County cancer registry (Cancer Surveillance Program; CSP) between May 1, 2004 and March 31, 2008. CSP staff review pathology reports on a monthly basis to identify patients eligible for research studies. Additional details of the RCA process are available from the CSP [12]. Eligibility criteria included cases that were English-speaking residents of Los Angeles County between the ages of 20 and 79 years old and not previously diagnosed with Human immunodeficiency virus (HIV), NHL, Hodgkin's disease, multiple myeloma, or leukemia. Of the 1006 NHL cases enrolled in the parent study, 230 were identified as having FL from

the CSP (International Classification of Diseases for Oncology 3rd edition codes 9690, 9691, 9695, 9698). For evaluation of survival outcomes, cases were followed for clinical endpoints through medical record abstractions and data linkages, as described below, through December 31, 2016. As previously described, 1038 controls matched on age, sex, and race/ethnicity were enrolled in the study [11]. The 5-year curve of women in the study (85%) was similar to that of the eligible SEER population in Los Angeles from which the cases were drawn (82%).

2.2 Genetic Analyses

A majority of participants, 93% (n=936) of cases and 93% (n=969) of controls, provided samples using buccal swabs. Of the 230 FL cases, 93% (n=213) provided buccal swabs. DNA was extracted and whole genome amplification was conducted using Repli-G Mini kits (Qiagen, Hilden, Germany). Genotyping was conducted using Fluidigm Dynamic arrays (Fluidigm, San Francisco, California).. Duplicate samples (n=62) were included as genotype quality controls to remove assays of low quality. The final genetic dataset for this analysis included 148 FL cases and 679 controls. FL cases with genetic data were less likely to be smokers and more likely to receive radiotherapy, but otherwise did not differ significantly from cases without genotyping data (Supplemental Table 3).

2.3 Covariates

In addition to retrieving 209 patient medical records, cases were linked to two administrative databases: (i) the California Office of Statewide Health Planning and Development (OSHPD) inpatient hospitalization discharge records (n=221), and (ii) the SEER-Medicare database (n=77 of 84 aged 65 or older at diagnosis). Additional information has been published on our validation efforts linking these databases (Zhong C et al, in press). Although records for chemotherapy and stage/number of nodal sites were sufficient (89% complete), we found that insufficient availability in medical record abstraction for lactic acid dehydrogenase (LDH) and hemoglobin (Hgb) laboratory values prohibited us from recreating the full FL-IPI (n=79 with both values). Based on these sources of clinical data, we therefore approximated the FL-IPI, which included age (>60), stage (III-IV), extranodal status, and Eastern Cooperative Oncology Group (ECOG) performance score (3-4). Other clinical variables collected and evaluated included treatment (yes/no) administered, including chemotherapy, surgery, and radiotherapy.

2.4 Survival outcomes

Overall survival (OS) and event-free survival (EFS) at 12 and 24 months were ascertained based on clinical data abstracted from multiple sources. Data on deaths, disease progression, and relapse/refractory disease were abstracted from medical records. Deaths were also obtained from the CSP, which routinely links to state and national death indices. OS was defined as the time from date of initial diagnosis to the date of death or last known follow-up. Event-free survival at 12 months (EFS12) and 24 months (EFS24) was defined as time from the date of initial diagnosis to 12 or 24 months free of disease progression, relapse/refractory disease, or death.

2.5 Statistical Methods

The polygenic risk score (PRS) was created by taking a weighted average of the log odds of previously published, significant SNPs identified in the National Human Genome Research Institute-European Bioinformatics Institute genome wide association study catalog [9]. The PRS consisted of the following SNPs: rs12195582, rs13254990, rs17749561, rs4245081 (tag SNP for reported rs4937362), and rs4938573 [9]. A weighted average of the reported log odds ratios was computed from these five SNPS and tertiles were created based on PRS values in the controls. Risk associations were estimated through logistic regression, calculating the odds ratios (OR) and 95% confidence intervals (95% CI) between PRS with FL risk using an additive model. We stratified our results by race/ethnicity. Multivariate analyses were conducted, adjusting for demographic factors and known FL risk factors, including smoking status, BMI, and family history of hematologic malignancies; which were collected by questionnaire at study enrollment. Associations with FL survival outcomes were estimated under a Cox proportional hazards model by calculating the hazards ratios (HR) and 95% CI for the three FL survival outcomes (OS, EFS12, and EFS24). In the Cox model, the timescale was defined in days from date of diagnosis until the date of the outcome of interest. Multivariate analyses were conducted, adjusting for clinical factors with the alternative FL-IPI. All analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC).

3. Results

3.1 FL risk associations

Genetic allele frequencies for the five SNPs included in the PRS are consistent with those previously reported [9], and are available in Supplemental Table 1. Two individual SNPs were significantly associated with increased FL risk in the overall sample: rs4938573 (per allele OR 1.52; 95% CI 1.13-2.05) and rs12195582 (per allele OR 1.65; 95% CI 1.27-2.14) and for the subset of non-Hispanic whites (rs4938573 OR 1.71; 95% CI 1.19-2.45: rs12195582 OR 1.74; 95% CI 1.26-2.41). In the group of non-Hispanic White women, we observed an overall increased FL risk associated with the third tertile of the FL PRS (OR 2.42, 95% CI 1.47-4.00) compared to the first tertile (Table 1). Sample sizes for other race/ethnic groups were limited but the direction of association appeared consistent in Hispanic women.

3.2 FL survival associations

The median follow-up time among FL cases was 8.5 years (interquartile range: 7.1-10.1 years). During follow-up, 50 (22%) FL cases died, 198 (86%) achieved EFS12, and 186 (81%) achieved EFS24. The most common treatment was chemotherapy (n=124), followed by surgery (n=63) and radiotherapy (n=32). Most (102/111 with regimen information, Supplemental Table 3) of the cases that received chemotherapy received a rituximab based regimen. Surgical treatment was significantly associated with worse overall survival (HR 2.06, 95% CI 1.20-3.55). In non-Hispanic White women, the approximated FL-IPI was significantly associated with OS (HR 3.55, 95% CI 1.00-12.58, Table 2), but not significantly with EFS12 (HR 3.34, 95% CI 0.37-30.1) or EFS24 (HR 3.06, 95% CI 0.63-14.8, Supplemental Table 2). The PRS was also associated with improved overall

survival in multivariate analyses for non-Hispanic White women, after adjustment for the alternative FL-IPI (HR 0.31, 95% CI 0.10-0.96). Evaluation of FL survival endpoints by individual SNPs suggested a strong contribution from rs12195582 (HR 0.62, 95% CI 0.37-1.04).

In our limited sample size of Hispanic White women, we also observed an increased FL risk for surgical treatment (HR 4.16, 95% CI 1.04-16.7), but no association between PRS and OS (HR 1.58, 95% CI 0.14-17.5).

4. Discussion

In this evaluation of a FL PRS, we confirmed its association with FL risk among a non-Hispanic Caucasian population. Sample sizes were limited yielding insufficient statistical power among Hispanic and other race/ethnicities, but the direction of risk was consistent in Hispanics. We show for the first time that this FL PRS may also be associated with favorable FL outcomes, specifically OS, even after adjustment for key clinical and demographic factors. Specific SNPs appeared to have more prominent roles in this association, including rs12195582 which is in the HLA-DR region. This is potentially consistent with previous reports that have suggested a role for HLA-DRB1*13 in FL prognosis [13]. Foo and colleagues further reported evidence of specific amino acid and peptide binding for HLA-DRB1*13, though in relation to follicular lymphoma risk. [14]. As HLA-DRB1*13 has also been implicated in response to chemotherapy for breast cancer [15], further queries regarding the binding site and chemotherapy in relation to follicular lymphoma may be warranted. Future investigations in larger populations and other race/ethnic groups are also needed to replicate and fully understand these observations.

Our study strengths included the abstraction of key clinical data using three different sources, including medical records and linkages to inpatient hospitalization database and the SEER-Medicare database. Study limitations include the original study population which included only women and the subset of who agreed to genetic research and for whose samples provided high quality data. Our study was limited to a handful of a priori SNPs of high allele frequency, which may not entirely encompass the genetic complexity of FL [16]. Due to incomplete clinical laboratory data, we also were not able to re-create the FL-IPI in full; however, our approximated FL-IPI was associated with the prognostic outcomes. Finally, we acknowledge the possibility that our results for improved survival among “risk alleles” may reflect survival bias whereby patients with better prognosis typically enroll into population-based studies. However, comparison of our study FL patients to that of the broader SEER registry did not yield significant differences in survival or characteristics, and comparison of our study of FL patients who had genetic data compared to those without did not yield significant differences in their survival or clinical attributes.

In summary, we observed increased risk of FL with higher FL PRS, but favorable OS among FL cases with higher FL PRS. Further studies are warranted to replicate our results and to further our understanding of the biological mechanisms underlying the potential interactions between these loci for FL risk and survival.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

NHL	non-Hodgkin lymphoma
FL	follicular lymphoma
FLIPI	follicular lymphoma International Prognostic Index

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Highlights

- Polygenic risk score (PRS) created from identified follicular lymphoma (FL) risk loci
- Confirmed risk association between PRS and FL risk among non-Hispanic White women
- Higher PRS was associated with better overall survival among FL patients

Table 1.

Risk (OR: odds ratio and 95% CI: 95% confidence interval) for follicular lymphoma among non-Hispanic and Hispanic White women in the Los Angeles County non-Hodgkin Lymphoma case control study with genotyping data(RAF: risk allele frequency)

			Controls (n=679)		Overall (n=148)				non-Hispanic White (n=100)				Hispanic White (n=30)			
			n	**RAF**	**n**	**RAF**	**OR**	**95% CI**	**n**	**RAF**	**OR**	**95% CI**	**n**	**RAF**	**OR**	**95% CI**
Risk Association of Individual Alleles	rs4938573	TT	452		79		1.0 (ref)		50		1.0 (ref)		17		1.0 (ref)	
		CT	200		59		1.69	(1.16-2.46)	42		1.76	(1.12-2.79)	13		2.69	(1.15-6.28)
		CC	25	0.18	8		1.83	(0.80-4.20)	7		2.74	(1.07-7.07)	0		-	
		per allele				*0.18*	*1.52*	*(1.13-2.05)*		*0.19*	*1.71*	*(1.19-2.45)*		*0.15*	*1.55*	*(0.77-3.11)*
	rs4245081 *	CC	166		39		1.0 (ref)		21		1.0 (ref)		12		1.0 (ref)	
		CT	347		71		0.87	(0.57-1.34)	50		1.03	(0.59-1.80)	12		0.42	(0.17-1.04)
		TT	142	0.48	28		0.84	(0.49-1.43)	24		0.97	(0.51-1.85)	4		0.45	(0.13-1.60)
		per allele				*0.48*	*0.91*	*(0.70-1.19)*		*0.48*	*0.98*	*(0.72-1.36)*		*0.47*	*0.59*	*(0.31-1.13)*
	rs17749561	AA	2		0				0				0			
		AG	86		14		1.0 (ref)		13		1.0 (ref)		1		1.0 (ref)	
		GG	590	0.92	133		1.39	(0.76-2.51)	86		1.23	(0.65-2.32)	29		4.22	(0.56-33.3)
		per allele				*0.93*	*1.43*	*(0.80-2.57)*		*0.92*	*1.29*	*(0.69-2.39)*		*0.94*	*4.22*	*(0.56-33.3)*
	rs13254990	CC	346		75		1.0 (ref)		44		1.0 (ref)		17		1.0 (ref)	
		CT	265		51		0.89	(0.60-1.31)	39		0.9	(0.56-1.45)	9		1.1	(0.45-2.72)
		TT	54	0.32	20		1.71	(0.97-3.02)	15		1.6	(0.82-3.14)	4		3.44	(0.83-14.2)
		per allele				*0.28*	*1.15*	*(0.88-1.51)*		*0.32*	*1.15*	*(0.83-1.59)*		*0.20*	*1.53*	*(0.82-2.86)*
	rs12195582	CC	221		34		1.0 (ref)		20		1.0 (ref)		7		1.0 (ref)	
		CT	342		65		1.24	(0.79-1.93)	43		1.19	(0.67-2.11)	15		1.52	(0.57-4.08)
		TT	109	0.44	45		2.68	(1.63-4.43)	34		2.86	(1.54-5.30)	8		2.03	(0.65-6.34)
		per allele				*0.42*	*1.65*	*(1.27-2.14)*		*0.44*	*1.74*	*(1.26-2.41)*		*0.43*	*1.42*	*(0.81-2.51)*

			Controls (n=679)		Overall (n=148)				non-Hispanic White (n=100)				Hispanic White (n=30)			
			n	**RAF**	**n**	**RAF**	**OR**	**95% CI**	**n**	**RAF**	**OR**	**95% CI**	**n**	**RAF**	**OR**	**95% CI**
Polygenic risk score	Tertile 1		198		25		1.0 (ref)		14		1.0 (ref)		6		1.0 (ref)	
	Tertile 2		226		42		1.47	(0.87-2.50)	25		1.3	(0.65-2.61)	12		2.35	(0.80-6.94)
	Tertile 3		209		64		2.42	(1.47-4.00)	50		2.56	(1.35-4.86)	10		2.15	(0.70-6.56)
							p-trend	*0.001*			*p-trend*	*0.004*			*p-trend*	*0.26*

* tagSNP for previous reported rs4937362, Skibola et al 2014

Table 2.

Overall survival estimates (HR: hazard ratio and 95% CI: 95% confidence interval) for follicular lymphoma among non-Hispanic and Hispanic White women in the Los Angeles County non-Hodgkin Lymphoma case control study

		Overall (n=230)			**non-Hispanic White (n=157)**			**Hispanic White (n=43)**		
Univariate		n	HR	95% CI	n	HR	95% CI	n	HR	95% CI
Association of Individual Alleles	rs4938573		1.38	(0.81-2.34)		1.42	(0.79-2.53)		0.79	(0.13-4.78)
	rs4245081*		0.98	(0.60-1.59)		1.03	(0.59-1.82)		0.44	(0.10-1.94)
	rs17749561		0.57	(0.22-1.48)		0.59	(0.22-1.54)		NA	
	rs13254990		0.74	(0.45-1.20)		0.83	(0.49-1.40)		0.27	(0.40-1.91)
	rs12195582		0.68	(0.43-1.07)		0.62	(0.37-1.04)		1.16	(0.34-4.04)
Polygenic risk score (HR, 95% CI)	Tertile 1	25	ref		14	ref		6	ref	
	Tertile 2	42	0.59	(0.26-1.36)	25	0.56	(0.21-1.49)	12	1.4	(0.13-15.8)
	Tertile 3	64	0.37	(0.16-0.86)	50	0.29	(0.11-0.74)	10	1.58	(0.14-17.5)
			p-trend	0.07		p-trend	0.04		p-trend	0.93
International Prognostic Index (approximated)	Low	28	ref		17	ref		8	ref	
	Med	132	1.32	(0.46-3.78)	92	0.95	(0.27-3.27)	24	1.84	(0.22-15.36)
	High	26	4.00	(1.32-12.16)	22	3.55	(1.00-12.58)	2	2.81	(0.17-45.72)
Treatment										
Surgery	No	167	ref		112	ref		35	ref	
	Yes	63	2.06	(1.20-3.55)	45	2.14	(1.13-4.06)	8	4.16	(1.04-16.70)
Chemotherapy	No	106	ref		71	ref		21	ref	
	Yes	124	1.01	(0.59-1.73)	86	1	(0.53-1.90)	22	0.54	(0.13-2.25)
Radiotherapy	No	198	ref		135	ref		35	ref	
	Yes	32	1.28	(0.63-2.62)	22	1.21	(0.51-2.89)	8	2.54	(0.60-10.60)

		Overall (n=230)			non-Hispanic White (n=157)			Hispanic White (n=43)		
Multivariate **										
Polygenic risk score (HR, 95% CI)	Tertile 1	20	ref		13	ref		4	ref	
	Tertile 2	35	0.65	(0.24-1.74)	22	0.76	(0.23-2.57)	9	NA	
	Tertile 3	54	0.32	(0.13-0.82)	42	0.31	(0.10-0.96)	9	NA	
			p-trend	0.06		p-trend	0.11		p-trend	NA
*tagSNP for previous reported rs4937362, Skibola et al 2014										

** adjusted for IPI and treatment

Approximated IPI consists of : age (>60), stage (III-IV), extranodal status, and Eastern Cooperative Oncology Group (ECOG) performance score (3-4)