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Second Primary Cancers Following Non-Hodgkin's Lymphoma in Japan: Increased Risk of Hepatocellular Carcinoma

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We evaluated the risk of development of second primary cancers, with particular reference to subsequent hepatocellular carcinoma (HCC), in 592 patients diagnosed as non-Hodgkin's lymphoma (NHL), at Osaka Medical Center for Cancer and Cardiovascular Diseases. During 1978–1994, 2,163 person-years of observation were accrued, and 27 of the patients developed a second primary cancer, yielding an observed-to-expected ratio (O/E) of 1.53 [95% confidence interval (CI)=1.01–2.23]. Significant excess risk was noted for primary liver cancer (PLC; O/E=4.36, 95% CI=1.99–8.28; O=9) and non-lymphocytic leukemia (O/E=26.17, 95% CI=5.26–76.46; O=3). The excess risk of PLC was relatively constant within the first 10 years after the NHL diagnosis. Patients who received chemotherapy as the NHL treatment had a significantly increased risk of PLC (O/E=5.91, 95% CI=2.70–11.23; O=9). Their clinical reports indicated that all nine patients with PLC were diagnosed as HCC, and eight of them had clinical and/or histologic evidence of cirrhosis at the time of HCC diagnosis. None of the nine patients had a history of blood transfusion between the first NHL treatment and the diagnosis of HCC. These findings suggested that Japanese NHL patients might have an increased risk of developing HCC, and they indicated the importance of medical surveillance for liver malignancies, as well as subsequent leukemias. Possible explanations for the excess risk of subsequent HCC are discussed.

Key words: Non-Hodgkin's lymphoma — Second primary cancer — Hepatocellular carcinoma — Epidemiology

Non-Hodgkin's lymphomas (NHL) are diagnosed world-wide. The incidence rates show marked variations from country to country, ranging from 2 : 100,000 in Gambia to 17 : 100,000 in San Francisco Bay Area whites.[1)] The incidence rates of NHL in Japan are relatively lower than those in western countries, ranging from 3 to 7 : 100,000 depending on the prefecture.[1)] In Osaka there has been a steady increase in the incidence; a 2.6-fold increase was observed from 1963 to 1989,[2)] though the proportion represented by patients infected with human immunodeficiency virus was small.

Studies on second primary cancers provide clues to the understanding of cancer etiology as well as information useful for medical management. Recently it has been suggested that the hepatitis C virus (HCV) genome can replicate in human peripheral mononuclear cells.[3,4)] Ferri *et al.*[5)] have reported that the frequency of HCV infection is markedly higher in patients with NHL of B-cell origin than in the general population or in patients with other chronic diseases. Stasi *et al.*[6)] reported that the most common extrahepatic primary cancers among hepatocellular carcinoma (HCC) patients were NHL of B-cell origin in Italy, where the prevalence of HCV infection is higher than that in northern Europe and the United States.[7)]

Based on these findings, we hypothesized that excess risk of HCC among NHL patients might be observed, because HCV is a major etiological factor of HCC in Japan[8)] (as a shared risk factor). We also speculated that if this hypothesis were correct, such a finding would appear more clearly in HCV-endemic areas such as Osaka[9)] than in HCV-non-endemic areas.

We conducted a retrospective cohort study of NHL patients in Osaka, to evaluate the risk of second primary cancers among NHL patients, with special attention to the risk of HCC. The risks of other second primary cancers following NHL were also evaluated since consistent findings were not obtained in the few investigations of second cancer that have been conducted among Japanese NHL patients, because of small sample size[10)] or the small number of second primary cancers.[11)]

PATIENTS AND METHODS

A total of 770 patients who were diagnosed as NHL between January, 1978 and December, 1993 (International Classification of Diseases for Oncology (ICD-O) morphology codes: 9591–9642, 9690–9701 and 9750) were identified through the hospital cancer registry of Osaka Medical Center for Cancer and Cardiovascular

Diseases. The registry has continuously collected and updated basic demographic data and medical information for all patients diagnosed as having cancer at the hospital since 1978. Of those patients with NHL, 139 resided outside of Osaka Prefecture, 36 were younger than 20 or older than 79, and three had simultaneous primary cancers (stomach cancer in two and pharyngeal cancer in one) diagnosed on the same date as NHL. Excluding these patients, the remaining 592 were eligible for the study. Detailed clinical information that was not abstracted in the registry was obtained from the medical records.

In order to examine the incidence of second primary cancers and their prognoses, a computer file of the study subjects was linked to the file of the Osaka Cancer Registry (OCR). The method and the validity of OCR have been described elsewhere.[2, 12] In the OCR, second primary cancers are identified by the same rules as suggested in the ICD-O second edition.[13] Cases with subsequent diagnoses of NHL and lymphocytic leukemia were not considered as showing second primary cancers, since these could represent a progression of the initial malignancies.

We accumulated person-years of observation from the date of NHL diagnosis to the date of diagnosis of the second primary cancer, date of death, or the closing date of the study (December 31, 1994), whichever occurred first. The observed number of second primary cancer cases was compared with the expected number, which was calculated by applying sex-, 5-year age-, 5-year calendar time, and site-specific incidence rates among the general population of Osaka. Statistical tests of the ratio of observed-to-expected numbers (O/E ratio) were based on the assumption that the observed number followed a Poisson distribution. If the 95% confidence interval (CI) of the O/E ratio did not contain 1.0, the O/E ratio was considered statistically significant ($P<0.05$).

RESULTS

There were 353 males and 239 females in the study cohort. The mean age at the diagnosis of NHL was 56.3 years. Overall, 2,163 person-years of observation were accrued, with an average follow-up of 3.7 years (range, 0.1 to 16.5 years). Twenty-seven cases of second primary cancer were diagnosed (Table I), compared to 17.62 cases expected (O/E=1.53, 95% CI=1.01–2.23). There were no second primary cancer cases who were diagnosed at autopsy only. Primary liver cancer (PLC) composed one-third of all second primary cancers (O=9), and its O/E ratio was significantly elevated (O/E=4.36, 95% CI=1.99–8.28). The total observed number of

Table I. Observed (O) and Expected (E) Numbers of Second Primary Cancers among Patients with NHL

Cancer type or site	Males			Females			Total		
	353[a]			239			592		
	56.4[b]			56.0			56.3		
	1,233[c]			930			2,163		
	O	E	O/E	O	E	O/E	O	E	O/E
All second primary cancers	20	12.65	1.58	7	4.98	1.41	27	17.62	1.53[e]
Primary liver cancer (PLC)	7	1.77	3.95[f]	2	0.29	6.84	9	2.06	4.36[f]
Stomach	2	3.37	0.59	3	1.05	2.86	5	4.42	1.13
Lung	3	2.14	1.40	0	0.48		3	2.62	1.15
Buccal cavity and pharynx	1	0.25	3.96	0	0.06		1	0.31	3.20
Biliary tract	1	0.30	3.33	0	0.24		1	0.54	1.86
Pancreas	1	0.45	2.23	0	0.21		1	0.66	1.52
Ovary				1	0.14	7.18	1	0.14	7.18
Prostate	1	0.33	2.99				1	0.33	2.99
Bladder	1	0.42	2.40	0	0.08		1	0.50	2.02
Kidney	1	0.16	6.41	0	0.04		1	0.20	5.00
All solid cancers[d]	18	12.16	1.48	6	4.77	1.26	24	16.93	1.42
All solid cancers except PLC	11	10.39	1.06	4	4.48	0.89	15	14.87	1.01
Leukemia	2	0.16	12.90[e]	1	0.07	14.87	3	0.22	13.50[f]
Non-lymphocytic leukemia	2	0.08	24.19[f]	1	0.03	31.30	3	0.11	26.17[f]

a) Number of study subjects.
b) Mean age at NHL diagnosis (yr).
c) Person-years of observation (yr).
d) All second primary cancers except cancers affecting the hematopoietic system.
e) $P<0.05$.
f) $P<0.01$.

Table II. Observed (O) and Expected (E) Numbers with PLC by Various NHL Variables

Variable	$n^{a)}$	O	E	O/E
Follow-up period				
0– yr	592	0	0.45	
1–4 yr	427	7	1.01	6.93[d)]
5–9 yr	156	2	0.47	4.29
10+yr	50	0	0.13	
1+yr	427	9	1.61	5.59[d)]
Age at NHL diagnosis				
20–54 yr	247	1	0.37	2.67
55–79 yr	345	8	1.69	4.74[d)]
Cell origin[b)]				
B cell	149	6	0.50	11.96[d)]
T cell	27	0	0.05	
not available	416	3	1.51	1.99
Chemotherapy				
yes	455	9	1.52	5.91[d)]
no	137	0	0.54	
Radiation therapy				
yes	230	4	0.85	4.69[c)]
no	362	5	1.21	4.13[c)]

a) The numbers of subjects censored at the beginning of each follow-up period.
b) Immunohistochemical markers: B cell, MB-1 (CD45R), L26 (CD20); T cell, MT-1 (CD43), UCHL-1 (CD45RO).
c) $P<0.05$.
d) $P<0.01$.

cases of all solid cancers except PLC was 15, which was almost the same as the expected number (E=14.87). No significant excess risk of any solid cancers other than PLC was evident. Three NHL patients developed leukemia. This observed number was statistically significantly higher than the expected number (O/E=13.50, 95% CI =2.71–39.44). These three patients had acute myelocytic leukemia (AML), so the O/E ratio was increased when the calculation of the expected number was limited to non-lymphocytic leukemia only (O/E=26.17, 95% CI= 5.26–76.46). These AML cases were diagnosed between 1.1 and 2.5 years after the diagnosis of NHL.

To clarify the characteristics of the NHL patients who subsequently developed PLC, we calculated the O/E ratios according to a range of variables (Table II). All of the nine patients developed PLC more than one year after the NHL diagnosis, while up to 1.61 cases were expected during the same period (O/E=5.59, 95% CI= 2.55–10.62). The study subjects aged 55–79 years at the enrollment had a significantly increased risk of PLC (O/E=4.74, 95% CI=2.04–9.34). Significant excess risk was evident in patients with NHL of B-cell origin (O/E =11.96, 95% CI=4.73–26.03), although the cellular origin was determined in only a limited number of cases. The study subjects who received chemotherapy in the first or subsequent NHL treatment had a significantly increased risk of PLC (O/E=5.91, 95% CI=2.70–11.23). Significant excess risk of PLC was observed regardless of the history of radiation therapy for the NHL.

Table III presents the clinical findings for the nine NHL patients who subsequently developed PLC. All of them had intermediate histological grade as classified in the *Working Formulation*. Six patients showed NHL of B-cell origin. There were no cases who had received blood transfusion between the initial treatment of the NHL and the diagnosis of PLC, although patient 3 underwent partial jejunectomy and splenectomy in the initial NHL treatment. HCC was histologically confirmed in four patients with PLC, and in the remaining five it was diagnosed on the basis of liver-selective angiographic and/or computed tomographic imaging, together with determination of elevated serum alpha-fetoprotein levels by latex photometric immunoassay (range, 28 to 12,282 ng/ml; normal, <20 ng/ml). The mean duration between the diagnosis of NHL and HCC was 46 months (range, 15 to 111 months). In patient 3, who had early stage HCC, a solitary tumor with the greatest dimension of 1.2 cm, without vascular invasion, was found in resected tissue from segment 4 of the liver. The remaining eight patients were diagnosed as HCC of stage II or more advanced. Eight of nine HCC patients had clinical and/or histologic evidence of cirrhosis. Patient 7 had clinical evidence of chronic hepatitis as diagnosed on the basis of elevated serum transaminase levels and liver ultrasonographic findings. Seven HCC patients were tested for antibody to HCV (anti-HCV) at the time of HCC diagnosis, and six of them were positive. All nine patients were tested for hepatitis B virus surface antigen (HBsAg), and all of them were negative for HBsAg. None had a history of heavy drinking, defined as drinking more than 80 grams of ethanol per day for at least 10 years.

DISCUSSION

Elevated risk of second solid cancers after NHL has been reported in western countries. Increased incidence of cancers of the stomach,[14] lung,[14–16] kidney,[15, 16] bladder,[15, 16] brain,[14, 16] and connective tissue,[14] squamous-cell carcinoma of the skin,[17] and melanoma[15, 16] has been observed in large cohort studies. A significantly increased risk of non-lymphocytic leukemia has been well documented.[15, 16, 18, 19] To our knowledge, however, no significant excess risk of second hepatic malignancy has yet been reported.

In our study, the patients with NHL had 4.4 times higher risk of PLC than the general population. Approximately 92% of PLC cases are HCC in Japan,[20] so the O/E ratio of HCC in this cohort is considered to be

Table III. Characteristics of NHL Patients with Subsequent HCC

No.	NHL								HCC					
	Age/Sex	Site	Stage[a]	Histology[b]	Cellular origin[c]	Operation	Chemotherapy[d]	Radiotherapy	Interval (mo)	Stage[e]	Background[f]	Anti-HCV[g]	HBsAg[h]	Alcohol abuse[i]
1	58/M	node	II	DSC	B	−	CPM, VCR ADM, PSL	+	36	II	LC	+ (PHA)	−	−
2	64/M	node	I	DL	B	−	CPM, VCR PSL	+	21	III	LC	+ (ELISA)	−	−
3	56/M	jejunum spleen	IIIES	DL	B	+	CPM, VCR ADM, PSL	−	79	I	LC	+ (ELISA)	−	−
4	63/F	node	II	DL		−	CPM, VCR ADM, PSL	−	52	II	LC	+ (PHA)	−	−
5	56/M	node	II	DM		−	CPM, VCR, ETP ADM, PSL, 6-MP	−	23	II	LC	+ (PHA)	−	−
6	59/M	node	I	DL	B	−	CPM, VCR ADM, PSL	+	35	II	LC	+ (PHA)	−	−
7	61/M	stomach spleen	IVE	DM	B	−	CPM, VCR, ADM, PCZ PSL, ETP, MTX	−	43	IVA	CH	− (PHA)	−	−
8	65/M	mediastinum	IIIE	DL	B	−	CPM, VCR ADM, PSL, ETP	−	15	IVB	LC		−	−
9	53/F	node	I	DM		−	CPM, VCR PSL	+	111	III	LC		−	−

a) Ann Arbor staging classification.
b) Working Formulation. DSC, diffuse small cleaved cell; DL, diffuse large cell; DM, diffuse mixed cell.
c) See the footnote to Table II.
d) Prescribed at the first or subsequent NHL treatment. CPM, cyclophosphamide; VCR, vincristine; ADM, adriamycin; PSL, prednisolone; PCZ, procarbazine; ETP, etoposide; 6-MP, 6-mercaptopurine.
e) Stage grouping from the Union Internationale Contra le Cancer.
f) Liver status at the diagnosis of HCC. LC, liver cirrhosis; CH, chronic hepatitis.
g) Antibody to hepatitis C virus. PHA, passive hemagglutination assay for antibody to the pHCV-34, c100-3, pHCV-31 viral peptides (Dainabot,Tokyo); ELISA, enzyme-linked immunosorbent assay for antibody to the c100-3 viral peptide (Ortho Diagnostics, Tokyo). Patients 8 and 9 developed HCC before the test for anti-HCV became available in April, 1990.
h) Hepatitis B surface antigen tested by reversed passive hemagglutination.
i) Defined as those who have a history of drinking more than 80 grams of ethanol per day for at least 10 years.

higher than that of PLC. The likelihood of detecting early HCC in the NHL patients seems to be higher than that in the general population because of the intensive clinical surveillance (detection bias). However, the distribution of the clinical stage of HCC was not different between the patients with NHL and the general population of Japan.[20] Since the study subjects were newly diagnosed as NHL regardless of pre-existing hepatic disorders in our hospital, it is difficult to consider that they had substantially higher risk of developing HCC than the other Japanese NHL patients (selection bias). In addition, the number of all solid cancers except PLC was almost the same as the expected number, which suggests a high specificity of the risk estimation for the subsequent PLC. It is therefore unlikely that the increased risk of HCC in this cohort was due solely to detection bias or selection bias.

Some possible theoretical explanations exist for the increased risk of HCC following NHL that we observed. The significant excess risk of HCC was observed only in the patients with NHL who had received chemotherapy in the first or subsequent NHL treatment. This finding may be explained by the increased risk of liver inflammation due to antineoplastic agents in hepatitis virus-endemic areas. In hepatitis virus carriers treated with antineoplastic agents for hematologic malignancies, liver complications often occur and range from a slight increase of serum transaminase levels to severe hepatitis.[21, 22] If antineoplastic agents for hepatitis virus carriers do exert hepatocarcinogenicity by promoting liver inflammation, the risk of subsequent HCC among NHL patients would be greater in hepatitis virus-endemic areas such as Japan[9] than in western countries,[7] even if the protocols for the regimen are similar.

The excess risk of HCC following NHL may be explained by postulating two or more etiological agents with similar routes of transmission, that induce NHL and HCC independently. History of blood transfusion has been reported as a risk factor for NHL[23–25] as well as for HCC. Human T-cell leukemia virus type I, a causative agent of adult T-cell leukemia/lymphoma, is transmitted parenterally.[26, 27] However, six of our NHL patients with

HCC were determined to have NHL of B-cell origin. Furthermore, none was diagnosed as having AIDS-associated NHL on the basis of the clinical manifestations. Therefore, coinfection of these known lymphotropic viruses and hepatitis viruses sharing a route of transmission would not account for the excess risk of HCC in this cohort. The possibility of some unknown blood-borne lymphotropic agents, however, may not be excluded entirely.

Finally, HCV infection may be associated with the development of both NHL and HCC. A case-control study conducted in Italy[5] suggested the possibility that HCV infection is a risk factor of B-cell NHL. To estimate the prevalence of HCV infection among NHL patients in Osaka, we collected data on results for anti-HCV (second generation passive hemoagglutination assay) before the initial treatment of NHL among 97 patients in our hospital between 1992 and 1995. Of these, 17 (17.5%) were anti-HCV positive, and this was significantly higher than the expected number calculated from the sex- and age-standardized prevalence of anti-HCV among blood donors in Osaka[9] ($17/4.73 = 3.59$, $P < 0.05$, unpublished data). In the present study, in turn, six of the seven NHL patients who developed HCC and underwent the test for anti-HCV were positive for it, whereas the HBsAg tests were negative in all of the nine NHL patients with HCC. None of these nine patients received blood transfusion between the first NHL treatment and the diagnosis of HCC. The duration between the diagnosis of NHL and anti-HCV positive-HCC was shorter (21–79 months) than the reported latency period between HCV transmission and the development of HCC among HCV carriers.[28] It is therefore considered that at least the six patients with anti-HCV positivity had probably already been infected with HCV before they developed NHL. Japan is one of the endemic areas for HCV, particularly in the older age groups.[9] Approximately 70% of HCC cases show positive reaction for anti-HCV.[29] In these circumstances, unlike in HCV non-endemic countries, the excess risk of HCC observed in this study might be explained by HCV infection as a shared risk factor, although further studies are needed to confirm whether and how HCV participates in the pathogenesis of NHL.

In summary, our retrospective cohort study suggests that Japanese patients with NHL are at increased risk of developing HCC. The excess risk cannot be explained solely by the intensive clinical surveillance. Further analytical studies of HCC following NHL are needed to clarify the roles of antecedent chemotherapy, host immunity, shared risk factors, and other etiologic influences. This result also points to the importance of continued medical surveillance of Japanese NHL patients for liver malignancies as well as for subsequent non-lymphocytic leukemias.

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