Original Article

Characteristics of patients with liver cancer in the BioBank Japan project

Shigekazu Ukawa, Emiko Okada, Koshi Nakamura, Makoto Hirata, Akiko Nagai, Koichi Matsuda, Zentaro Yamagata, Yoichiro Kамата, Toshiharu Ninomiya, Yutaka Kiyohara, Kaori Muto, Michiaki Kubo, Yusuke Nakamura, BioBank Japan Cooperative Hospital Group, Akiko Tamakoshi.

**Department of Public Health, Hokkaido University Graduate School of Medicine, Hokkaido, Japan**

**Laboratory of Genome Technology, Institute of Medical Science, The University of Tokyo, Tokyo, Japan**

**Department of Public Policy, Institute of Medical Science, The University of Tokyo, Tokyo, Japan**

**Laboratory of Molecular Medicine, Institute of Medical Science, The University of Tokyo, Tokyo, Japan**

**Department of Health Sciences, University of Yamanashi, Yamanashi, Japan**

**Laboratory for Statistical Analysis, RIKEN Center for Integrative Medical Sciences, Kanagawa, Japan**

**Department of Epidemiology and Public Health, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan**

**Hisayama Research Institute for Lifestyle Diseases, Fukuoka, Japan**

**RIKEN Center for Integrative Medical Sciences, Kanagawa, Japan**

**article info**

**Article info**

**Article history:**
Received 18 October 2016
Accepted 11 December 2016
Available online 15 February 2017

**Keywords:**
Liver cancer
Cohort
Lifestyle
Tumor biomarkers
Survival rate

**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.

© 2017 The Authors. Publishing services by Elsevier B.V. on behalf of The Japan Epidemiological Association. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

**Introduction**

Liver cancer is the second leading cause of death worldwide, accounting for 745,000 deaths in 2012, and the fifth cause of cancer-related deaths in Japan. 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. 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.

The most prevalent type of primary liver cancer is hepatocellular carcinoma (HCC), accounting for 94% of liver cancers in Japan. 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, accounting for approximately 70% of cases of HCC. However, the importance of the chronic liver diseases nonalcoholic fatty liver

* Corresponding author. Department of Public Health, Hokkaido University Graduate School of Medicine, N15 W7, Kita-Ku, Sapporo 060-0812, Japan.
E-mail address: tamaa@med.hokudai.ac.jp (A. Tamakoshi).

Peer review under the responsibility of The Japan Epidemiological Association.

BioBank Japan Cooperative Hospital Group are listed in Appendix.

http://dx.doi.org/10.1016/j.je.2016.12.007
0917-5040/© 2017 The Authors. Publishing services by Elsevier B.V. on behalf of The Japan Epidemiological Association. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
disease (NAFLD) and nonalcoholic liver steatohepatitis (NASH) as risk factors for HCC has recently increased. 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. 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. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters and categorized as <18.5 kg/m², 18.5–24.9 kg/m², 25.0–29.9 kg/m², ≥30 kg/m², or unknown.

Birth year; sex; time to entry in this cohort, from the diagnosis of liver cancer; 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 alphafetoprotein (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. 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. 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
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

![Fig. 2. Age-specific distribution of the patients with liver cancer for men (a) and women (b).](image-url)
Table 2

Characteristics of the study participants with liver cancer.

| Variable                | Men (n = 1316) | Women (n = 417) |
|-------------------------|----------------|-----------------|
|                         | n   | %  | n   | %  |%
| **Body mass index (kg/m²)** |     |     |     |     |
| <18.5                   | 144 | 10.9 | 47  | 11.3 | 11.9 |
| 18.5–24.9               | 892 | 67.8 | 246 | 59.0 | 62.4 |
| 25.0–29.9               | 228 | 17.3 | 77  | 18.5 | 19.5 |
| ≥30                     | 32  | 2.4  | 24  | 5.8  | 6.1  |
| Unknown                 | 50  | 3.8  | 23  | 5.5  |      |
| **Drinking status**     |     |     |     |     |
| Never                   | 309 | 23.5 | 309 | 74.1 | 74.1 |
| Former                  | 450 | 34.2 | 46  | 11.0 | 11.0 |
| Current (g/day)         |     |     |     |     |
| <15                     | 163 | 12.4 | 27  | 6.5  | 6.5  |
| 15–29                   | 77  | 5.9  | 5   | 1.2  | 1.2  |
| ≥30                     | 173 | 13.1 | 6   | 1.4  | 1.4  |
| Unknown                 | 144 | 10.9 | 24  | 5.8  | 5.8  |
| **Smoking status**      |     |     |     |     |
| Never                   | 261 | 19.8 | 310 | 74.3 | 78.7 |
| Former                  | 582 | 44.2 | 45  | 10.8 | 11.4 |
| Current                 |     |     |     |     |
| <20 pack years          | 75  | 5.7  | 15  | 3.6  | 3.6  |
| ≥20 pack years          | 228 | 17.3 | 18  | 4.3  | 4.6  |
| Unknown                 | 37  | 2.8  | 3   | 0.7  | 0.7  |
| **Physical activity**   | (times/week) |     |     |     |
| ≥3                      | 197 | 15.0 | 71  | 17.0 | 20.9 |
| 1–2                     | 31  | 2.4  | 9   | 2.2  | 2.7  |
| Not habitually          | 863 | 65.6 | 259 | 62.1 | 76.6 |
| Unknown                 | 225 | 17.1 | 78  | 18.7 | 18.7 |
| **Had a family history of** |     |     |     |     |
| Liver cancer            | 118 | 9.0  | 42  | 10.1 | 10.1 |
| No/Unknown              | 1198| 91.0 | 375| 89.9 |      |

Table 3

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

| Variable                | Men (n = 1316) | Women (n = 417) |
|-------------------------|----------------|-----------------|
|                         | n   | %  | n   | %  |%
| **CEA (ng/mL)**         |     |     |     |     |
| <5                      | 464 | 35.3 | 133| 31.9 | 71.5 |
| 5–9                     | 92  | 7.0  | 34 | 8.1  | 16.7 |
| 10–19                   | 61  | 4.6  | 22 | 5.3  | 11.8 |
| Unknown                 | 699 | 53.1 | 231| 55.4 | 55.4 |
| **CA 19-9 (U/mL)**      |     |     |     |     |
| <37                     | 359 | 27.3 | 93 | 22.3 | 61.2 |
| 37–99                   | 103 | 7.8  | 38 | 9.1  | 25.0 |
| ≥100                    | 45  | 3.4  | 21 | 5.0  | 13.8 |
| Unknown                 | 809 | 61.5 | 265| 63.5 | 63.5 |
| **AFP (U/mL)**          |     |     |     |     |
| <10                     | 758 | 57.6 | 194| 46.5 | 60.2 |
| 10–99                   | 106 | 8.1  | 39 | 9.4  | 12.1 |
| ≥100                    | 216 | 16.4 | 89 | 21.3 | 27.6 |
| Unknown                 | 236 | 17.9 | 95 | 22.8 | 22.8 |
| **Hepatitis B**         |     |     |     |     |
| Yes                     | 154 | 11.7 | 24 | 5.8  | 5.8  |
| Hepatitis C             | 577 | 43.8 | 220| 52.8 | 52.8 |

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 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. 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; approximately 70% and 16% of HCC cases were caused by HBV and HCV 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, habitual alcohol consumption, and smoking. According to the National Health and Nutrition Examination Survey in Japan, 28% of men and 22% of women are obese (BMI ≥25.0 kg/m²). 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, 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. 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 chemotherapy25,26 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.

Acknowledgements

We express our gratitude to all the participants in the BioBank Japan Project. We thank all the medical coordinators of the cooperating hospitals for collecting samples and clinical information, as well as Yasushi Yamashita and staff members of the BioBank Japan Project for administrative support. We also thank Dr. Kumao Toyoshima for his overall supervision of the BioBank Japan project. This study was supported by funding from the Tailor-Made Medical Treatment with the BBJ Project from Japan Agency for Medical Research and development, AMED (since April 2015), and the Ministry of Education, Culture, Sports, Science, and Technology (from April 2003 to March 2015).

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 Tanai (Nippon Medical School); Sumio Watanabe, Noriko Fujisaka and Atsuyuki Yamataka (Juntendo University); Satoshi Asai, Mitsuhiro Moriyama and Yasuo Takahashi (Nihon University); Tamaaki Fujisaka and Wataru Ohara (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 Koresuto and Eiji Mita (National Hospital Organization, Osaka National Hospital); and Kozo Morimoto (Fukujyuji Hospital).

References

1. World Health Organization. World Cancer Report 2014. Geneva: International Agency for Research on Cancer; 2014.
2. Ministry of Health. Labor and Welfare. Vital Statistics, 2015; 2016. http://www.mhlw.go.jp/toukei/saikin/hw/jinkou/suikei15/index.html. Accessed 26 September 2016 [in Japanese].
3. Hori M, Matsuda T, Shibata A, et al. Cancer incidence and incidence rates in Japan in 2009: a study of 32 population-based cancer registries for the Monitoring of Cancer Incidence in Japan (MCIJ) project. Jpn J Clin Oncol. 2015;45:884–891.
4. Feraly J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBCAN 2012. Int J Cancer. 2015;136:E359–E386.
5. Kudo M, Izumi N, Ichida T, et al. Report of the 19th follow-up survey of primary liver cancer in Japan. Hepatol Res. 2016;46:372–390.
6. Goh GB, Chang PE, Tan CK. Changing epidemiology of hepatocellular carcinoma in Asia. Best Pract Res Clin Gastroenterol. 2015;29:919–928.
7. Tokushige K, Hashimoto E, Horie Y, Tanai M, Higuchi S. Hepatocellular carcinoma in Japanese patients with nonalcoholic fatty liver disease, alcoholic liver disease, and chronic liver disease of unknown etiology: report of the nationwide survey. J Gastroenterol. 2011;46:1230–1237.
8. Nakamura Y. The BioBank Japan project. Clin Adv Hematol Oncol. 2007;5:696–697.
9. Shinryo Jyouhou Nyuryoku Sheet Ver.7.1.4. 2015. https://biobankjp.org/sample/pdf/list7.1.4.pdf. Accessed 26 September 2016 [in Japanese].
10. Nagai A, Hirata M, Kamatani Y, et al. Overview of the BioBank Japan project: study design and profiles. J Epidemiol. 2017;27:52–58.
11. Hirata M, Nagai A, Kamatani Y, et al. Cross-sectional analysis of BioBank Japan clinical data: a large cohort of 200,000 patients with 47 common diseases. J Epidemiol. 2017;27:59–521.
12. Hirata M, Nagai A, Kamatani Y, et al. Overview of BioBank Japan follow-up data in 32 diseases. J Epidemiol. 2017;27:522–528.
13. Ministry of Health, Labor and Welfare. Japan. Abridged Life Tables for Japan. Patient Survey, 2005; 2005. http://www.mhlw.go.jp/toukei/saikin/hw/jinkou/05/ . Accessed 26 September 2016 [in Japanese].
14. Cancer Registry and Statistics, Cancer Information Service, National Cancer Center, Japan. Cohort Life Table; 2016. http://ganjoho.jp/reg_stat/statistics/qaa_words/cohort01.html. Accessed 26 September 2016 [in Japanese].
15. The Japan Society of Hepatology, 2003; 2016. http://www.jsh.or.jp/medical_guidelines/jsh_guidelines/examination_jp. Accessed 5 October 2016 [in Japanese].
16. Borena W, Strohmaier S, Lukanova A, et al. Metabolic risk factors and primary liver cancer in a prospective study of 578,700 adults. *Int J Cancer*. 2012;131:193–200.

17. Morgan TR, Mandayam S, Jamal MM. Alcohol and hepatocellular carcinoma. *Gastroenterology*. 2004;127:587–596.

18. Tanaka K, Tsuji I, Wakai K, et al. Cigarette smoking and liver cancer risk: an evaluation based on a systematic review of epidemiologic evidence among Japanese. *Jpn J Clin Oncol*. 2006;36:445–456.

19. Office for National Statistics. *The Time Use Survey*, 2005; 2005. Available at: [http://www.ons.gov.uk/ons/rel/lifestyles/time-use/2005-edition/time-use-survey-2005–how-we-spend-our-time.pdf](http://www.ons.gov.uk/ons/rel/lifestyles/time-use/2005-edition/time-use-survey-2005–how-we-spend-our-time.pdf). Accessed 26 September 2016 [in Japanese].

20. Infectious Disease Surveillance Center. *Hepatitis C in 1999–2009*; 2009. Available at: [http://idsc.nih.go.jp/disease/hepatitisC/2011week21.html](http://idsc.nih.go.jp/disease/hepatitisC/2011week21.html). Accessed 26 June 2016 [in Japanese].

21. Japanese Association of Clinical Cancer Centers. *Five- and Ten-year Relative Survival Rate in All Cases in 2004–2007*; 2007. [http://www.gunma-cc.jp/sarukihan/seizonritu/seizonritu2007.html#10](http://www.gunma-cc.jp/sarukihan/seizonritu/seizonritu2007.html#10). Accessed 26 September 2016 [in Japanese].

22. Arii S, Yamaoka Y, Futagawa S, et al. Results of surgical and nonsurgical treatment for small-sized hepatocellular carcinomas: a retrospective and nationwide survey in Japan. *The Liver Cancer Study Group of Japan. Hepatology*. 2000;32:1224–1229.

23. Eguchi S, Kanematsu T, Arii S, et al. Comparison of the outcomes between an anatomical subsegmentectomy and a non-anatomical minor hepatectomy for single hepatocellular carcinomas based on a Japanese nationwide survey. *Surgery*. 2008;143:469–475.

24. Hasegawa K, Makuuchi M, Takayama T, et al. Surgical resection vs. percutaneous ablation for hepatocellular carcinoma: a preliminary report of the Japanese nationwide survey. *J Hepatol*. 2008;49:585–594.

25. Takayasu K, Arii S, Ikai I, et al. Prospective cohort study of transcatheter chemembolization for unresectable hepatocellular carcinoma in 8510 patients. *Gastroenterology*. 2006;131:461–469.

26. Nouso K, Miyahara K, Uchida D, et al. Effect of hepatic arterial infusion chemotherapy of 5-fluorouracil and cisplatin for advanced hepatocellular carcinoma in the Nationwide Survey of Primary Liver Cancer in Japan. *Br J Cancer*. 2013;109:1904–1907.