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Original Article

Characteristics of patients with liver cancer in the BioBank Japan project

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ABSTRACT

Background: Liver cancer is the fifth cause of cancer-related deaths in Japan. The BioBank Japan (BBJ) project included 200,000 patients with 47 diseases and samples; their clinical information can be used for further studies.
Methods: Patients diagnosed with liver cancer (n = 1733; 1316 men, 417 women) were included. Histology, patient characteristics, clinical characteristics, and causes of death were collected. Cumulative and relative survival rates for liver cancer were calculated.
Results: Of the 1354 patients with available liver cancer histology, 91.9% had hepatocellular carcinoma (HCC). Compared with the National Health and Nutrition Examination Survey, greater proportions of the male patients in this cohort were daily alcohol consumers (26%), and a greater proportion of the men was overweight/obesity (22%). Although Japan is the only Asian country with a predominance of hepatitis C virus (HCV)-related HCC, the prevalence of HCV infection (44%) was lower than that in a previous study. The 3-, 5-, and 10-year cumulative survival rates were 57%, 47%, and 25% in men, respectively, and 49%, 41%, and 27% in women, respectively.
Conclusions: The present results provide an overview of the patients with liver cancer in the BBJ project. We are planning further analyses combined with various high-throughput 'omics' technologies.

Introduction

Liver cancer is the second leading cause of death worldwide, accounting for 745,000 deaths in 2012,[1] and the fifth cause of cancer-related deaths in Japan.[2] According to the Japanese National vital statistics, a total of 40,099 persons (19,208 men and 20,891 women) died of liver cancer in 2014.[2] Also, data from the population-based cancer registries in Japan indicate that 43,677 persons (28,623 men and 15,054 women) were diagnosed with liver cancer in 2012.[3]

The most prevalent type of primary liver cancer is hepatocellular carcinoma (HCC),[4] accounting for 94% of liver cancers in Japan.[5] Although hepatitis B viral (HBV) infection is a predominant cause of HCC in many Asian countries such as China, South Korea, Singapore, Thailand, Malaysia, India, the Philippines, and Taiwan, the main cause of HCC in Japan is hepatitis C viral (HCV) infection,[6] accounting for approximately 70% of cases of HCC. However, the importance of the chronic liver diseases nonalcoholic fatty liver

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disease (NAFLD) and nonalcoholic liver steatohepatitis (NASH) as risk factors for HCC has recently increased.[7]

The BioBank Japan (BBJ) project is a large patient-oriented cohort consisting of more than 200,000 patients with 51 diseases, and DNA and serum samples and clinical information can be used for further studies. In this report, we aimed to provide an overview of the patients with liver cancer in the BBJ project.

Materials and methods

Study population

The BBJ project was established in 2003.[8–12] Briefly, we enrolled 199,982 participants with 47 diseases from 12 medical institutes consisting of 67 hospitals in Japan between the fiscal years 2003 and 2007. Written informed consent was obtained from all participants. The study protocol of the BBJ project was approved by the Research Ethics Committees of the Institute of Medical Science, the University of Tokyo, RIKEN Yokohama Institute, and 12 cooperating hospitals. Clinical information for participants with liver cancer (n = 1733; 1316 men, 417 women) was used in this analysis.

Data collection

Information about smoking habits (never, former, current smoker of <20 pack years, current smoker of ≥20 pack years, current smoker of unknown pack years, or unknown), alcohol consumption habits (never, former, current drinker of <15 g/day, current drinker of 15–29 g/day, current drinker of ≥30 g/day, or unknown), height, weight, physical activity frequency (none, 1–2 times/week, ≥3 times/week, or unknown), family history of liver cancer (yes, no/unknown), and medical history of HBV or HCV infection (yes, no/unknown) was obtained through medical records and interviews using a standardized questionnaire at the time of enrollment.[9–12] Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters and categorized as <18.5 kg/m^2, 18.5–24.9 kg/m^2, 25.0–29.9 kg/m^2, ≥30 kg/m^2, or unknown.

Birth year; sex; time to entry in this cohort, from the diagnosis of liver cancer; age at entry in this cohort; liver cancer histology; laboratory examinations such as blood chemical markers including serum carcinoembryonic antigen (CEA; <5 ng/mL, 5–9 ng/mL, ≥10 ng/mL, or unknown), carbohydrate antigen 19-9 (CA 19-9; <37 U/mL, 37–99 U/mL, ≥100 U/mL, or unknown), and alpha-fetoprotein (AFP; <10 U/mL, 10–99 U/mL, ≥100 U/mL, or unknown) levels; and imaging data were collected from medical records. Liver cancer histology was based on tissue obtained at biopsy or cytological samples, and missing data for histological types were complemented by data from tissue samples. Liver cancer stage was categorized according to the Japanese Classification of Liver Cancer, the Fourth (2000) and Fifth (2008) Editions (stage I, II, III, IV, or unknown). Pathologic stage was primarily used for classification, and missing data for pathologic stage were complemented with clinical stage results.

Follow-up

The follow-up survival survey was implemented from 2010 to 2014 to collect patient vital status, and the data were coded according to the 10th revision of the International Classification of Disease.

Statistical analysis

Sex-specific statistical analyses were conducted. First, we described the distribution of time from the initial diagnosis of prostate cancer to entry into the study cohort. Second, we drew an age-specific distribution of the patients with liver cancer and compared that with the Patient Survey in Japan, 2005.[13] We report the liver cancer histology, patient characteristics, patient clinical characteristics, liver cancer stage, and causes of death. Third, we calculated the cumulative and relative survival rates of liver cancer. We calculated the cumulative survival rate using the Kaplan–Meier method. We limited the survival rate calculation to patients who entered the cohort ≤90 days from the diagnosis of liver cancer. To calculate the expected survival rates, we obtained the survival rate table for the reference cohort from the Cancer Registry and Statistics, Cancer Information Service, National Cancer Center, Japan.[14] The survival rate table was based on sex- and age-specific mortality rates and Gompertz–Makeham's Law in Abridged Life Tables, published annually by the Statistics and Information Department of

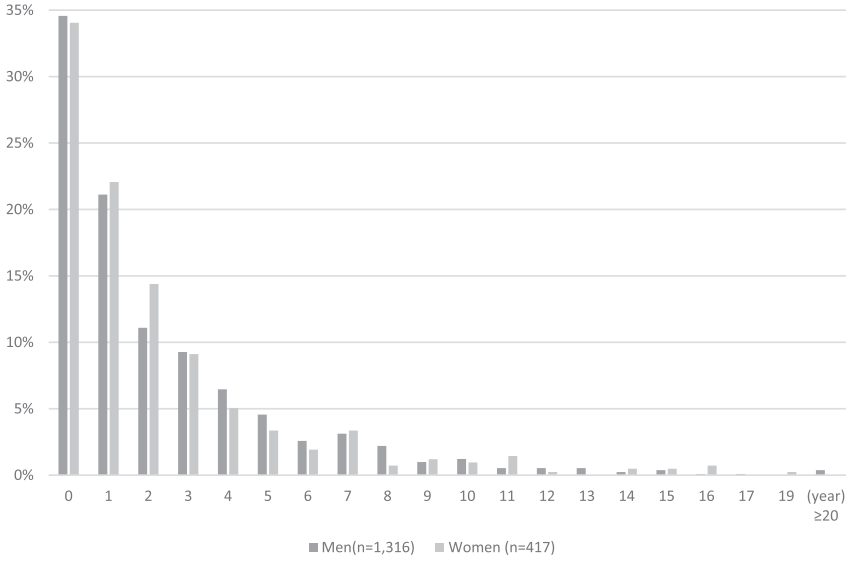

Fig. 1. Distribution of time from the initial diagnosis of liver cancer to entry into the study cohort.

Ministry of Health, Labor and Welfare, Japan. The relative survival rates were calculated by dividing the cumulative survival rates by age-adjusted expected survival rates. All statistical analyses were performed using SAS software (version 9.4; SAS Institute Inc., Cary, NC, USA).

Results

The distribution of time from the initial diagnosis of liver cancer to entry into the study cohort is displayed in Fig. 1. The proportion of patients who enrolled <1, 1, and 2 years after the initial diagnosis of liver cancer were 34.6%, 21.1%, 11.1%, and 33.2% in men and 34.1%, 22.1%, 14.4%, and 29.4% in women, respectively. The mean ± standard deviation age of the patients was 68.0 ± 8.5 (range, 32–92) years (Fig. 2). Patients in this study appeared to be slightly younger than patients in the national survey in Japan.[13]

Of the 1354 patients with information on the histology of liver cancer, 91.9% had HCC, and 3.7% had intrahepatic cholangiocarcinoma (Table 1). Of all the included patients, 20.1% of men and 25.6% of women were obese; 31.4% of men and 9.1% of women were current alcohol drinkers; 25.6% of men and 8.4% of women were current smokers; and 79.1% of men

Table 1
Histology of liver cancer.

Diagnosis	Men (n = 1316)	Women (n = 417)	Total (n = 1733)	%
Hepatocellular carcinoma	503	119	622	91.9
Intrahepatic cholangiocarcinoma	16	9	25	3.7
Combined	5	1	6	0.9
Cholangiolocellular carcinoma	0	0	0	0
Cystadenocarcinoma	0	1	1	0.1
Hepatoblastoma	0	0	0	0
Undifferentiated carcinoma	0	0	0	0
Others	6	3	9	1.3
Unknown	12	2	14	2.1
Missing	744	282	1056	–

Combined, combined hepatocellular and intrahepatic cholangiocarcinoma.

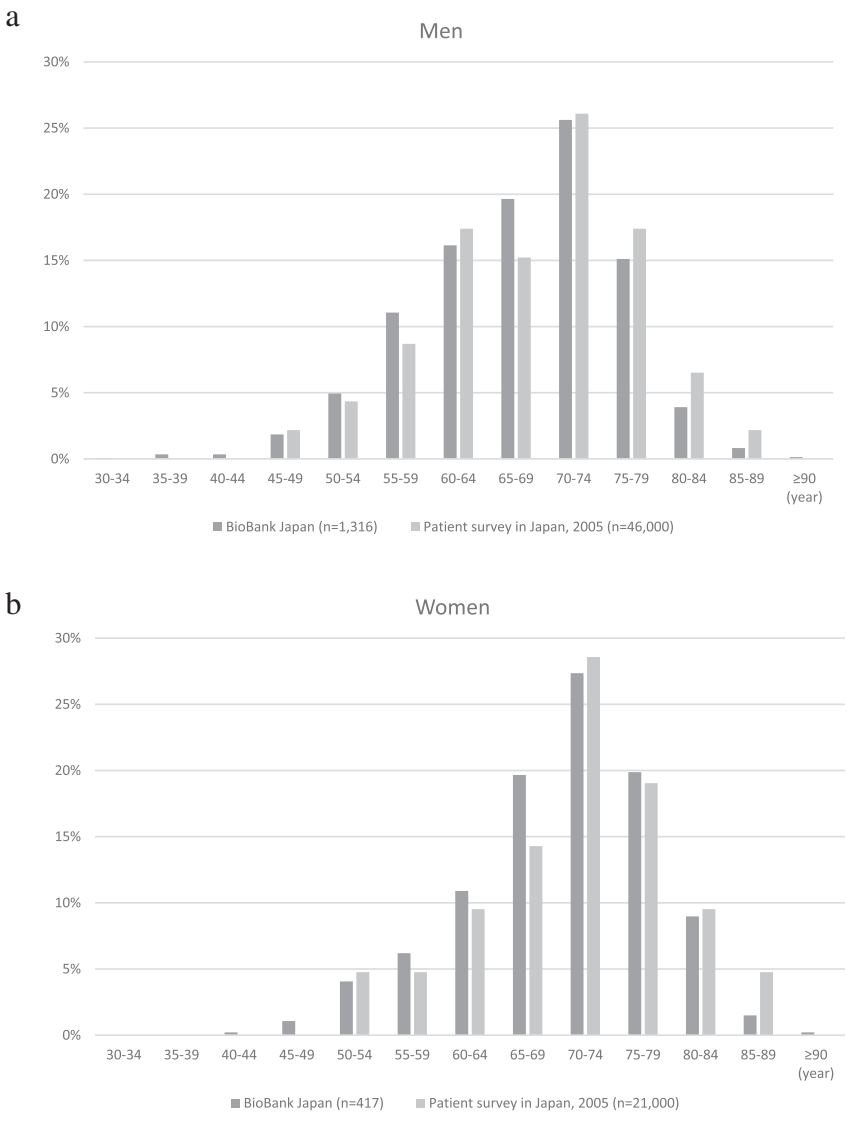

Fig. 2. Age-specific distribution of the patients with liver cancer for men (a) and women (b).

Table 2
Characteristics of the study participants with liver cancer.

Variable	Categorization	Men (n = 1316)			Women (n = 417)		
		n	%	%	n	%	%
Body mass index (kg/m^2)							
	<18.5	144	10.9	11.1	47	11.3	11.9
	18.5–24.9	892	67.8	68.8	246	59.0	62.4
	25.0–29.9	228	17.3	17.6	77	18.5	19.5
	≥30	32	2.4	2.5	24	5.8	6.1
	Unknown	50	3.8	–	23	5.5	–
Drinking status							
Never		309	23.5	23.5	309	74.1	74.1
Former		450	34.2	34.2	46	11.0	11.0
Current (g/day)	<15	163	12.4	12.4	27	6.5	6.5
	15–29	77	5.9	5.9	5	1.2	1.2
	≥30	173	13.1	13.1	6	1.4	1.4
Unknown		144	10.9	–	24	5.8	–
Smoking status							
Never		261	19.8	22.1	310	74.3	78.7
Former		582	44.2	49.2	45	10.8	11.4
Current	<20 pack years	75	5.7	6.3	15	3.6	3.8
	≥20 pack years	228	17.3	19.3	18	4.3	4.6
	Unknown	37	2.8	3.1	6	1.4	1.5
Unknown		133	10.1	–	23	5.5	–
Physical activity (times/week)							
	≥3	197	15.0	18.1	71	17.0	20.9
	1–2	31	2.4	2.8	9	2.2	2.7
	Not habitually	863	65.6	79.1	259	62.1	76.4
	Unknown	225	17.1	–	78	18.7	–
Had a family history of							
Liver cancer	Yes	118	9.0	–	42	10.1	–
	No/Unknown	1198	91.0	–	375	89.9	–
CEA (ng/mL)	<5	464	35.3	75.2	133	31.9	71.5
	5–9	92	7.0	14.9	31	7.4	16.7
	≥10	61	4.6	9.9	22	5.3	11.8
	Unknown	699	53.1	–	231	55.4	–
CA 19-9 (U/mL)	<37	359	27.3	70.8	93	22.3	61.2
	37–99	103	7.8	20.3	38	9.1	25.0
	≥100	45	3.4	8.9	21	5.0	13.8
	Unknown	809	61.5	–	265	63.5	–
AFP (U/mL)	<10	758	57.6	70.2	194	46.5	60.2
	10–99	106	8.1	9.8	39	9.4	12.1
	≥100	216	16.4	20.0	89	21.3	27.6
	Unknown	236	17.9	–	95	22.8	–
Had a medical history of							
Hepatitis B	Yes	154	11.7	–	24	5.8	–
Hepatitis C	Yes	577	43.8	–	220	52.8	–

CEA, carcinoembryonic antigen; CA 19-9, carbohydrate antigen 19-9; AFP, alpha-fetoprotein.

Table 3
Causes of death for patients who entered the cohort ≤90 days from the diagnosis of liver cancer.

	Men (n = 311)			Women (n = 88)		
	n	%	%	n	%	%
Alive	108	34.7		28	31.8	
Total deaths	203	65.3		60	68.2	
Cancer-related	148		72.9	48		80.0
Hepatic failure	1		0.5	0		–
Rupture of esophageal varices	1		0.5	0		–
Other causes	25		12.3	8		13.3
Unknown	28		13.8	4		6.7

and 76.4% of women were not habitually physically active (Table 2). About 9.0% of men and 10.1% of women had a family history of liver cancer. Of the information we obtained, normal CEA, CA 19-9, and AFP levels were present in 75.2%, 70.8%, and 70.2% of men, respectively, and 71.5%, 61.2%, and 60.2% of women, respectively. About 11.7% of men and 5.8% of women had a medical history of HBV infection, and 43.8% of men and 52.8% of women had a medical history of HCV infection. The clinical stage of liver cancer was not identified for almost all participants (99.8%).

Table 3 shows the causes of death due to liver cancer among the patients who entered the cohort ≤90 days from the diagnosis of liver cancer. The mortality rate during the study period was about 75% for men and 73% for women. Cancer-related mortality occurred for 65% of the men and 68% of the women who died, and the remaining patients died because of hepatic failure (0.5% of men), rupture of esophageal varices (0.5% of men), or other reasons. The 3-, 5-, and 10-year cumulative survival rates were 57%, 47%, and 25% in men, respectively, and 49%, 41%, and 27% in women, respectively (Fig. 3). The 5- and 10-year relative survival rates were 53% and 34% in men, respectively, and 47% and 38% in women, respectively.

Discussion

The results of the present study provide an overview of the patients with liver cancer in the BBJ project, which is a large patient-based biobank. A strength of this cohort study is its prospective design with a large number of patients who were recruited from hospitals located nationwide in Japan.

The histology of liver cancer was not available for 61% of the patients because current guidelines for liver cancer from the Japan Society of Hepatology[15] indicate that only the use of imaging results in an accurate diagnosis of HCC. The most prevalent type (91.9%) of primary liver cancer was HCC, similar to the reported 94% in Japan.[5] Therefore, HCC might have been present for a large proportion of the patients without identified histology.

Japan is the only Asian country with a predominance of HCV-related HCC[6]; approximately 70% and 16% of HCC cases were caused by HCV and HBV infection, respectively. In our analysis, 44% and 12% of men and 53% and 8% of women had a medical history of HCV and HBV infection, respectively. The lower prevalence of HBV or HCV intention might have resulted from misclassification because we obtained the medical history of HCV/HBV infection only when the patients experienced. There are several risk factors for liver cancer other than infections, such as NASH, which is associated with obesity,[16] habitual alcohol consumption,[17] and smoking.[18] According to the National Health and Nutrition Examination Survey in Japan,[19] 28% of men and 22% of women are obese (BMI ≥25.0 kg/m^2), 5% of men and 9% of women reportedly currently drink alcohol, and 47% of men and 11% of women are current smokers. Compared with the National Health and Nutrition Examination Survey, a greater proportion of the male patients in the present study were daily alcohol consumers, and a greater proportion of women was overweight/obesity. Since the number of people with HCV infection is gradually decreasing in Japan,[20] these lifestyle choices might have resulted in the lower prevalence of HBV and HCV infections.

The Japanese Association of Clinical Cancer Centers reported that the 5- and 10-year relative survival rates for liver cancer were 34.8% and 15.3%, respectively.[21] The relative survival rates in the present study were much higher. However, because the data regarding factors that affect survival rate, such as stage, surgery,[22–24] or chemotherapy[25,26] were missing, the results may have been biased.

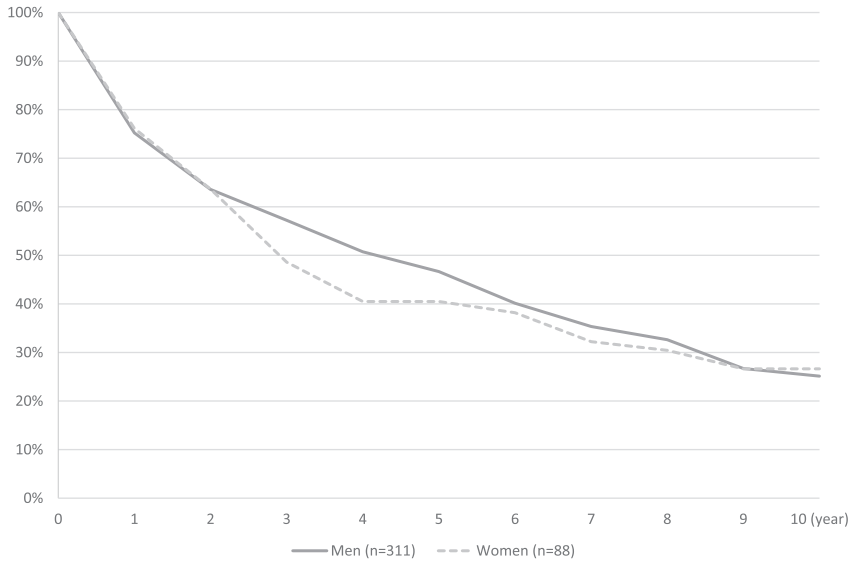

Fig. 3. Cumulative and relative survival rates (%) of liver cancer in the BioBank Japan (BBJ) project for patients who entered the cohort ≤90 days after diagnosis.

Conclusion

The present study provides an overview of the patients with liver cancer in the BBJ project. We are planning further analyses combined with various high-throughput 'omics' technologies using DNA and serum samples from the BBJ project. However, the interpretation of the forthcoming results may require careful consideration because of the missing data of not only newly diagnosed cases but also prevalent cases.

Conflicts of interest

The authors declare that they have no conflict of interest with respect to this research study and paper.

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Appendix

Members of medical institutions cooperating on the BioBank Japan Project who coauthored this paper include Hiromasa Harada, Kiyoshi Kaneko, Shuichi Matsumoto and Masaki Shiono (Tokushukai Hospitals); Shiro Minami, Hiroshi Yoshida and Nobuhiko Taniai (Nippon Medical School); Sumio Watanabe, Noriko Fujiwara and Atsuyuki Yamataka (Juntendo University); Satoshi Asai, Mitsuhiko Moriyama and Yasuo Takahashi (Nihon University); Tomoaki Fujioka and Wataru Obara (Iwate Medical University); Seijiro Mori and Hideki Ito (Tokyo Metropolitan Institute of Gerontology); Satoshi Nagayama and Yoshio Miki (The Cancer Institute Hospital of JFCR); Akihide Masumoto and Akira Yamada (Aso Iizuka Hospital); Yasuko Nishizawa and Ken Kodama (Osaka Medical Center for Cancer and Cardiovascular Diseases); Shigeyuki Naka and Yoshihiro Endo (Shiga University of Medical Science); Yukihiro Koretsune and Eiji Mita (National Hospital Organization, Osaka National Hospital); and Kozo Morimoto (Fukujuji Hospital).

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