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Female reproductive factors and risk of lymphoid neoplasm: The Japan Public Health Center-based Prospective Study

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Although a possible role of reproductive factors in lymphomagenesis has been hypothesized, results of epidemiological studies have been inconsistent. Here, we investigated the association between reproductive factors and the risk of lymphoid neoplasm and its subgroups. We used data from a large-scale, population-based prospective study in a Japanese cohort with 42 691 eligible women aged 40-69 years from 1990 to 1994. During a mean follow up of 18.7 years, we identified 176 cases of lymphoid neoplasm and 90 of non-Hodgkin lymphoma (NHL). A multivariable-adjusted Cox proportional hazards regression model was used to estimate hazard ratios (HR) and 95% confidence intervals (95% CI) for the risk of lymphoid neoplasms and its subgroups according to self-reported reproductive factors. Parous women had an increased risk of lymphoid neoplasm compared with nulliparous women (HR = 2.51, 95% CI, 1.03-6.13). An increased risk of lymphoid neoplasms was found in women with later onset of menarche (≤13 years old; reference: 14-15; HR = 1.75, 95% CI = 1.10-2.79: ≥16; HR = 1.93, 95% CI = 1.17-3.19: *P*-trend: 0.01) and a shorter menstrual cycle (28-29 days; reference: ≤27; HR = 1.60, 95% CI = 1.05-2.43, *P*-trend = 0.81). No association was observed between lymphoid neoplasms and other reproductive factors, including age at first birth, breastfeeding, type of menopause, or exogenous hormone use. Our study suggests that ever parity, late age at menarche and a short menstrual cycle length may be associated with the development of lymphoid neoplasms. The inconsistency seen in epidemiological research to date warrants further investigation.

KEYWORDS
epidemiology, Japan, lymphoid neoplasms, prospective cohort, reproductive factors

Abbreviations: BCL, B-cell lymphoma; BMI, body mass index; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; HL, Hodgkin lymphoma; HR, hazard ratio; ICD-10, International Classification of Diseases, 10th Edition; JPHC Study, the Japan Public Health Center-based Prospective Study; NHL, non-Hodgkin lymphoma; PCM, plasma cell malignancy; TCL, T-cell lymphoma.

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1 | INTRODUCTION

Lymphoid neoplasms, a group of tumors arising from cells of the immune system, rank among the top 10 cancers by disease burden globally.[1,2] One well-established risk factor for these neoplasms is severe disruption of immune function, due to conditions such as immunodeficiency disorders, infectious agents, autoimmune diseases and organ transplantation. Nevertheless, the etiology of lymphoid neoplasm remains largely unknown.[2,3] Worldwide, lymphoid neoplasms are generally more common in men than women for most subtypes.[2] Although the reason for this discrepancy is not clear, one possible explanation is immune-mediated associations of sex hormones with lymphomagenesis.[3-5] In particular, estrogens have important immunomodulatory roles, including a biphasic effect on regulating immune responses, release of relevant cytokines, induction of B-cell differentiation, and induction of proliferation or apoptosis through hormone receptors.[5-8]

Previous studies have hypothesized that there is a link between lymphomagenesis and female reproductive factors through long-term and high exposure to female sex hormones.[2,3] Although attention has focused on pregnancy as a protective factor against the risk of non-Hodgkin lymphoma (NHL) owing to its dramatic alternations in female sex hormones and immune response, a recent systematic review and a meta-analysis suggested only a weak or null association.[3,9] Associations between the risk of NHL and late age at first birth were positive[10,11] or negative,[12] but most studies and a pooled analysis reported a null association.[13-16] Hormones released during lactation or missed ovulations due to breastfeeding were suggested as a possible mediator of lymphomagenesis, but evidence to determine the effect of breastfeeding is scarce.[10,17,18] While early age at menarche, late age at menopause and a long reproductive period are likely indicators of long exposure to female sex hormones,[10,13,16,18-20] only 1 cohort study has reported a suggestive decreased risk of NHL with longer reproductive years.[18] These inconsistent findings in epidemiological studies may have been due to selection bias; unclear definitions of exposure; the heterogeneity of lymphoma, given that its subtypes may have different etiology; and changes to coding system classification.

Findings from people with different reproductive patterns and incidence distribution would likely help elucidate the etiology of lymphoid neoplasms. To date, however, no evidence from Japanese populations has appeared. We hypothesized that early and/or, longer exposure to female sex hormones might reduce the risk of lymphoid neoplasms. Here, we aimed to investigate the association between reproductive factors and the risk of lymphoid neoplasms and subtypes among Japanese women.

2 | MATERIAL AND METHODS

2.1 | Study population and baseline survey

We used data from the Japan Public Health Center-based Prospective Study (JPHC study). The JPHC study enrolled 140 420 participants aged 40-69 years residing nationwide in 11 public health center areas from 1990 to 1994 (68 722 men and 71 698 women). Study participants were asked about their lifestyle, sociodemographic characteristics, personal and family medical history, diet and reproductive history using a basic questionnaire at entry. Response rate to the initial survey was 81%. Details of the study design have been described elsewhere.[21] Ethical approval was obtained from the institutional review board of the National Cancer Center (approval number: 2001-021).

Of the 71 698 women, we excluded those with non-Japanese nationality (n = 20), pre–commencement emigration (n = 86), incorrect birth date (n = 5), duplicate registration (n = 4) or a late report of migration or death before the start of the follow-up period (n = 4598). Of the 66 958 eligible subjects, 59 934 women (89.5%) returned the completed questionnaire. Subjects residing in the Katsushika area (n = 4163) were excluded because of the unavailability of cancer incidence data. We further excluded those who were diagnosed with cancer before the baseline survey (n = 164) or reported a past history of any cancer at study baseline (n = 1422), leaving 54 185 women in the analyses.

2.2 | Follow up

Residency registration was used to identify participant survival or emigration. Person-years of follow up were calculated from study entry until the date of diagnosis of lymphoid neoplasm, emigration from the study area, death or the end of follow up (31 December 2013), whichever came first. Subjects from the Suita area were scheduled to be followed until December 2012. Of the eligible subjects, 31 (.02%) were lost to follow up during the follow-up period.

2.3 | Identification of lymphoid neoplasms

Cancer cases were identified from cancer registers, and/or through active patient notification from local hospitals in the study areas. Cancers were coded according to the International Classification of Diseases for Oncology, 3rd edition (ICD-O-3). Death certificates were used as an auxiliary to check the cause of death, resulting in a death-certificate-only rate of less than 1%. For patients who developed multiple primary cancers at different times, the date of earliest cancer diagnosis was used. We grouped all lymphoid neoplasm cases into NHL (9591, 9599, 9670-71, 9673, 9675, 9678, 9680, 9684, 9687, 9689, 9690-91, 9695, 9698-99, 9700, 9702, 9705, 9709, 9714, 9718-19, 9761, 9766-67, 9823, 9826), HL (9650-52, 9659, 9663), lymphoid neoplasm NOS (9590) and Plasma Cell Neoplasms (PCN) (9731-34). We further divided NHL into subgroups: the B-cell type, diffuse large B-cell neoplasms (DLBCL), follicular lymphoma (FL) and T/NK neoplasms. Adult T-cell leukemia/lymphoma (9827) (ATL) was not assessed in this study because HTLV-1 is an established cause of ATL and data on HTLV-1 was limited.[22]

2.4 | Exposure assessment

Reproductive events in the baseline survey were selected and categorized based on frequency distribution within the cohort, as follows: total number of live or still births (nulliparous versus parous,

and 1-2, 3 or ≥4 births), experience of breastfeeding (no or yes), age at first birth (≤23, 24-26 or ≥27 years), age at menarche (≤13, 14-15 or ≥16 years), exogenous hormone use (never or ever) and length of menstrual cycle (≤27, 28-29, ≥30 days or irregular). Women with a regular cycle were asked about the length of their menstrual cycle. Specific details of the frequency and duration of breastfeeding were not available. Because of the markedly low use of exogenous hormones in Japan at the time of study initiation,[23] we did not ask for specific information on formulation, dose or duration of exogenous hormones.

As half of the study subjects were in menopausal transition during follow up, we additionally used 5-year and 10-year follow-up data for menopausal type (pre–menopause, natural menopause or surgical menopause) and age at menopause among premenopausal women in the baseline survey. Because closed-ended questions in the 5-year and 10-year surveys limited our ability to obtain a specific value for age at menopause, we conducted a predictive mean matching method to impute menopausal age, and then created a category based on the frequency distribution (≤47, 48-50 or ≥51 years). We also calculated total fertility years as the interval between menarche and imputed menopause (≤32, 33-35 or ≥36 years). Subjects who were diagnosed as having any lymphoid neoplasm before the age of menopause were verified and excluded in the analysis of age at menopause, total fertility years and menopausal type (n = 3).

2.5 | Statistical analysis

We used a Cox proportional hazards regression model to estimate hazard ratios (HR) and 95% confidence intervals (CI) for the risk of lymphoid neoplasms and subtypes according to exposure. We were not able to analyze for HL, FL, T/NK neoplasms or lymphoid neoplasms NOS because of the small numbers of these cases. We used attained age as the time scale.[24] We included the following variables in the models as potential confounders based on prior research: study area (10); height (≤150, 151-154 or ≥155 cm)[25]; smoking status (never or ever)[26]; and alcohol consumption (no, occasional or regular).[27] The proportional hazards (PH) assumption was verified using Schoenfeld residuals and no variable violated the PH assumption.

We excluded those participants with missing data on age, height, smoking status, alcohol consumption, parity, age at first birth, experience of breastfeeding, age at menarche, age at menopause, menopausal status, exogenous hormone use and length of the menstrual cycle at baseline survey (n = 11 494). This left a total of 42 691 women in the primary analyses. The minimum model was built with stratification by study area to allow different baseline hazards because of the different distribution of incidence across Japan.[28] The multivariate model was adjusted for potential confounders as mentioned above. Parity, age at menarche, menopausal status, and exogenous hormone use were included in the final model. Age at first birth and breastfeeding were additionally adjusted for when analyses were restricted to parous women. *P*-values for linear trends by assigning ordinal variables and the effects of unit increase of continuous variables were assessed for parity, age at first birth, age at menarche, age at menopause and total fertility years. We conducted a likelihood ratio test to compare models with and without interaction terms and to calculate a *P*-value for statistical interaction between all confounders and reproductive factors.

Secondary analyses were conducted using a model stratified by age group to assess the cohort effect. This is because we assumed that women born at different times may have a different distribution for reproductive history; namely, older subjects may have had a later onset of menarche and greater parity. Furthermore, because the prevalence of infectious status, such as infection with hepatitis B and C viruses, has been declining over time in Japan,[29] the risk of developing lymphoid neoplasms owing to an infectious status may differ by birth cohort. To ascertain the effect of viral infection, further analysis was conducted using a model that excluded subjects with a history of chronic hepatitis or cirrhosis (n = 415) as a possible surrogate of infectious status for hepatitis viruses. For sensitivity analysis, we included subjects who did not provide answers for all relevant variables (n = 11 494) to avoid potential selection bias arising from complete case analysis under the assumption that answers were missing at random. We performed a multiple imputation by chained equations procedure using all the variables described above as well as adding vital status and incidence of lymphoid neoplasms with 20 times' iteration. Estimations were then combined using Rubin's rule. Details of the imputation procedure are provided in the footnote of Table S1. All *P*-values reported were 2-sided, and $P < .05$ was set as the level of significance. All analyses were performed with STATA version 14.0 software (StataCorp LP, College Station, TX, USA).

3 | RESULTS

During a mean follow up of 18.7 years for 42 691 women (801 174 person-years), a total of 176 cases of newly diagnosed lymphoid neoplasms were identified, including 61 of PCN and 90 of NHL. Subtypes of NHL were 82 of B-cell neoplasm and 49 of DLBCL. Median age at diagnosis of lymphoid neoplasm was 69 years old (interquartile: 63-75 years old).

Table 1 shows the characteristics of subjects at baseline. When we compared the distribution between women born before and after 1940, women in the older cohort (n = 22 342) reported a lower height, less smoking, less alcohol consumption, earlier age at first birth, higher rate of ever breastfeeding, later age at menarche, later age at menopause, shorter fertility span and less use of exogenous hormones. Most women in the younger cohort (n = 22 349) reported having 2 children (41.3%), versus 4 or more in the older cohort (27.5%). Similarly, the distribution of age at menarche varied by age group. Among eligible subjects, 21.2% had at least 1 missing value for relevant confounders and exposures. When we looked at female to male incidence rate ratios, women were less likely to develop lymphoid neoplasms and any type of lymphoma than men (Figure S1).

The multivariable-adjusted HR with 95% CI for the association between reproductive factors and lymphoid neoplasms and subtypes are shown in Tables 2 and 3. We found that parous women

TABLE 1 Basic characteristics of study subjects at baseline survey of the Japan Public Health Center-based Prospective Study

Characteristic	Total	Birth year		*P*-value[a]
		≥1940	<1940	
Number of subjects (n)	42 691	22 349 (52.4%)	20 342 (47.6%)	
Age at recruitment, y[b]	51.3 (8.0)	45.0 (3.8)	58.3 (5.1)	<.01
Height (cm)[b]	152.2 (5.6)	153.5 (5.3)	150.7 (5.57)	<0.01
Non-smoker, %	91.7	89.8	93.4	<0.01
Non-drinker, %	76.2	68.3	84.0	<0.01
Reproductive factors				
Parity, %				
0	7.2	7.4	7.0	<0.01
1	7.2	7.7	6.8	
2	34.7	41.3	27.5	
3	27.8	28.9	26.7	
≥4	23.6	14.8	32.9	
Age at first birth, y[b,c]	24.9 (3.5)	25.1 (3.4)	24.8 (3.5)	<0.01
Ever breastfed, %[c]	87.5	84.3	91.4	
Age at menarche, y, %				
≤13	29.3	43.0	14.2	<0.01
14-15	45.4	48.0	42.5	
16+	25.3	9.0	43.3	
Age at menopause, y,[b,d]	48.8 (3.9)	48.2 (3.9)	49.3 (4.0)	<0.01
Total fertility years[b,d]	33.3 (4.5)	31.6 (4.8)	33.7 (4.4)	<0.01
Menopausal types, %[d]				
Natural menopause	88.1	85.4	90.2	<0.01
Surgical menopause	11.9	14.6	9.8	
Ever use of exogenous hormone, %	12.4	13.7	11.0	<0.01
Length of menstrual cycle, d[b]	27.7 (5.0)	27.7 (4.7)	27.6 (5.4)	0.09

[a]Analysis of variance (ANOVA) for continuous variables or the χ^2 test for categorical variables.
[b]Mean (standard deviation).
[c]Parous women only.
[d]Postmenopause using baseline, 5-y and 10-y surveys.

had an increased risk of lymphoid neoplasm compared to nulliparous women (HR = 2.51, 95% CI = 1.03-6.13). Positive associations with lymphoid neoplasm were found for later age at menarche (≤13 years old; reference: 14-15; HR = 1.75, 95% CI = 1.10-2.79: ≥16; HR = 1.93, 95% CI = 1.17-3.19: *P*-trend: .01) and a shorter menstrual cycle length (28-29 days; reference: ≤27; HR = 1.60, 95% CI = 1.05-2.43: ≥30; HR = 1.38, 95% CI = .96-1.96: *P*-trend: .81).

Regarding site-specific lymphoma, trends for increased risk of PCM were found in women with later age at menarche (*P*-trend: .06), later age at menopause (*P*-trend: .02; 1-year increase = 1.11, 95% CI = 1.02-1.21) and longer fertility years (*P*-trend: .02; 1-year increase = 1.10, 95% CI = 1.01-1.20). An increased risk of PCM was associated with a shorter length of menstrual cycle (28-29 days; reference: ≤27; HR = 2.05, 95% CI = 1.03-4.10). A trend towards increased risk of the B-cell type of NHL was observed in women with late age at menarche (*P*-trend: .04). A positive association was seen between risk of DLBCL and a shorter length of menstrual cycle (28-29 days;

TABLE 2 Multi-adjusted HR (95% CI) for risk of lymphoid neoplasms and plasma cell neoplasms according to reproductive factors in the JPHC Study[a]

			Lymphoid neoplasm				Plasma cell neoplasm			
Variable	Category	Person-years	Cases	HR	95% CI	*P*-trend[b]	Cases	HR	95% CI	*P*-trend[b]
Parous	No	52 951	5	1[c]	Reference		1	1[c]	Reference	
	Yes	748 367	171	2.51	1.03-6.13		60	4.36	0.60-31.5	
Number of births[d]	1-2	332 950	69	1	Reference	0.78	30	1	Reference	0.54
	3	229 026	48	0.97	0.66-1.42		15	0.73	0.38-1.38	
	≥4	186 390	54	1.08	0.70-1.66		15	0.85	0.40-1.79	
	1-child increase			1.02	0.91-1.16			0.91	0.72-1.15	
Age at first birth, y[d]	≤23	264 385	62	1	Reference	0.79	14	1	Reference	0.22
	24-26	288 650	71	1.12	0.79-1.59		29	1.85	0.96-3.57	
	≥27	195 331	38	0.92	0.60-1.41		17	1.60	0.76-3.35	
	1-y increase			0.98	0.93-1.03			1.01	0.94-1.09	
Breastfeeding[d]	Never	93 196	19	1	Reference		6	1	Reference	
	Ever	655 170	152	0.91	0.56-1.48		54	1.26	0.53-2.97	1.26
Age at menarche, y	≤13	232 123	24	1	Reference	0.01	8	1	Reference	0.06
	14-15	367 092	85	1.75	1.10-2.79		33	2.29	1.04-5.03	
	≥16	202 103	67	1.93	1.17-3.19		20	2.33	0.97-5.61	
	1-y increase			1.02	0.86-1.22			1.02	0.74-1.41	
Age at menopause, y[e]	≤47	210 624	41	1	Reference	0.34	9	1	Reference	0.02
	48-50	244 329	54	0.87	0.57-1.33		17	1.35	0.58-3.20	
	≥51	248 415	71	1.16	0.77-1.75		29	2.32	1.03-5.26	
	1-y increase			1.02	0.98-1.07			1.11	1.02-1.21	
Total fertility span, y[e]	≤32	205 679	43	1	Reference	0.34	7	1	Reference	0.02
	33-35	216 156	58	1.42	0.94-2.14		22	3.48	1.44-8.44	
	≥36	308 065	66	1.26	0.81-1.94		26	3.35	1.33-8.43	
	1-y increase			1.02	0.98-1.07			1.10	1.01-1.20	
Menopausal type[e]	Natural	621 080	152	1	Reference		50	1	Reference	
	Surgical	82 288	14	0.80	0.46-1.37		5	0.78	0.31-1.98	
Exogenous hormone use	Never use	698 099	161	1	Reference		53	1	Reference	
	Ever use	103 219	15	0.80	0.46-1.40		8	1.28	0.60-2.77	
Length of menstrual cycle, d	≤27	138 118	34	1.60	1.05-2.43	0.81[f]	14	2.05	1.03-4.10	0.87[f]
	28-29	365 233	65	1	Reference		20	1	Reference	
	≥30	211 437	60	1.38	0.96-1.96		22	1.68	0.91-3.10	
	Irregular	86 528	17	1.31	0.76-2.27		5	1.15	0.42-3.12	
	1-d increase[f]			1.00	0.97-1.03			0.99	0.94-1.04	

[a]Cox proportional hazards models (using attained age as time scale) stratified by public health center area and adjusted for smoking status; alcohol consumption; height; parity; age at menarche; menopausal status; and exogenous hormone use.
[b]*P*-value for linear trend across categories of variable.
[c]Adjustments as in footnote "a" except the parity.
[d]Parous women only with additional adjustment for age at first birth and breastfeeding.
[e]Menopausal women only.
[f]Subjects with an irregular cycle were excluded.
CI, confidence interval; HR, hazard ratio; JPHC, Japan Public Health Center-based Prospective Study.

reference: ≤27; HR = 2.90, 95% CI = 1.41-5.95). Overall, no association was found between lymphoid neoplasms or any subtype and most reproductive factors, including age at first birth, breastfeeding, menopausal type and exogenous hormone use. The results of the minimal model were not substantially different from those of the final model.

TABLE 3 Multi-adjusted HR (95% CI) for risk of non-Hodgkin lymphoma and its subtypes according to reproductive factors in the JPHC Study[a]

			Non-Hodgkin lymphoma				B-cell type of NHL				DLBCL			
Variable	Category	Person-years	Cases	HR	95% CI	*P*-trend[b]	Cases	HR	95% CI	*P*-trend[b]	Cases	HR	95% CI	*P*-trend[b]
Parous	No	52 951	4	1[c]	Reference		4	1[c]	Reference		2	1[c]	Reference	
	Yes	748 367	86	1.58	0.58-4.34		78	1.41	0.51-3.87		47	1.66	0.40-6.88	
Number of births[d]	1-2	332 950	34	1.00	Reference	0.75	31	1.00	Reference	0.71	19	1	Reference	0.85
	3	229 026	26	1.04	0.62-1.77		24	1.09	0.63-1.89		16	1.16	0.58-2.30	
	≥4	186 390	26	1.10	0.60-2.04		23	1.13	0.58-2.17		12	0.87	0.36-2.08	
	1-child increase			1.00	0.84-1.20			1.03	0.86-1.24			0.92	0.71-1.18	
Age at first birth, y[d]	≤23	264 385	38	1	Reference	0.16	34	1	Reference	0.14	18	1	Reference	0.43
	24-26	288 650	31	0.77	0.47-1.26		30	0.84	0.50-1.39		21	1.08	0.57-2.08	
	≥27	195 331	17	0.66	0.36-1.22		14	0.61	0.32-1.18		8	0.66	0.27-1.58	
	1-y increase			0.96	0.89-1.03			0.96	0.88-1.03			0.94	0.85-1.04	
Breastfeeding[d]	Never	93 196	10	1	Reference		10	1	Reference		7	1	Reference	
	Ever	655 170	76	0.80	0.41-1.57		68	0.70	0.36-1.39		40	0.55	0.24-1.26	
Age at menarche, y	≤13	232 123	13	1	Reference	0.10	10	1	Reference	0.04	7	1	Reference	0.59
	14-15	367 092	42	1.55	0.82-2.93		40	1.97	0.97-4.00		23	1.32	0.56-3.10	
	≥16	202 103	35	1.79	0.90-3.54		32	2.20	1.03-4.71		19	1.29	0.52-3.21	
	1-y increase			0.91	0.71-1.18			0.87	0.66-1.15			0.97	0.69-1.35	
Age at menopause, y[e]	≤47	210 624	26	1	Reference	0.72	22	1	Reference	0.91	14	1	Reference	0.73
	48-50	244 329	28	0.73	0.41-1.27		26	0.83	0.45-1.50		18	0.88	0.42-1.85	
	≥51	248 415	33	0.87	0.50-1.50		31	0.99	0.55-1.79		17	0.87	0.41-1.86	
	1-y increase			0.99	0.93-1.05			0.99	0.93-1.06			1.00	0.93-1.09	
Total fertility span, y[e]	≤32	205 679	27	1	Reference	0.87	24	1	Reference	0.95	16	1	Reference	0.71
	33-35	216 156	28	1.08	0.62-1.88		26	1.16	0.65-2.08		16	1.06	0.51-2.20	
	≥36	308 065	32	0.96	0.54-1.72		29	1.03	0.56-1.91		17	0.87	0.40-1.90	
	1-y increase			0.99	0.94-1.05			1.00	0.94-1.06			1.00	0.93-1.08	
Menopausal type[e]	Natural	621 080	78	1	Reference		70	1	Reference		43	1	Reference	
	Surgical	82 288	9	1.03	0.51-2.06		9	1.16	0.57-2.33		6	1.26	0.53-2.99	
Exogenous hormone use	Never use	698 099	84	1	Reference		77	1	Reference		46	1	Reference	

(*Continues*)

TABLE 3 (Continued)

Variable	Category	Person-years	Non-Hodgkin lymphoma				B-cell type of NHL				DLBCL			
			Cases	HR	95% CI	*P*-trend[b]	Cases	HR	95% CI	*P*-trend[b]	Cases	HR	95% CI	*P*-trend[b]
	Ever use	103 219	6	0.57	0.24-1.33		5	0.51	0.20-1.27		3	0.55	0.17-1.83	
Length of menstrual cycle, d	≤27	138 118	17	1.39	0.78-2.48	0.28[f]	17	1.54	0.86-2.78	0.12[f]	14	2.90	1.41-5.95	0.05[f]
	28-29	365 233	39	1	Reference		35	1	Reference		17	1	Reference	
	≥30	211 437	25	0.97	0.58-1.61		21	0.91	0.53-1.58		14	1.22	0.60-2.51	
	Irregular	86 528	9	1.12	0.53-2.37		9	1.23	0.58-2.63		4	1.22	0.40-3.73	
	1-day increase[f]			0.99	0.95-1.03			0.98	0.94-1.02			0.98	0.93-1.02	

[a]Cox proportional hazards models (using attained age as time scale) stratified by public health center area and adjusted for smoking status; alcohol consumption; height; parity; age at menarche; menopausal status; and exogenous hormone use.
[b]*P*-value for linear trend across categories of variable.
[c]Adjustments as in footnote "a" except for parity.
[d]Parous women only with additional adjustment for age at first birth and breastfeeding.
[e]Menopausal women only.
[f]Subjects with an irregular cycle were excluded.
CI, confidence interval; DLBCL, diffuse large B-cell lymphoma; HR, hazard ratio; JPHC, Japan Public Health Center-based Prospective Study.

When subjects were stratified by age group, *P*-values for interaction were insignificant for all reproductive factors and risk of lymphoid neoplasm (Table 4). However, the magnitude and direction of association for some reproductive factors differed by age group. Regarding parity, parous women had a higher risk of lymphoid neoplasm than nulliparous women in the older cohort, versus no association in the younger cohort. A positive association of late age at menarche with risk of lymphoid neoplasm was found in women of the older cohort only, whereas the association between late age at menopause and risk of lymphoid neoplasm was statistically significant in the younger cohort. Among the 415 women who reported a history of chronic hepatitis or cirrhosis, only 1 subject developed PCN during the follow-up survey. The estimation for all malignant lymphoma and PCM using a model that excluded subjects with a history of chronic hepatitis or cirrhosis did not change substantially (data not shown). Estimations using multiple imputed datasets showed similar results for the overall results, but in the results for parous versus nulliparous women in the risk of lymphoid neoplasms, age at menarche, age at menopause and total fertility years in the risk of PCM became null while the association between late age at menarche and risk of NHL changed to significant (Table S1).

4 | DISCUSSION

In this large-scale and well-designed prospective cohort study, we focused on reproductive factors as possible markers for the risk of lymphoid neoplasm and its common subtypes. Results showed positive associations between late age at menarche and lymphoid neoplasm, and possibly PCM, NHL and the B-cell type of NHL. Ever parity may increase the risk of developing lymphoid neoplasm, whereas no dose-response effect was found for parity. Possible associations were found between PCM and late age at menopause and long fertility years. A shorter length of menstrual cycle was associated with risk of lymphoid neoplasms, PCM and DLBCL compared to the reference group. Our data also revealed null associations between risk for any type of lymphoid neoplasm and several reproductive factors, including age at first birth, experience of breastfeeding, type of menopause and exogenous hormone use.

While 1 study suggested that late onset at menarche conferred an increased risk of NHL,[20] other studies and a pooled analysis reported null associations with NHL and its common subtypes.[13,16] Here, however, we observed that late age at menarche was associated with the overall risk of lymphoid neoplasm, and was a suggestive risk for PCM, NHL and the B-cell type of NHL. Women with early onset of menarche have more prolonged and intense exposure to estrogen than those with late menarche.[30,31] Genetic interaction with environmental factors, which determine the initiation of menarche, and early exposure to various hormones such as growth-related hormones may represent possible mechanisms that influence lymphomagenesis.[32] Regarding menopausal age, while 1 study suggested a decreased trend for the risk of NHL with longer reproductive years,[18] others reported no association between lymphoma risk

TABLE 4 HR (95% CI) of risk of lymphoid neoplasm according to reproductive factors stratified by age group in the JPHC Study[a]

		Women born after 1941 (n = 22 349) person-time: 421 069				Women born before 1940 (n = 20 349) person-time: 380 249				
Variable	Category	Cases	HR	95% CI	*P*-trend[b]	Cases	HR	95% CI	*P*-trend[b]	*P*-interaction
Parous	No	3	1[c]	Reference		2	1[c]	Reference		0.17
	Yes	55	1.28	0.40-4.10		116	4.41	1.09-17.9		
Number of births[d]	1-2	27	1	Reference	0.64	42	1	Reference	1.00	0.72
	3	16	1.00	0.52-1.90		32	0.93	0.58-1.49		
	≥4	12	1.25	0.56-2.79		424	1.01	0.60-1.69		
	1-child increase		1.19	0.94-1.50			0.98	0.85-1.13		
Age at first birth[d], y	≤23	19	1	Reference	0.92	43	1	Reference	0.61	0.61
	24-26	22	0.96	0.51-1.80		49	1.14	0.75-1.75		
	≥27	14	0.97	0.47-1.98		24	0.83	0.49-1.42		
	1-y increase		1.00	0.92-1.08			0.96	0.90-1.02		
Breastfeeding[d]	Never	9	1	Reference		10	1	Reference		0.88
	Ever	46	0.96	0.46-1.97		106	0.87	0.45-1.68		
Age at menarche, y	≤13	18	1	Reference	0.34	6	1	Reference	0.01	0.31
	14-15	32	1.32	0.73-2.39		53	2.88	1.23-6.71		
	≥16	8	1.53	0.64-3.66		59	3.20	1.37-7.48		
	1-y increase		1.51	1.02-2.22			0.94	0.76-1.15		
Age at menopause[e], y	≤48	20	1	Reference	0.02	38	1	Reference	0.89	0.04
	49-51	17	0.67	0.27-1.65		45	0.92	0.56-1.50		
	≥52	11	2.17	1.03-4.56		35	0.95	0.58-1.56		
	1-y increase		1.08	0.98-1.18			1.01	0.96-1.07		
Total fertility span[e], y	≤32	9	1	Reference	0.18	34	1	Reference	0.70	0.71
	33-35	15	1.89	0.79-4.57		43	1.30	0.81-2.07		
	≥36	25	1.95	0.79-4.83		41	1.12	0.67-1.86		
	1-y increase		1.05	0.96-1.15			1.02	0.97-1.07		
Menopausal type[e]	Natural	41	1	Reference		111	1	Reference		0.19
	Surgical	7	1.17	0.52-2.63		7	0.63	0.29-1.35		
Exogenous hormone use	Never use	54	1	Reference		107	1	Reference		0.19
	Ever use	4	0.43	0.15-1.20		11	1.02	0.97-1.07		
Length of menstrual cycle, d	≤27	16	1.44	0.76-2.73	0.40[f]	18	1.63	0.93-2.85	0.64[f]	0.62
	28-29	23	1			42	1	Reference		

(*Continues*)

TABLE 4 (Continued)

Variable	Category	Women born after 1941 (n = 22 349) person-time: 421 069				Women born before 1940 (n = 20 349) person-time: 380 249				
		Cases	HR	95% CI	*P*-trend[b]	Cases	HR	95% CI	*P*-trend[b]	*P*-interaction
	≥30	13	1.04	0.52-2.07		47	1.53	1.01-2.34		
	Irregular	6	0.92	0.37-2.29		11	1.61	0.81-3.21		
	1-d increase[f]		1.00	0.95-1.06			1.00	0.96-1.03		

[a]Cox proportional hazards models (using attained age as time scale) stratified by public health center area and adjusted for smoking status; alcohol consumption; height; parity; age at menarche; menopausal status; and exogenous hormone use.
[b]*P*-value for linear trend across categories of variable.
[c]Adjustments as in footnote "a" except the parity.
[d]Parous women only with additional adjustment for age at first birth and breastfeeding.
[e]Menopausal women only.
[f]Subjects with an irregular cycle were excluded.
CI, confidence interval; HR, hazard ratio; JPHC, Japan Public Health Center-based Prospective Study.

and age at menopause,[13,16] total ovulatory years[20] and/or natural versus surgical menopause.[13,18] Although our study observed positive associations between risk of age at menopause, total fertility years and risk of PCM in the complete-case analysis, the association became insignificant in the sensitivity analysis. Taken together, our present and these previous findings suggest that the timing of menarche may play a role in lymphomagenesis, rather than menopause or fertility span.

A novel finding of our study was the association between length of menstrual cycle and risk of lymphoma. Given that a shorter than average menstrual cycle length is associated with decreased levels of luteal estrogens, the possible link between cycle length and risk of lymphoid neoplasm may involve lower cumulative exposure to estrogen.[33]

The null result for a dose-response effect of parity on the risk of lymphoid neoplasm was consistent with a recent meta-analysis.[9] In contrast, we also observed a positive association between ever parity and risk of lymphoid neoplasm compared to nulliparity. Nevertheless, the evidence for parous versus nulliparous in this association is scarce, and the experience of childbearing may be an important marker regardless of the number of births. The dramatic increase in estrogen levels during pregnancy leads to a shift from the prevailing cell-mediated immunity (Th1) to antibody-mediated humoral immune (Th2) to protect the fetus.[7] Aggressive development or progression of pregnancy-induced lymphoma may be associated with the development of lymphoid neoplasm.[34] Among women of reproductive age, the prevalence of aggressive lymphoma such as DLBCL is much higher among pregnant than non-pregnant women.[34] The prevalence of extra nodal lymphoma in reproductive organs is also increased during pregnancy.[34] Furthermore, the antibody production-enhancing Th2 immune response during pregnancy may lead women to be susceptible to antibody-mediated autoimmune diseases, which would, in turn, increase subsequent lymphoma risk.[35,36] Although controversial, 1 group has proposed a potential link between fetal microchimerism during pregnancy and autoimmune disease as an intermediate in the development of lymphoid neoplasm.[37] Nevertheless, given the small number of cases among nulliparous women, we cannot exclude the possibility that our finding was due to chance.

With regard to the timing of pregnancy, 1 cohort study with 2 million women found a reduced risk of NHL with delayed age at first birth,[12] whereas 2 case-control studies reported that early age at first birth was associated with a significantly reduced risk of NHL[11,38] or null results[13-16] The results should, therefore, be considered inconclusive, and age at first birth may not be attributable to the risk of lymphomagenesis.

Regarding the use of exogenous hormones such as oral contraceptives and hormone therapy, previous findings have yielded inconsistent results.[3,6] The substantial change in exogenous hormone availability and pattern of use over the years prevents comparison of associations with various defined exogenous hormones across studies. For this reason, we were also unable to provide estimations by formulation of exogenous hormones or duration of usage.

Taken as a whole, our results are unlikely to explain why the incidence of lymphoid neoplasm is higher in men than women. Other proposals made to explain the male predominance in the incidence of lymphoid neoplasm include male sex hormones,[39] and lifestyle-related and occupational-related exposure to radiation and chemical substances, such as smoking, pesticides and benzene.[40] We were unable to assess these factors in this study.

4.1 | Strengths and limitations

To our knowledge, this is the first large-scale prospective study of the association between reproductive factors and risk of lymphoid neoplasms. Several advantages of this study warrant mention: its large sample size, high response rate (81%), long duration of follow up and low loss to follow up. Information on many reproductive factors enabled us to assess a variety of potentially relevant exposures. Study subjects consisted of a general population from across Japan, making our findings applicable to the entire Japanese population.

Several limitations should also be mentioned. First, specific data on exogenous hormone use were not available, preventing us from assessing the effects of oral contraceptives and hormone therapy separately. Second, the main findings were obtained from subjects who responded to all relevant questions, which may have introduced a risk of selection bias. However, we aimed to mitigate this issue by using the imputation approach. Third, although we took account of important confounders, we cannot exclude the possibility of other unknown factors. Fourth, the lack of information on possible risk factors may have introduced biased estimations, including infectious status (eg, HBV and HCV) and radiation exposure, even though additional analysis excluded subjects with a history of liver disease which may have been influenced by hepatitis viruses. Finally, because our study subjects were Japanese, the results should be generalized to other populations with care.

In conclusion, we found that late age at menarche, a shorter length of menstrual cycle and ever parity were positively associated with the overall risk of lymphoid neoplasm in the Japanese population. Delayed exposure to various hormones in early life and pregnancy-induced change in immune response may both play a role in the development of lymphoid neoplasm in later life. The various inconsistent findings among studies conducted to date warrant further investigation to determine the mechanisms underlying the effect of reproductive factors in the development of lymphoid neoplasm.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTION

MI and NS designed this project; ST, NS and MI contributed to the study design and survey; STa conducted the statistical analysis and interpreted the results; STa wrote the manuscript; all authors reviewed, contributed to discussion and approved the final version of the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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