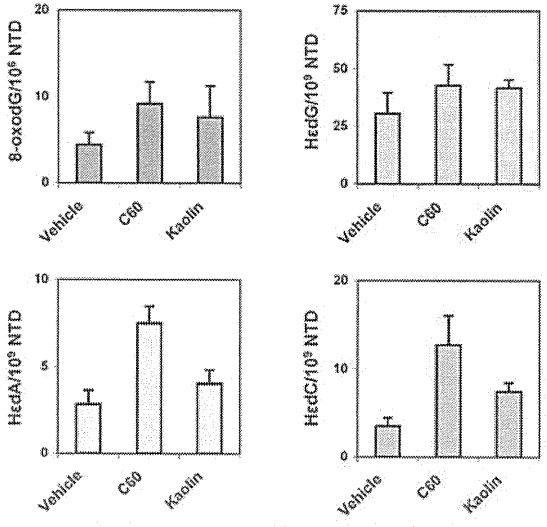

Fig. 4. Oxidative and lipid peroxide related DNA adduct formation in the lungs of ICR mice induced by nanoparticle exposure. DNA was extracted from lungs of mice 24 h after intratracheal instillation of 0.2 mg/body of C60 or kaolin, and digested enzymatically. Control animals were exposed to saline containing 0.05% Tween80. The 8-oxodG and 3 kinds of Hε-adducts were quantified by the stable isotope dilution LC-MS/MS method described by Chou *et al.* (10).

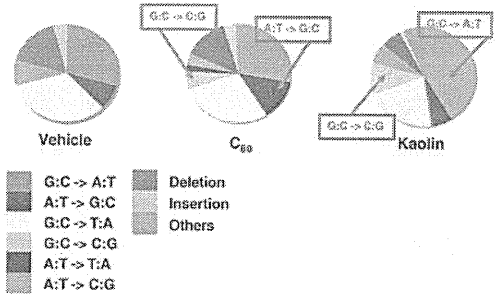

Fig. 5. Classification of *gpt* mutations from the lungs of control and nanoparticle treated mice.

tics induced by particles by PCR and DNA sequencing analysis of 6-TG resistant mutants. Classes of mutations found in the *gpt* gene are shown in Fig. 5. Interestingly, G:C to C:G transversions were increased in common with both particle treatments. Since these mutations were commonly increased regardless of the constituents (i.e., C_{60} is graphite and kaolin is aluminum silicate), the mechanisms might be the same. It has been reported that various oxidative stresses caused by sunlight, UV radiation, hydrogen peroxide and peroxy radicals frequently induce G:C to C:G transversions in various *in vitro* assay systems (14–17). Moreover, a variety of oxidative lesion products of guanine other than 8-oxodG, including imidazolone (Iz), oxazolone (Oz), spiroiminodihydantoin (Sp) and guanidinohydantoin (Gh), have been reported (18–24). Three such molecules, Oz, Sp and Gh are now thought to be key causes G to C transversions with translesion synthesis systems (22–25). Therefore, it is suggested that G:C to C:G transversions induced by C_{60} and kaolin could involve Oz, Sp and Gh formation. In addition, G:C to A:T transitions were also significantly increased by instillation of kaolin but not C_{60}. In general, G to A (or C to T) transitions have commonly been observed in spontaneous and chemically-induced mutants, and deamination of guanine or 5-methylcytosine might be involved. Burney *et al.* reported that nitric oxide induces DNA damage. NO can form N_2O_3, and direct by this agent can lead to DNA deamination via diazonium ion formation (26). Moreover, nitric oxide is produced by activated macrophages in inflamed organs. In fact, test substance-phagocytized macrophages and granulomas were frequently observed in the lungs of mice (4).

Immunohistochemical Analysis of Inflammation Factors

In order to confirm enhancement of nitric oxide production by C_{60} and kaolin, we examined immunohistochemical staining of an inflammation factor, nitrotyrosine (NT), in the lungs of *gpt* delta mice treated with these nanoparticles using the same procedure reported previously (27) with minor modification. As shown in Fig. 6, the pattern of NT staining corresponded to the areas of inflammation within lung parenchyma. In the case of C_{60} exposure, many regions of the lungs stained positively (data not shown), and intense NT staining was localized in test substance-phagocytized macrophages and granulomas. Similarly, staining with NT antibodies was observed in macrophages and alveolar epithelial cells in the lungs of mice exposed to kaolin, although to a lesser extent as compared with C_{60}.

Conclusion

Our results clearly demonstrated that both *in vitro* and *in vivo* genotoxicity are induced by C_{60} and kaolin. However, the mechanisms have yet to be fully clarified, and oxidative stress might be at least partly involved. There are a number of ways in which reactive oxygen species (ROS) could be generated: i) nanoparticles might trigger ROS production by iron-catalysed Fenton reactions; ii) nanoparticles could accumulate in cells due to phagocytosis, then enhance the production of ROS by NADPH oxidase (28,29). Recently, innate immune activation through Nalp3 inflammasomes has been suggested to play an important role in pulmonary fibrotic disorders of silicosis and asbestosis (30,31). It has been reported that proinflammatory cytokines, such as interleukin 1β are key molecules for pneumoconiosis. At

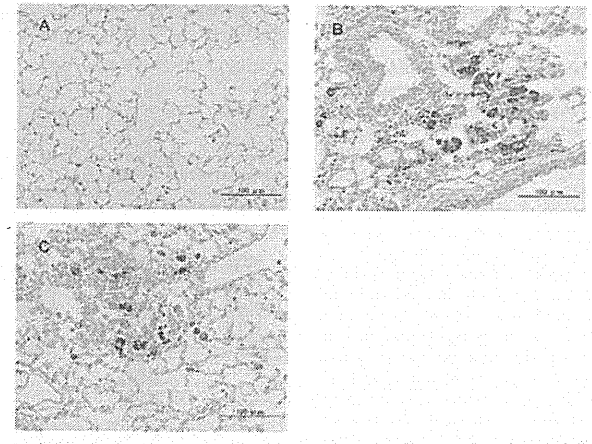

Fig. 6. Immunohistochemical localization of nitrotyrosine (NT). Since C_{60} is brown in color, we used an SG substrate kit (Vector Laboratories, USA) for peroxidase, with positive cells stained dark blue-gray. A: alveolar region in a control mouse, with no significant staining for NT. B: alveolar region in a mouse exposed to C_{60}, with positive macrophages phagocytizing test substance and epithelial cells. The brown colored material is C_{60}. C: alveolar region in a mouse exposed to kaolin. Note intense staining for NT in the granulomatous region.

present, no data are available for activation of the Nalp3 inflammasome pathway by C_{60} and kaolin. However, it is likely that both nanoparticles can activate in the same way as asbestos and silica, because oxidative stress was increased in the lungs of treated mice. Further studies of the mechanisms of genotoxicity are needed.

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Review Article

Hepatitis B and C Virus Infection and Hepatocellular Carcinoma in China: A Review of Epidemiology and Control Measures

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ABSTRACT

China has one of the highest carrier prevalences of hepatitis B virus (HBV) in the world: nearly 10% of the general population. The disease burden of HBV infection and hepatocellular carcinoma (HCC) is also believed to be among the world's largest, and that of hepatitis C virus (HCV) infection is likely to be substantial as well. However, the epidemiology and measures to control HBV and HCV infection in China remain relatively unknown outside the country. We review the epidemiology of HBV and HCV infection, the disease burden of and risk factors for HCC, and current control measures against HBV and HCV infection in China. We also discuss the relevant literature and implications for future studies of hepatitis and HCC in China.

Key words: China; hepatitis; hepatocellular carcinoma; epidemiology; control

1. INTRODUCTION

Infection with hepatitis B and C virus (HBV and HCV, respectively) and hepatocellular carcinoma (HCC) are responsible for heavy disease burdens in China. In 2006, the Ministry of Health of China (MOH) estimated that, among Chinese aged 1 to 59 years as of 1992, the national prevalence of HBV infection (positivity for HBsAg or any HBV marker) and HBV carriers was 57.63% and 9.75%, respectively, which corresponds to 690 million infected persons and 120 million carriers, as well as 20 million people with chronic hepatitis.[1] This disease burden is very large, even when compared with that of tuberculosis, which was responsible for 1.4 million new cases in 2000.[2] Chronic hepatitis B is one of the most serious infectious diseases in China. Unfortunately, we lack a clear picture of the national impact of HCV infection. The nationwide prevalence of HCV infection in 1992 was estimated to be 3.2%, which was higher than in Japan, the United States, and most countries of the European Union. HCC is the second most common malignancy in China, and its most frequent cause is chronic HBV infection.

To date, the MOH has taken several measures to address these diseases. In its National Plan for Prevention and Treatment against Hepatitis B for 2006–10, the MOH states that chronic hepatitis B causes serious consequences for patients, their families, and society as a whole and that it is a major cause of poverty and a health issue of the highest priority.

From a global perspective, China has one of the highest HBV carrier prevalences in the world[3] and is also estimated to have the highest incidence of HCC (37.9 and 14.2 for males and females, respectively, per 100 000 world standard

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List of abbreviations: CHO: Chinese hamster ovary; CI: 95% confidence interval; CIV: Cancer Incidence in Five Continents (a report by the International Agency for Research in Cancer on cancer incidences from cancer registries around the world); DSP: disease surveillance points; ELISA: enzyme-linked immunosorbent assay; EIA: enzyme-linked immunoassay; HB: hepatitis B; HBV: hepatitis B virus; HBsAg: hepatitis B surface antigen; HBeAg: hepatitis B e antigen; HBcAg: hepatitis B core antigen; anti-HBc: antibody to hepatitis B core antigen; anti-HBs: antibody to hepatitis B surface antigen; anti-HBe: antibody to hepatitis Be antigen; Hepatitis C: Hepatitis C; HCC: hepatocellular carcinoma; HCV: hepatitis C virus; anti-HCV: antibody to hepatitis C virus; IARC: International Agency for Research in Cancer; MOH: Ministry of Health of China; *N*: sample size; NPHB: the National Plan for Prevention and Treatment against Hepatitis B; OR: odds ratio; aOR: adjusted odds ratio; mOR: odds ratio obtained from meta-analysis; PLC: primary liver cancer; RIA: radioimmunoassay; RR: relative risk.

population as of 2002[4]), accounting for 55% (approximately 340 000 cases) of newly diagnosed cases in the world (approximately 630 000 cases) in 2002.[4] Despite the magnitude of the burden of chronic viral hepatitis and HCC in China, the epidemiology and control measures for these diseases are relatively unknown outside the country. In this descriptive review, we hope to increase understanding of the trends, the studies that revealed the trends, and the challenges for future research. In selecting studies to be reviewed, we focused on those that were published in internationally accredited English journals and had a full description of their methodology. We also discuss the results of reports in Chinese and Japanese, when information was not available in English.

2. PREVALENCE OF HEPATITIS B AND C VIRUS INFECTION

2.1 Surveys up to 1990

The first nationwide survey of HBV infection in China was conducted in 1979,[5] which coincided with the start of economic reform in the country. The overall standardized carrier prevalence was reported to be 8.8%, with a higher prevalence in rural (10.2%) than urban (7.9%) areas. However, this figure may be an underestimate because a reverse passive hemagglutination assay (RPHA) was used for HBsAg testing.[6] Another survey was conducted in 1980[7] in 5 provinces; the prevalence of HBV infection was 42.6% and HBsAg carrier prevalence was 10.3% (tested by RIA). The prevalence of HBV infection and HBV carrier status was higher in southern and rural areas than in northern and urban areas. In another survey[8] from 1984 through 1987 of the 4 provinces of Hunan, Henan, Hebei, and Heilongjiang, the prevalence of HBV infection and HBV carrier status was 58.2% and 10.1%, respectively (tested by RIA).

2.2 The nationwide seroepidemiologic survey of hepatitis in 1992

With financial assistance from the World Bank, a nationwide cross-sectional seroepidemiologic survey of hepatitis A, B, C, D, and E infection was carried out in 1992.[9] It used the Nationwide Disease Surveillance Points (DSPs) system, which was established in 1989. As of 1992, the DSP system comprised 145 reporting sites in 30 province-level divisions (provinces, and provincial-level autonomous regions/municipalities),[10,11] which were selected by stratified cluster random sampling. The DSPs covered 1% of representative samples of the Chinese population and have a combined population structure similar to that in the national census. In the survey, 3 subcluster areas, each consisting of about 35 households, were randomly selected from each DSP, and all individuals aged 1 to 59 years in each household were the subjects of the surveillance, for a total of approximately 68 000 subjects. A solid-phase radioimmunoassay was used for detection of HBsAg, anti-HBc, and anti-HBs; EIA was used for HBeAg; and a second-generation UBI EIA was used for anti-HCV. In this section, we summarize and interpret the results of this survey.

2.2.1 Prevalence of hepatitis B infection by age and sex

The estimated overall HBV carrier prevalence among those aged 1 to 59 years was 9.75% (range of prevalence in provinces: 4.49%–17.85%), which was comparable to the results of earlier studies, shown in section 2.1. Age-specific carrier prevalence was 9.67% among those aged 1 to 4 years and 10.22% among those aged 5 to 9 years; it peaked among those aged 10 to 14 years (11.27%). This increasing trend among individuals younger than 15 years suggests the presence of age effects (horizontal transmission) and/or cohort effects. Prevalence was comparable across the ages of 15 to 49 years (range of prevalence in provinces: 9.22%–10.35%). Those aged 50 to 59 had a significantly lower prevalence (7.58%; $P < 0.01$). With regard to sex, males had a significantly higher carrier prevalence (11.3%) than did females (8.2%; $P < 0.01$), as was reported in other countries in East Asia.[12,13] The prevalence of anti-HBs, anti-HBc, and HBV infection was 27.42%, 49.81%, and 57.63%, respectively. The age-specific prevalence of HBV infection increased with age from 38.47% among those aged 1 to 4 to 70.69% among those aged 50 to 59. The overall prevalence of HBeAg among HBV carriers was 31.94%, and it decreased with age from 53.32% among those aged 1 to 14 to 12.30% among those aged 40 to 59. Although the prevalence of HBV infection was higher in China, the age and sex characteristics of HBV carriers were comparable to those observed in Japan and Korea.[12,13]

2.2.2 Prevalence of hepatitis B infection across regions

HBV carrier prevalence varied across geographic areas. It was significantly higher in rural than in urban areas (10.49% vs. 8.08%; $P < 0.01$). Among the 6 major administrative regions in China as of 1992 (Figure 1), carrier prevalence was 12.75% in the South Central region, 10.71% in the Northeast, 9.94% in the East, 8.90% in the Southwest, 8.68% in the Northwest, and 5.53% in the North Central region. As compared with the national level, carrier prevalence was significantly higher in the South Central region and lower in the Northwest and North Central regions. Geographic disparities in carrier prevalence might represent differences in ethnic distribution, socioeconomic conditions, unsafe medical practices, and access to HBV immunization services.

When the 30 province-level divisions were grouped by HBV carrier prevalence, 10 were classified as high endemic areas (>11%), 11 as moderate endemic areas (7–11%), and the remaining 9 as low endemic areas (<7%). Notably, prevalence was still high even in low endemic areas, as compared with the international standard. In each area, prevalence showed an increasing trend with age up to age 15 years.

2.2.3 Prevalence of HCV infection

The nationwide prevalence of anti-HCV was 3.2% among

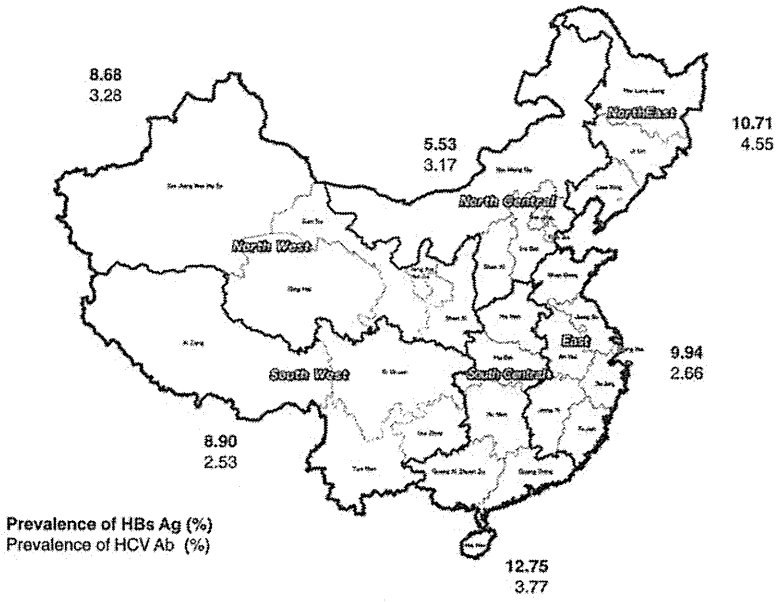


Figure 1. Map of seroepidemiologic survey of hepatitis virus infection in 1992 and prevalence of HBs antigen and anti-HCV by region

those aged 1 to 59 years (range of prevalence in provinces: 0.9%–5.1%). It increased significantly with age, from 2.08% among those aged 1 to 4 years to 3.96% among those aged 50 to 59 years. There was no significant difference in prevalence by sex (3.10% for males and 3.30% for females). These prevalences were higher than those reported for first-time Japanese blood donors aged 16 to 64 years in 1995–2000 (0.49%; CI: 0.48%–0.50%)[12] and the 1988–1994 participants of NHANES III in the United States (1.8%; CI: 1.5%–2.3%).[14]

The difference in the seroprevalence of anti-HCV across administrative regions was less pronounced than that for HBV carrier prevalence. The prevalence of anti-HCV was 4.55% in the Northeast, 3.77% in the South Central region, 3.28% in the Northwest, 3.17% in the North Central region, 2.66% in the East, and 2.53% in the Southwest. As compared with the national level, the prevalence of HCV infection was significantly ($P < 0.01$) higher in the Northeast and South Central regions and lower in the East and Southwest. This regional variation might reflect differences in high-risk practices, such as unsafe medical practices and injecting drug use, as discussed below.

When the 30 province-level divisions were grouped by anti-HCV prevalence, 15 were classified as high endemic areas (3.0%–6.0%) and the remaining 15 as low endemic areas (1.0%–2.9%). In each category, the prevalence of HCV infection tended to increase with age. In the high endemic areas, the prevalence of HCV infection ranged from 2.69% among those aged 5 to 9 years to 5.20% among those aged 40 to 49 years. In the low endemic areas, the prevalence of HCV ranged from 1.37% among those aged 1 to 4 years to 3.07% among those aged 50 to 59 years. The statistically significant rural–urban disparity in the prevalence of HBV infection was not observed in the prevalence of HCV infection (3.42% vs. 3.14%, respectively).

2.3 The nationwide seroepidemiologic survey of HBV in 2006

After the introduction in 1988 of a universal HBV vaccination program in China and its gradual expansion (see section 6.1), the MOH conducted a nationwide seroepidemiologic survey in 2006 to assess the prevalence of HBV infection, its risk factors, and the impact of the program.[15] As in 1992, the 2006 survey used 2-stage clustered sampling. A total of 369 townships were randomly selected (1–4 per county) to represent 160 DSPs in 31 province-level divisions as of 2006 (note: there are 5 levels of local government in China: the province, prefecture/city, county, township, and village).

Table 1. Prevalence of HCV infection in different geographic areas of China

Area (authors)	Reporting year	Characteristics of subjects	No. of subjects	Prevalence of HCV infection	Testing method	Reference no.
Beijing (Sherlock)	1993	apparently healthy people	164	6%	First-generation antibody test	20
Jiangsu (Ito)	1994	blood donors	451	0.7%: anti-HCV 0.2%: HCV RNA	Second-generation antibody test (Dinabo Co, Japan) and ELISA (Ortho Co, USA), and HCV RNA	21
Gansu (Wu, Mizokami)	1995	blood donors (40 volunteer donors and 80 paid donors)	120	Volunteer donor: 2.5%; Paid donor: 35%	EIA 2 (Ortho Diagnostics, Raritan, NJ)	22
Guanxi (Yuan)	1996	hospitalized patients (non-liver disease)	141	0.7%	ELISA Version 2.0 (Ortho Diagnostics, Raritan, NJ)	23
Henan (Zhang, Qiao)	2005	residents aged ≥55 years (participants in an interventional study)	500	9.6%	ELISA Version 3.0 (Ortho Diagnostics, Raritan, NJ)	24
Henan (Liu)	2009	participants in esophageal cancer screening (age 25–65 years)	8226	0.9%	HCV ELISA 3.0 (Autobio Co. Zhengzhou, China)	25

Then, 1 village was randomly selected from each township, and a sample population was randomly selected in each village with a weighted sampling method in the age groups 1 to 4 years, 5 to 14 years, and 15 to 59 years. The total sample population was 82 078. Blood samples were collected, and background information for each person (date of birth, sex, ethnicity, place of birth, occupation, educational level, and immunization history) was also compiled. The immunization status of children younger than 15 years was confirmed by reviewing their immunization record. All serum specimens were tested for HBsAg, anti-HBc, and anti-HBs by ELISA at the National Hepatitis Laboratory in the Chinese Centers for Disease Control and Prevention in Beijing.

The estimated national prevalence among those aged 1 to 59 years was 7.2% for HBsAg, 50.1% for anti-HBs, and 34.1% for anti-HBc. The age-specific carrier prevalence was 1.0% (CI: 0.8%–1.2%) for age 1 to 4 years, 1.4% (CI: 1.2%–1.7%) for 5 to 9 years, 3.2% (CI: 2.6%–3.8%) for 10 to 14 years, 5.4% (CI: 4.4%–6.4%) for 15 to 19 years, and 8.5% to 10.5% for 20 years or older. A marked reduction was observed among those younger than 15 years who participated in the nationwide HBV immunization program, as well as among those aged 15 to 19 years who were partially immunized when the program started in 1988. Using multinomial logistic regression analyses, the risk factors for HBV carrier state among those aged 15 to 59 were identified, namely, lack of HBV immunization (OR: 2.5), male sex (OR: 1.7), and public worker (OR: 3.8) ($P < 0.01$). Among those aged 1 to 14, the major risk factors for HBV carrier state were lack of immunization (OR: 2.5), age 10 to 14 years (OR: 1.9), and birth at a township hospital (OR: 2.1) or at home (OR: 4.0) ($P < 0.01$). Based on these results, the MOH determined that the immunization program contributed to reducing the carrier rate. It also cited the possible beneficial effects of other programs to prevent horizontal infection and promote safe injection.

In addition, the MOH analyzed the immunization status and background information of those born from 1992 to 2005 (age 1–14 years).[16] Three-dose coverage of HBV vaccination increased from 30.0% for children born in 1992 to 93.4% for those born in 2005. A similar increase was noted—from 22.2% to 82.6%—for those receiving a timely birth dose (ie, within 24 hours after birth). The risk factors for undervaccination (neither a full vaccine series nor a timely birth dose) included older age (5 to 14 years), rural residence, birth at a township hospital or at home, and Tibetan or Uigur ethnicity ($P < 0.01$).

To assess the impact of the HBV immunization program, another survey was conducted in Zhejiang province in 2007[17] and the results showed a low prevalence (1.52%) of HBV carrier state among those aged 0 to 8 years ($N = 5047$), while the prevalence of anti-HBs was high (65%), which supported the findings of the 2006 survey.

2.4 Other reports on the prevalence of HBV and HCV infection

Several other surveys, conducted in limited areas, found prevalences of HBV infection that were comparable with those from the 1992 and 2006 seroepidemiologic surveys, depending on the year they were conducted. Some studies from Tibet[18] and the Guangxi region[19] reported very high prevalences of HBV carriers (19%; $N = 262$ and 2132, respectively). With regard to HCV, there are few reports on infection prevalence. The results of those with a comparatively large sample size ($N \geq 120$) and a detailed description of their testing method[20–25] are summarized in Table 1.

3. EPIDEMIOLOGY OF HBV INFECTION

3.1 Distribution of HBV genotypes in China

The epidemiologic and clinical characteristics of HBV infection partly depend on virus genotype. In East Asia, genotypes B and C are most prevalent.[26] Previous studies of genotype distribution in China[27,28] showed that genotypes B and C were most common, while genotypes A and D were also present. The distribution of genotypes B and C differed by geographic region. Genotype C was more prevalent in northern provinces, while genotype B was more prevalent in southern provinces. In general, liver cirrhosis and HCC are more likely to result from chronic hepatitis due to HBV genotype C than that due to HBV genotype B. It has been reported that the severity of liver disease induced by HBV genotype B differs by HBV genotype B subgenotype. The Ba subgenotype, which is common in China, has a higher potential for oncogenicity than subtype Bj, which is dominant in Japan.[29]

3.2 Carrier status and perinatal and horizontal transmission of HBV

As in other countries in East Asia, perinatal infection plays an important role in the development of HBV carrier state in China. Children born to carrier mothers have a significantly higher risk of becoming an HBV carrier than those born to noncarrier mothers (relative risk 5.3).[30] Another report found that perinatal infection accounted for 35% to 50% of HBsAg carriers.[31]

Horizontal transmission during childhood is also considered to be common[32] and an important factor in carrier status. A study in the Guangxi Zhuang Autonomous Region ("Guangxi region" hereafter) showed that, out of 289 children aged 1 to 10 years who had HBsAg-negative parents, 36% were infected with HBV during childhood.[32] A study from Sichuan province[33] reported an annual HBV infection rate of 13% among 448 susceptible children in nurseries and preschools.

Previous seroepidemiologic surveys found that horizontal infection had an impact on carrier status. The first nationwide survey, in 1979,[5] showed increasing carrier prevalence with age: 3.2% among children younger than 1 year, 8.9% among those aged 1 to 4 years, and higher than 10% among those aged 5 to 9 years. A similar prevalence trend was found in the 4-province survey in 1984–87[8]: 3.8% among children younger than 1 year, 8.7% among those aged 1 year, and 9.4% to 12.6% among those aged 2 to 9 years. The results of the nationwide survey in 1992 indicated that when an immunization program was already present in some areas of the country, the impact of horizontal infection was not as clear as in preceding surveys, but increasing trends with age were observed in carrier prevalence, with a peak between age 10 and 19 years. These findings strongly suggest that horizontal infection plays an important role in the development of HBV carrier state in China.

The impact of horizontal infection on carrier status can vary with socioeconomic status and geographic area, with the latter being linked to the genotype distribution of HBV. Some reports estimated that the proportion of individuals with positive carrier status attributable to perinatal transmission was as low as 13% to 20%.[32] However, it appears that further studies are necessary to confirm these estimates.

3.3 Horizontal transmission of HBV among adults

Horizontal transmission has been documented not only among children, but also among adults. The risk of sexual transmission of HBV among newly married couples has also been reported.[34] In that report, 57 couples comprising 1 HBsAg/anti-HBc positive partner and 1 HBV-susceptible partner (case group) and another 61 couples that were negative for HBV markers (control group) were followed-up for an average of 27 months. HBV transmission was observed in 53% of couples in the case group and only 16% of those in the control group.

Other than sexual and iatrogenic transmission, risk factors for horizontal transmission among adults have seldom been investigated.[35] However, a case-control study in Shanghai[36] demonstrated that—in addition to invasive medical procedures, household contact with HBV carriers, and lack of HBV vaccination—body care and beauty treatments were independently associated with the occurrence of acute hepatitis B. That study also found that HBV genotype C2 was an independent risk factor for the progression of acute infection to chronic infection.

3.4 Iatrogenic transmission of HBV

Since the 1990s, the World Health Organization has expressed concern regarding the potential transmission of hepatitis viruses due to unsafe medical practices, especially the use of contaminated medical instruments, and has called for implementation of control measures.[37] Injection is the most common and preferred invasive intervention in medical and preventive (immunization) services in East Asia. As of 2007, China had high prevalences of HBV and HCV infection and an estimated HIV prevalence of 0.1%[38]; thus, reuse of syringes and needles in the absence of sterilization exposes millions of people to the risk of contracting these viruses and other blood-borne diseases.

Because iatrogenic infection can cause substantial health problems, some researchers challenged the necessity and safety of injection services in China.[39,40] The national immunization assessment in 2004 showed that only 40% of clinics that provide immunizations used single-use syringes and needles.[41] Province-level reports are also available. In Shandong province—one of the wealthiest provinces of China—a cross-sectional study of 3 administrative levels of health units (village clinic, township health center, and county hospital) in 1 urban and 1 rural area was performed in 2001. Of 468 health practitioners who provided injection services,

Table 2. Annual mortality rate (per 100 000 persons) for 5 common malignant neoplasms in China, by sex (2004–5)

Rank	Total		Males		Females	
	Disease	Death Rate (%)	Disease	Death Rate (%)	Disease	Death Rate (%)
1	Lung	30.6	Lung	41.1	Lung	19.6
2	Liver	26.1	Liver	37.4	Stomach	16.4
3	Stomach	24.5	Stomach	32.3	Liver	14.3
4	Esophagus	15.0	Esophagus	20.5	Esophagus	9.4
5	Colorectum	7.4	Colorectum	8.3	Colorectum	6.3

6.2% had unsafe injection practices and 7.6% had improperly handled used disposable syringes.[42] Another survey of a county in Chongqing city, Sichuan province[43] found that improperly sterilized glass syringes were found in 52% of health facilities and that injection practices were not correct in 31% of those facilities.

Data on the disease burden from iatrogenic HBV infection in China are limited. A survey by the Centers for Disease Control and Prevention of the Guangxi region showed that 55% of HBV infections in that region were attributable to unsafe injections.[44] A study in northeastern China, which combined a cross-sectional survey of immunization practice with mathematical modeling of HBV infection, estimated that the annual number of HBV infections due to unsafe immunization injection was at least 135 to 3120 cases among 100 000 fully immunized children.[45]

3.5 Other epidemiologic reports on HBV infection

A prospective cohort study of residents in Haimen,[46] Jiangsu province, a city near Shanghai, found that HBV carriers had a significantly higher risk of dying of non-liver diseases as compared with noncarriers: the relative risk (RR) was 1.2 (CI: 1.1–1.3) in men and 1.4 (CI: 1.1–1.7) in women. When the analysis was limited to all non-liver cancers as the cause of death, the RR was 1.2 (CI: 1.0–1.4) for men and 1.7 (CI: 1.2–2.3) for women. In addition, for non-liver, non-cancer deaths, carriers had significantly higher RRs: 1.2 (CI: 1.1–1.4) and 1.2 (CI: 0.9–1.6) in men and women, respectively. Possible reasons for the increased risk include socioeconomic conditions and behavioral factors associated with carrier status.

4. EPIDEMIOLOGY OF HCV INFECTION

In China, reports of epidemiologic studies on hepatitis C are limited, as compared with those on Hepatitis B. As for HBV, the epidemiologic and clinical characteristics of HCV infection partly depend on the genotype of the virus. Several studies reported that the most common genotype identified in China was genotype Ib.[47–49]

A community-based cross-sectional study of the risk of HCV infection in 4 counties of Hebei province[25] found that anti-HCV was detected in 0.9% out of 8226 residents aged 25 to 65 years. A subsequent case-control study found that blood transfusion (OR: 4.55), esophageal balloon examination (OR: 3.78), and intravenous injection (OR: 5.83) were significantly ($P < 0.05$) associated with HCV infection.

Some studies of the transmission route for HCV suggested that sexually transmitted diseases and injecting drug use were associated with infection. A follow-up study of heroin users showed an extremely high incidence rate of HCV infection of 37.6 per 100 person-years.[50] Studies of the prevalence of HCV among injecting drug users showed marked geographic variation; prevalence was 72% in Guangxi region ($N = 597$),[50] 11% in Shanxi province, and 90% in Hubei[51] ($N = 10\,724$). A meta-analysis based on a systematic review of the prevalence of HCV infection among injecting drug users[52] reported that the pooled prevalence among injecting drug users in China was 61.4% (CI: 55.7–67.2%) and that the epidemic was most severe in the southern inland provinces of Hubei, Hunan, Yunnan and Guangxi, and the westernmost Xinjiang Autonomous Region. It also found a significant association between infection and ethnic-minority status.

5. EPIDEMIOLOGY OF HEPATOCELLULAR CARCINOMA

5.1 Mortality and incidence of primary liver cancer (PLC)

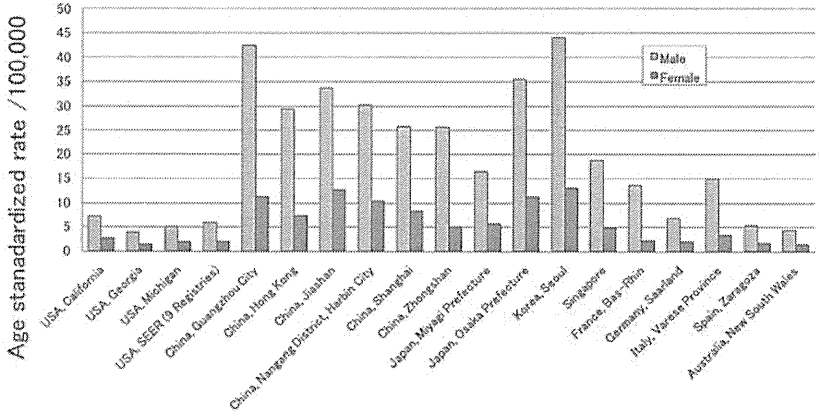
Table 2 shows the distribution of mortality rates for the 5 most common anatomical sites for cancer in China during 2004–2005 by sex (data from health statistics of the MOH[53]). Overall, and in males, PLC ranked as the second most frequent cause of cancer death, after lung cancer. In females, it was the third most common cause of cancer death, after lung and stomach cancers. The mortality rate from PLC was higher in males (37.4/100 000) than in females (14.3/100 000). When we compared mortality between urban and rural dwellers (Table 3), HCC was the second most common cause of cancer death in urban areas and the most common cause in rural areas. The slightly lower mortality rate in urban areas (24.4/100 000) than in rural areas (26.9/100 000) might reflect, at least in part, a disparity in carrier prevalence.

Although no incidence data are available for the whole country, Yang et al estimated[54] the incidence rates for major cancer sites in China in 2005, using mortality rates during

Table 3. Annual mortality rate (per 100 000 persons) for 5 common malignant neoplasms in China, by area of residence (2004–5)

Rank	Urban		Rural	
	Disease	Death Rate (%)	Disease	Death Rate (%)
1	Lung	39.9	Liver	26.9
2	Liver	24.4	Lung	25.7
3	Stomach	22.5	Stomach	25.6
4	Esophagus	10.6	Esophagus	17.3
5	Colorectum	9.7	Colorectum	6.1

Data source: CHINESE HEALTH STATISTICAL DIGEST 2010 by Ministry of Health, China
http://www.moh.gov.cn/publicfiles//business/htmlfiles/zwgkzt/ptjty/digest2010/index.html



Incidence per 100,000 person-years; world standard population

Data source: Cancer Incidence in Five Continents, Vol.9, IARC

Figure 2. Age-standardized Incidence of primary liver cancer in East Asia, Australia, USA and EU countries, 1998–2002.

2000–5 and data from 7 cancer registries reported in the Cancer Incidence in Five Continents (CIV) Volume 8.[55] The estimated incidence rate of HCC was 40.0 in males and 15.3 in females per 100 000 world standard population, ranking it as the second most common cancer, after lung cancer, in both sexes (49.0 in males and 22.9 in females). Using data from CIV Volume 9, Figure 2 shows the annual HCC incidence rate per 100 000 world standard population, as reported in cancer registries in East Asia, Australia, the United States, and selected countries in the European Union. Overall, China has the highest incidence rates.

5.2 Temporal trends in PLC incidence

Four Chinese registries that met the data quality requirements of the IARC and appeared in the CIV Volume 9 reported temporal trends in PLC incidence. The age-adjusted incidence rate of PLC has been decreasing in Shanghai city since the 1970s[56] and in Tianjin city[57,58] and Hong Kong[59] since the 1980s. In Qidong city, near Shanghai, the incidence rate showed no apparent temporal change since 1978, except that the age-specific rate for individuals aged 15 to 34 years has been decreasing during 1988–2002.[60] In addition to registries in the CIV, there are reports of PLC incidence since the 1970s in Henan, Fujian, and Hebei provinces, but temporal trends varied in these areas.

5.3 Risk factors for HCC

5.3.1 HBV infection

There have been several reports on the prevalence of HBsAg among patients with HCC and primary liver cancer.[61–65] The results of studies that provided a detailed description of methodology, had a sample size of at least 100, and were published after 1993 are listed in Table 4. Although there were differences in prevalence, due to variation in the methods

Table 4. Prevalence of HBV and HCV infection among patients with hepatocellular carcinoma (HCC) in different geographic areas

Area (first author)	Reporting year	Characteristics of subjects	No. of subjects	Virus type	Prevalence of virus (%)	Testing method	Reference no.
Shanghai (Cong et al)	1993	HCC patients	713	HBV	70.8 (Male) 59.7 (Female)	HBsAg	62
Guanxi (Okuno et al)	1994	HCC patients	186	HBV	70	HBsAg	63
10 different regions (Yang et al)	2004	primary liver cancer	3250	HBV	81.0	HBsAg	64
Beijing (Gao et al)	2005	HCC patients	119	HBV	82.4	HBsAg	65
Guanxi (Okuno et al)	1993	HCC patients	186	HCV	5.4	HCV EIA II (Abbott, Dinabot Co, Tokyo)	63
10 regions (Yang et al)	2004	primary liver cancer	3250	HCV	13.2	anti-HCV (details of testing method not shown)	64
Beijing (Gao et al)	2005	HCC patients	119	HCV	11.8	HCV EIA (AxSYM HCV Dynapack Abbott, Tokyo)	65

used for selection of patients and testing for infection, the findings indicated that most HCC cases in China were associated with HBV carrier status. In contrast, HCV was the most important risk factor in Japan, the United States, and the selected European Union countries. Table 5 summarizes recent reports[66–70] in English on the RR of HBV carrier state for developing HCC. There are many more Chinese-language reports on relative risk. One systematic review and meta-analysis[70] of 32, mostly Chinese-language studies, reported a wide range in relative risk (3.8–103). The pooled odds ratio (mOR) was 15.6 (CI: 11.5–21.3) for HBsAg positivity alone and 35.7 (CI: 26.2–48.5) for dual infection with HBV (HBsAg) and HCV (anti-HCV).

5.3.2 HCV infection

Since the 1990s, there have been several reports on the prevalence of HCV infection among HCC or primary liver cancer patients. As mentioned above, the reported prevalences are summarized in Table 4. Prevalence can partly depend on patient selection and the testing method, but these findings suggest that the prevalence of HCV infection among patients with HCC varies by geographic area.

Regarding the relative risk of HCV infection for developing HCC, there are few reports in English that include a detailed description of the study methodology. Among them, reports from Haimen city[68] and Henan province[67] reported aORs of 0.77 (CI: 0.19–3.18) and 2.57 (CI: 0.57–12.03). The abovementioned systematic review of studies in Chinese[70] reported an mOR of 8.1 (CI: 5.0–13.0) for anti-HCV-only positivity.

5.3.3 Alcohol intake

Worldwide, alcohol intake is considered a probable cause of HCC.[71] Analytical studies in China that assessed risk, after adjusting for HBV carrier status, have had variable results. A case-control study from Henan province[72] found that an alcohol intake of 50 g/day or more at least once a week for 1 or more years was associated with a weak but significant risk (aOR: 1.06; $P < 0.05$). They also found a dose-response relationship between alcohol intake and development of HCC, namely, heavy drinkers (>5000 grams of alcohol per month) had an approximately 3- to 4-fold risk as compared with nondrinkers. This increased risk was not significant in another case-control study from Haimen city[68] that compared ever- and never-drinkers (aOR: 1.38, CI: 0.68–2.81). A prospective cohort study from Haimen city found no increased risk associated with drinking 4 or more drinks/week (aRR: 0.57 for males and 0.9 for females). Another cohort study that observed 145 male HBV carriers for 10 years also found no association between HCC incidence and consumption of more than 1000 mL/month of alcohol.[73] The differences in the findings of these studies might be partially due to variation in the criteria for and confirmation of alcohol consumption and/or adjustment for confounding factors such as HCV infection.

5.3.4 Smoking

China has a very high prevalence of smoking among males, and the disease burden from tobacco is believed to be substantial. One study estimated that 1 in 4 smokers was killed by smoking in the 1980s.[74] The relationship between smoking and the development of HCC in China has only recently been studied. A case-control study in Haimen city that estimated the relative risk of smoking after adjusting for HBV carrier state and alcohol intake,[68] and a cohort study of HCV carriers in the same area, found no increased risk due to smoking.[73] In contrast, a cohort study in Shanghai that followed-up 18 244 men[75] found that the risk of dying from HCC was significantly higher (aRR: 1.8; $P < 0.05$) for smokers who smoked 20 or more cigarettes per day as compared with never smokers, after adjusting for alcohol use. More recently, a large-scale case-control study was carried out to determine whether smoking was a cofactor for HCC development.[76] It analyzed data from 36 000 people who died of HCC as cases and 17 000 who died

Table 5. Association of hepatocellular carcinoma (HCC) with hepatitis B virus carrier status

Author and year	Reference no.	Study area	Type of study	No. of HCC cases	No. of controls/size of cohort	Person-years observed	RR (95% CI) for HBV carrier state	Adjusted covariates	Other information
Qian et al 1994	66	Shanghai	nested case-control study	55	267	69 393	OR = 7.3 (2.2–24.4)	age, residence, aflatoxin intake assessed by urinary markers	
Zhang et al 1998	67	Henan	case-control study, hospital-based	152	115	—	OR = 28.82 (11.18–78.78)	age, sex	OR = 31.22 (13.86–72.15) (HBV infection)
Yu et al 2002	68	Haimen, Jiangsu	case-control study, population-based	248	248	—	OR = 13.9 (5.78–33.6)	age, sex, residence, history of IV drug use, average income, and eating habits	
Evans et al 2002	69	Haimen, Jiangsu	cohort study, population-based	1092	58 545	434 718	RR = 18.6 (16.0–22.1) (males) RR = 33.2 (17.0–65.0) (females)	age, sex, history of acute hepatitis, family history of HCC, occupation, current alcohol and tea intake, history of drinking well water	end-point was HCC death
Shi et al 2005	70	reports from China	meta-analysis based on systematic review	3201	4005	—	mOR: 15.6 (CI: 11.5–21.3)	—	based on 32 case-control studies reported from 1966–2004, mOR is for HBsAg-positive and HCV-Ab-negative state

Note: Hepatitis B virus infection status was identified by the presence of HBs antigen; only English-language reports that were published after 1990 and adjusted for potential confounders were selected.
Abbreviations: CI: confidence interval, HBV: hepatitis B virus, HCV: hepatitis C virus, RR: relative risk of developing HCC, OR: adjusted odds ratio by multiple logistic regression analysis, mOR: odds ratio obtained by meta-analysis, HCC: hepatocellular carcinoma.

of liver cirrhosis as controls from 24 cities and 74 rural counties, to represent geographic differences. The RR for liver cancer death, standardized for age and locality, showed a 36% excess risk of death among male smokers aged 35 years or older (RR: 1.36; CI: 1.29–1.43; $2P < 0.000\,01$; attributable fraction, 18%) and 17% excess risk among female smokers (RR: 1.17; CI: 1.06–1.29; $2P = 0.003$; attributable fraction, 3%). These figures suggest that approximately 50 000 liver cancer deaths are caused by smoking every year in China. Another, more recent report showed that the attributable fraction of liver cancer due to smoking was 18.72% for men and 0.95% for women.[77]

5.3.5 Aflatoxin

Aflatoxins are classified as established carcinogens by the IARC[78] and are considered an important cause of HCC in some developing areas in the world. In China, exposure to aflatoxins is the second most-studied risk factor for HCC, after hepatitis viruses. It is hypothesized that the decreasing incidence of HCC in Hong Kong and Singapore is at least partially due to the decrease in aflatoxin contamination in food, which resulted from economic development.[79]

Regarding the relationship between aflatoxin and HCC, several ecological studies[80–82] were reported in the 1980s, but the results were not consistent. Later, some case-control studies[68,72] found a significant correlation between HCC and intake of peanuts and corn, which are believed to be among the most contaminated foods in China. In these studies, exposure to aflatoxin was assessed by estimates of aflatoxin ingestion obtained via population-based estimates of food intake, food sampling analyses, or in-person food frequency interview. Because these indirect estimates of exposure were not sufficiently reliable, a more recent nested case-control study in Shanghai[66] used urinary aflatoxins and their metabolites as a marker for exposure. It showed that the RRs for HCC development among noncarriers exposed to aflatoxin, unexposed HBV carriers, and exposed carriers were 3.4 (CI: 1.1–10.0), 7.3 (CI: 2.2–24.4), and 59.4 (CI: 16.6–212.0), respectively, when unexposed noncarriers were used as the reference. The results suggested that aflatoxins were risk factors for both carriers and noncarriers and that positive interaction existed between carrier status and aflatoxin exposure. These results were consistent with those of 2 independent cohort studies of HBV carriers in Qidong City, which showed that the RR of aflatoxin exposures for development of HCC, as assessed by the presence of urinary aflatoxin markers and the 249ser-p53 mutation, was 3.3 (CI: 1.2–8.7; attributable risk: 0.553)[73] and 3.5 (CI: 1.5–8.1),[83] respectively.

5.3.6 Other risk factors

Familial clustering of HCC has been documented.[84,85] A

population-based case-control study in Taixing city, Jiangsu province[86] demonstrated that relatives of HCC patients had a significantly increased risk (OR: 3.06; CI: 1.48–6.33) of HCC as compared with relatives of controls, after adjusting for age and sex. However, after adjustment for HBV carrier status, the OR was no longer statistically significant. On the other hand, a case-control study in Henan province[72] and a cohort study in Jiangsu province[69] found that a familial HCC history was a risk factor, with aORs of 11.80 (CI: 2.75–50.61) and 2.3 (CI: 1.9–2.7; males only), respectively, independent of HBV carrier status, alcohol intake, or exposure to crops potentially contaminated with aflatoxin. However, these studies could not identify the specific causes for the increased risk associated with kinship.

Some studies have suggested that drinking contaminated pond water is a risk factor for development of HCC.[87] This potential risk has been attributed to microcystin produced by algae. However, this association was not confirmed by other reports,[68] and it is possible that this potential risk factor was confounded with other risk factors.

The Yangtze valley is known for a high endemicity of schistosomiasis, which causes liver cirrhosis. A case-control study in Sichuan on the development of HCC and its association with a previous diagnosis of schistosomiasis[88] found that infection was significantly associated with HCC (OR: 3.7; CI: 1.0–13.0). However, research in Japanese provinces where the infection was endemic found that the association with HCC was caused by a confounder, ie, hepatitis virus infection.[89] The association between schistosomiasis infection and HCC development is currently considered less likely because the infection does not cause major inflammation in the hepatic parenchyma.

As described in section 5.1, the incidence and mortality rate of HCC are higher in males than in females in China. This difference can partly be explained by sex differences in the carrier prevalence of HBV. In addition, a cohort study in Haimen city[90] found a significant synergistic effect in the interaction between sex and HBV infection on liver cancer mortality, after adjusting for smoking and alcohol intake. That study also found that approximately 60% of male deaths from HCC might be attributable to this synergistic effect alone.

6. CONTROL MEASURES AGAINST HEPATITIS B

6.1 HBV immunization

The first hepatitis B vaccine was derived from human carrier plasma and was licensed in the United States in 1981. As described above, China has had a very large disease burden from chronic HBV infection, and the introduction of HB vaccination was an urgent priority. However, there were challenges in procuring and financing the huge number of vaccines needed for an annual birth cohort of more than 20 million in the 1980s. To overcome these challenges, local production of the vaccine was mandated. In 1986, plasma-derived vaccines were locally produced for the first time in China, and clinical trials confirmed them to be safe and highly effective in preventing HBV infection in infants born to HBV carrier mothers.[91] In 1988, the vaccine was introduced to some areas of the country.[31] Because the supply was limited, the vaccine was mainly used for neonates born to HBV carrier mothers. As a result, the prevalence of carriers in Beijing among children aged 0 to 7 years decreased from between 5% and 7% to between 3% and 4%.[31]

To overcome the vaccine shortage and potential risk of plasma-derived vaccine, the MOH started a project to produce the vaccine from a recombinant expression system. In 1996, a Chinese hamster ovary (CHO)-cell HBsAg expression system was licensed to produce recombinant CHO hepatitis B vaccine. At approximately the same time, production of a yeast-based recombinant vaccine was started after a technology transfer from Merck & Dohme Co. The recombinant vaccine was confirmed to be safe and effective in clinical trials and eventually replaced the plasma-derived vaccine. Since 2001, all hepatitis B vaccine used in China has been recombinant (yeast or CHO).[91]

In 1992, the MOH started universal vaccination for newborns. This led to increased coverage in urban and areas of high socioeconomic status, but the coverage was less extensive in rural and less affluent areas. A national review of immunization in 1999 showed that immunization coverage with 3-dose HB vaccine was 70.7% for the whole country, but it varied from 99% in Beijing to 7.8% in Tibet. The lower coverage in less affluent areas was due to the cost of vaccination paid by parents, a lack of public awareness of the vaccine, and inadequate vaccine supplies.[91]

To raise coverage, the MOH began to provide all neonates with free vaccine in 2002 under the National Plan for HBV Immunization,[92] but parents were still charged an injection fee (US$1.10).[15] Meanwhile, together with the Global Alliance for Vaccines and Immunization, the MOH initiated a project to provide free vaccination to all neonates in 12 western provinces and some less privileged areas in other provinces. A survey in 2005 of 11 of the western provinces showed that average timely birth-dose coverage increased to 88% among neonates born in township hospitals.[91] After this success in the western provinces, the Chinese government introduced a policy in 2005 to provide all vaccines listed in the National Immunization Program free-of-charge to all neonates and infants in the country. Thereafter, it was reported that HB vaccine coverage in neonates was maintained at nearly 95.0% in urban areas of the country and that coverage in most rural areas increased to between 83.5% and 96.5%.[91]

The current HB vaccination schedule in China is based on that of the Expanded Program on Immunization of the WHO.[93] The first dose is given within 24 hours of birth, and the second and third doses are given in the second and sixth months. This schedule is based on a report[94] indicating that

approximately 90% of vertical transmission can be prevented without using HB immunoglobulin if the first dose is given within 24 hours of birth.

6.2 National Plan for Prevention and Treatment of Hepatitis B, 2006–10

In early 2006, the MOH adopted the National Plan for Prevention and Treatment against Hepatitis B (NPHB) for 2006–10. The NPHB was a reflection of the Ministry's acknowledgment that hepatitis B was a critical health challenge affecting patients, their families, and society as a whole, and that control of the disease was still insufficient despite the success of the immunization program. The NPHB had 3 major objectives, namely, (1) to reduce carrier prevalence to lower than 1% among children aged 0 to 5 years, (2) to reduce carrier prevalence in the overall population to lower than 7%, and (3) to reduce carrier prevalence by 1% in provinces where carrier prevalence among all residents was already lower than 7%. To achieve these objectives, the NPHB established a surveillance and testing system for HBV, strengthened the immunization program, enhanced safe injection practice in medical and immunization services, promoted knowledge of hepatitis among general public, and trained health care workers. Progress in implementation of the NPHB was assessed annually and its activities were modified accordingly.

While vertical transmission of HBV was controlled by the HBV immunization program, the NPHB also proposed measures to control horizontal infection. Among these measures was prevention at home, including HBsAg testing before marriage and immunization for noncarrier spouses, promotion of condom use for carrier spouses, and immunization of all noncarrier family members in a household with a carrier.

As mentioned above, prevention of iatrogenic infection is very important in heath care settings; however, reports on the implementation of safe injection measures are limited. A 6-year interventional study in village clinics in Hebei province reported that, after training health practitioners in clinics and providing single-use injection materials, HBV carrier prevalence among 2-year-old children born to noncarrier mothers dropped to 2.1%; prevalence was 11.6% in a control group with no intervention.[32]

In heath care facilities, provision of safe blood is also important. We discuss this topic in the next section.

6.3 The blood banking system and promotion of safe blood provision

Because of the high prevalence of HBV and HCV and the increasing numbers of HIV carriers,[95] provision of safe blood is a critical issue in China. The Chinese Society of Blood Transfusion reported that 3.1% and 1.1% of all whole blood donors in China were seropositive for HBsAg and anti-HCV, respectively, in 1999.[96] We briefly describe the blood banking system, based on the limited literature written in English and Japanese by Chinese authors.

Until the 1970s, provision of blood in health care settings depended on paid donors recruited by each facility. During the Cultural Revolution, the availability of blood and its safety were further compromised due to social instability. To ensure a safe blood supply, a compulsory blood donation system for citizens was introduced in 1978, and a national standard for blood donor qualification and donation practices was implemented by the MOH for the first time.[97] The system, however, retained a partial payment system, due to the presence of a donation quota for each employer and an honorarium for donation. The acceleration of economic reforms in the 1990s was accompanied by an increase in the number of unlicensed private blood collection centers, some of which used unsafe blood collection methods. For example, non-sterilized needles were often reused and donors did not undergo HIV testing. Donor-to-donor transmission of blood-borne viruses also occurred in these centers due to pooling of blood from multiple plasma donors and returning of red cell components to each donor.[96] Among current HIV carriers in China (approximately 1.5 million in 2010),[95] approximately 10% of HIV infection is attributable to these unsafe blood collection and provision practices.[98]

To ensure a stable blood supply and safety in blood transfusion, the government passed the Blood Donation Law in 1998.[99] The provisions of the law include strengthening of a nonremunerated blood donation system, clarification of the responsibility of local governments to secure and promote safety in blood donation, establishment of blood donation and supply centers at each level of local government, and establishment of systems and regulations in blood donation/provision and clinical practice, such as donor qualification, a blood screening system, and standards for blood transfusion practice at health care facilities.

Based on the provisions of the law, the blood donation and banking system came under the authority of the health department of the central and local governments. A provincial central blood center, a city central blood station, and prefectural blood donation stations were established. As of 2000, 95% of the 3 levels of local governments for the whole country were reported to have established blood centers/stations, including 325 central blood stations at city level or higher.[97] The requirements for donors were defined as a healthy person aged 18 to 55 years weighing 50 kg or more for men or 45 kg or more for women. The minimum interval between donations was 6 months. Donated blood was required to be screened for hemoglobin concentration and packed-cell volume, ABO group, HBsAg, anti-HCV, ALT, anti-HIV1/2, and syphilis infection. With the introduction of the Blood Donation Law, the proportion of blood donated by volunteers for clinical use increased from 11% in 1996 to 67% in 2000.[96] This proportion is believed to be increasing in urban areas. In Shanghai, for example, 90% of all donors in 2007 were volunteers.[100] Also, a compensation system for patients infected with HCV through blood transfusion was established there in 1996.[101] According to a recent report, the volume of blood used for transfusion in China continues to increase as a result of the increasing amount of surgery, and blood shortages occur even in Beijing during winter and summer, when students, the major donor population, temporarily leave the capital.[98]

7. DISCUSSION

China has the largest population and one of the largest territories in the world. Its diversity in socioeconomic conditions, ethnicity, and culture has a considerable influence on disease characteristics. The incidence and mortality of hepatitis and HCC, and their epidemiologic patterns, vary across the country. Therefore, it is not possible to fully describe the characteristics of these diseases with data from only a few areas, and we must be cautious in interpreting these reports. The scientific literature on hepatitis and HCC in China has been increasing very rapidly in the past decades, but we need more time before a clearer national picture of the epidemiology of these conditions emerges. In addition, English-language reports and assessments of recently introduced projects or systems, such as the HBV vaccination program and the establishment of a blood banking system, are still scarce. Thus, we also need to accumulate more balanced information on these developments.

The national seroepidemiologic survey in 1992 provided valuable information on the prevalence and epidemiology of hepatitis virus infection in China. The report, however, had some limitations, including an inadequate description of its methodology, a lack of references to validate information sources, and the absence of confidence intervals for prevalence data. Moreover, the survey's finding of an apparent limited impact of the HBV vaccination program among cohorts born after 1988 casts doubt on the appropriateness of the sampling and testing methods. Nevertheless, the results were consistent with observations in other studies: (1) as described in section 2, HBV carrier studies in various parts of the country showed prevalences ranging from 5% to 20%, which are consistent with values from subgroup analyses in the national survey, (2) a study of carrier prevalence among 22 707 Taiwanese born in various provinces of the mainland[102] showed that the overall carrier prevalence of HBV was 15.2% (testing by RIA), with variation by native province and a higher prevalence among those born in southern provinces. Therefore, the survey results are probably sufficiently reliable in describing the basic epidemiologic trends in hepatitis virus infection in China as of the early 1990s.

The prevalence of HCV infection varied considerably across reports from different areas in China. Some areas showed that the prevalence of HCV infection was higher than that in Japan, the United States, and European Union countries, in which the average prevalence is typically below 3%.[103] This variability might represent not only real differences in prevalence, but also differences in sampling and testing methods. However, the main sources of HCV infection in China are believed to be iatrogenic transmission and injecting drug use, both of which are associated with transmission risks that vary greatly according to the distribution of unsafe medical practices and high-risk populations in the society. Thus, it is also likely that there is wide variability in true carrier prevalence across geographic areas and population subgroups.

A systematic review of the RR of HBV carrier state for the development of HCC in China showed a wide range of ORs (3.8–103.0). During the 1980s and 1990s, studies in Japan showed a similarly wide range (6.9–58.2).[104–107] These results are roughly comparable, but any assessment of risk in these 2 countries must take into account the differences in methodology, particularly in the sampling method and adjustment for confounding factors such as alcohol use, smoking, and HCV carrier status. The pooled OR of HCV carrier state for the development of HCC in China was somewhat lower (mOR: 8.1) than ORs reported in Japan (range: 9–101).[108–111] This divergence might have been caused by differences in average life span, distribution of HCV genotypes, and prevalences of other risk factors, including alcohol consumption, which is higher per person in Japan than in China.[112] Additional data and analyses are needed in both China and Japan to identify the causes for this difference.

In China, HBV is the most important risk factor for the development of HCC. Although the HBV immunization program is expected to greatly reduce HCC incidence, it will require a few more decades before we start to see an obvious decrease among the general population. With the high cost of the current antiviral therapy for chronic HB, HCC control among existing carriers depends on the reduction of risk factors that accelerate the development of HCC among carriers. Among the risk factors we reviewed, only smoking, aflatoxin exposure, and alcohol intake are preventable by intervention measures. However, not all HCC patients were exposed to these risk factors, and the importance of obesity, diabetes, and other potential risk factors for HCC among carriers has yet to be carefully assessed. We need additional evidence on risk factors in order to develop more effective plans for their reduction.

China is a very important field for studying the relationship between aflatoxin and HCC development, due to the endemicity of this environmental carcinogen and HBV. Studies cited in this review appear to have established a causal link between aflatoxin exposure and HCC, at least among HBV carriers. However, there is still limited evidence from human biological monitoring on the geographic distribution of aflatoxin contamination, although

contamination in agricultural crops is relatively well documented. Further studies are needed to assess the population attributable risk of aflatoxin contamination on the disease burden of HCC in China.

In addition to host (human) and environmental factors, viral characteristics are also important in the development of HCC. Among these characteristics, information on HBV genotype has rapidly accumulated in the past decades.[113,114] Data on genotype, however, are still difficult to obtain in population-based epidemiologic studies. Researchers need to consider the potential effects of genotype when interpreting the results of epidemiologic studies.

With the introduction of HBV immunization, control of HBV infection is substantially progressing in China, which will lead to a dramatic decrease in the disease burden from HBV infection and HCC. However, the national prevalence of HCV is not negligible, and some areas have a very high prevalence. The comparative disease burden from HCV infection is expected to increase as the proportion of HBV-immunized cohorts grows in the country. There is as yet no promising candidate for a vaccine against HCV, and the current standard treatment, interferon, is not affordable for the general population in China. Under these conditions, the only obvious measure to curb the disease burden from HCV infection is prevention of its transmission, particularly through the iatrogenic route. To clarify the epidemiology and disease characteristics of HCV infection and related HCC, further studies are needed. It might therefore be beneficial for China to consider cooperation with other countries that have been actively studying these diseases.

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Japan: Universal Health Care at 50 Years 1

What has made the population of Japan healthy?

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See Comment page 1051
See Series page 1106

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People in Japan have the longest life expectancy at birth in the world. Here, we compile the best available evidence about population health in Japan to investigate what has made the Japanese people healthy in the past 50 years. The Japanese population achieved longevity in a fairly short time through a rapid reduction in mortality rates for communicable diseases from the 1950s to the early 1960s, followed by a large reduction in stroke mortality rates. Japan had moderate mortality rates for non-communicable diseases, with the exception of stroke, in the 1950s. The improvement in population health continued after the mid-1960s through the implementation of primary and secondary preventive community public health measures for adult mortality from non-communicable diseases and an increased use of advanced medical technologies through the universal insurance scheme. Reduction in health inequalities with improved average population health was partly attributable to equal educational opportunities and financial access to care. With the achievement of success during the health transition since World War 2, Japan now needs to tackle major health challenges that are emanating from a rapidly ageing population, causes that are not amenable to health technologies, and the effects of increasing social disparities to sustain the improvement in population health.

Introduction

Japan has caught the attention of the rest of the world because of the tremendous success it has achieved in improving the health status of its population in the 20th century. The improving health status of the Japanese population was noted as early as the 1920s when infant mortality rates started to fall.[1] Increased child survival rates were partly possible then through the enhanced education and increasing literacy of mothers—in the early 20th century, with the provision of free compulsory education, almost all girls attended primary schools.[2] However, after World War 2, Japan showed its strength in improving the health of its population. The country was devastated after its defeat. Per person gross domestic product was roughly international $3400 in 1950 (table), which is similar to that in India today (Gakidou E, Institute for Health Metrics and Evaluation, personal communication). The health status of the population was also poor—in 1947, male life expectancy in Japan at birth was only 50 years and female life expectancy was 54 years.[3]

Rapid economic growth started in the late 1950s and life expectancy started to increase at an unprecedented rate. Within a few decades Japan had caught up with and eventually surpassed many other developed nations (figure 1; figure 2). Since 1986, Japan has ranked first in terms of female life expectancy at birth, with the highest ever recorded worldwide life expectancy of 86 years in 2009.[3] The country had also maintained the best healthy life expectancy at birth in 2007 (73 years for men and 78 years for women).[10] With a low rate of total fertility, the proportion of people aged 65 years and older has quadrupled during the past 60 years to 23% in 2010,[4] making the Japanese people the oldest population in the world. Despite the ageing population, Japan's health expenditure is only 8·5% of gross domestic product, which put it in 20th position in terms of expenditure among the countries of the Organisation for Economic Co-operation and Development in 2008.[6]

What has made the population of Japan healthy? How has Japan achieved the longest life expectancy at birth worldwide? Will the Japanese population continue to be healthy in the future? Understanding what has contributed to making the Japanese population healthy in such a fairly short period is important for global health policy, particularly for countries struggling to improve health. Several aspects of the Japanese lifestyle provide appealing explanations for the first two questions. First, Japanese people give attention to hygiene in all aspects of their daily life. This attitude might partly be attributable to a complex interaction of culture, education, climate (eg, humidity, temperature), environment (eg, having plenty of water and being a rice-eating nation), and the old Shinto tradition of purifying the body and mind before meeting others.[11,12] Second, they are health conscious. In Japan, regular health check-ups are the norm. Mass screening is provided for everyone at school and work or in the community by local government authorities. A systematic check-up of the whole body, referred to as a human dry dock (panel 1), is another type of health screening, which is popular among business people—they stay at clinics or hospitals for several days to undergo thorough physical examinations. Third, Japanese food has a balanced nutritional benefit, and the diet of the Japanese population has improved in tandem with economic development over the five past decades.[15,16]

Healthy lifestyle is, however, only one dimension of Japanese life. Japan is now struggling to deal with several major health challenges, which are partly attributable to the striking changes taking place in the demographic and social structures of its rapidly maturing society. The population is projected to shrink from 128 million in 2005 to 95 million in 2050, while the proportion of people aged 65 years or older is expected to rise to 40%.[17] Since the early 1990s, prolonged political stagnation and economic recession have helped induce a feeling of increasing inequality among this ageing population. Moreover, overweight or obesity is an increasingly serious problem, emanating from a shift towards a western-style diet and sedentary lifestyle. About a third of men aged 30–59 years are overweight or obese,[18] although the prevalence of adult obesity (4%) is well below that in other developed nations.[6]

Key messages

- The early establishment of free compulsory primary education and a social insurance system before World War 2 and universal health insurance coverage in 1961 enabled the provision of equal opportunities for health promotion.
- Disparities in health across regions and socioeconomic groups are fairly small in this homogeneous and egalitarian society and have narrowed over time with increased average population health. However, the downward trend in socioeconomic inequality in health has been less obvious since the 1990s, which has coincided with income inequality gradually increasing.
- Japanese life expectancy at birth increased rapidly in the 1950s and early 1960s as a result of decreased mortality rates for communicable diseases in children and young adults, which was largely attributable to the government's strong stewardship in investing in key interventions for public health.
- Stroke mortality reduction was one of the major drivers of the sustained extension of Japanese longevity after the mid-1960s. The control of blood pressure improved through population-based interventions such as salt reduction campaigns and an increased use of cost-effective health technologies such as antihypertensive drugs under universal health insurance coverage.
- Further progress in Japan's longevity primarily depends on prevention of major risk factors for non-communicable diseases such as tobacco smoking and high blood pressure and several cardiovascular risks. Prevention of premature mortality from suicide is also a major challenge for population health.
- A rapidly ageing population as a result of improved survival is challenging Japan's health system in terms of its financing and quality of care. An effective link between medical and long-term care through both top-down and bottom-up approaches is necessary to enhance the welfare of the population throughout the country.

	1950	1960	1970	1980	1990	2000	2005	2010
GDP per person (2005 international $)*	3415	6249	13734	18545	26926	29396	31129	31329
GDP growth rate (%)†	NA	12·0‡	4·3	2·8	5·6	2·9	1·9	−5·2§
Total population (×1000)¶	82199	93189	103710	115915	122251	125720	126393	126536
Population older than 65 years (%)¶	4·9	5·7	7·0	9·0	11·9	17·2	19·9	22·7
Total fertility rate¶	3·0	2·0	2·1	1·8	1·5	1·3	1·3	1·45
Female life expectancy at birth (years)‖	61·5	70·2	74·7	78·8	81·9	84·6	85·5	86·4
Male life expectancy at birth (years)‖	58·0	65·3	69·3	73·4	75·9	77·7	78·6	79·6
Total health expenditure (% of GDP)**	NA	3·0	4·5	6·4	5·9	7·7	8·2	8·5¶

GDP=gross domestic product. NA=not available. *Gakidou E, Institute for Health Metrics and Evaluation, personal communication. †GDP growth rate in 1961. ‡GDP growth rate for 2009. §Total fertility rate of medium-fertility variant estimate for 2010–15. ¶Total health expenditure for 2008.

Table: **Socioeconomic and demographic characteristics of people in Japan during 1950–2010**

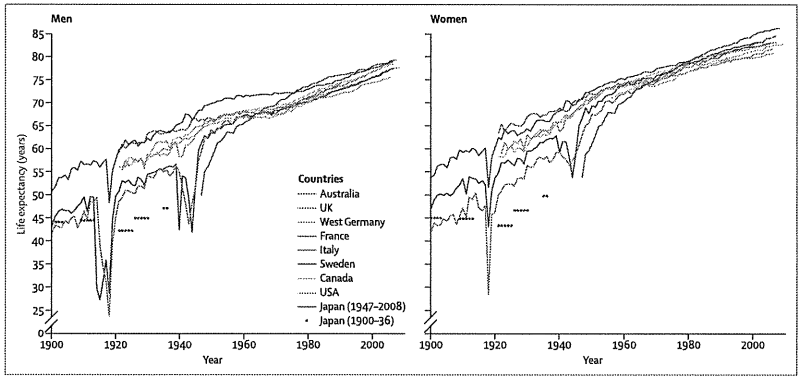

Figure 1: **Trends in life expectancy at birth, 1900–2008**
Data from University of California at Berkeley and Max Planck Institute for Demographic Research[3] and Ministry of Health, Labour and Welfare.[8]

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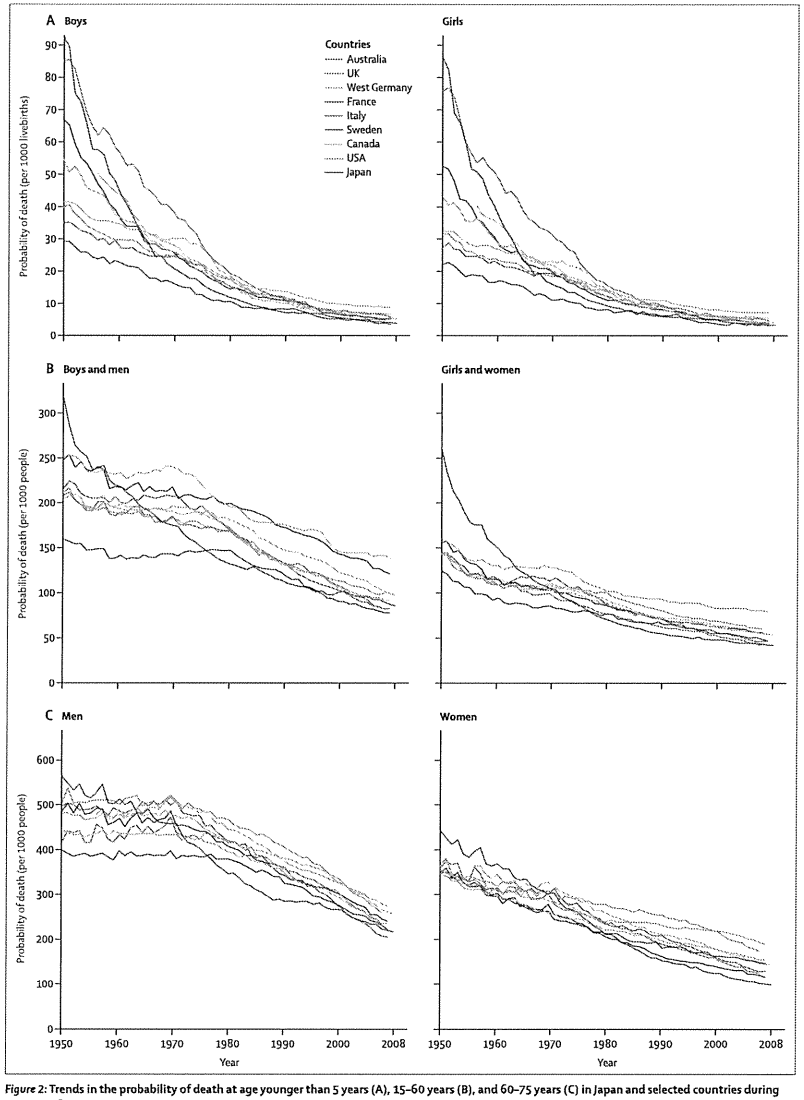

Figure 2: **Trends in the probability of death at age younger than 5 years (A), 15–60 years (B), and 60–75 years (C) in Japan and selected countries during 1950–2008**
Data from University of California at Berkeley and Max Planck Institute for Demographic Research.[1]

Furthermore, the working life of typical salaried workers in Japan seems anything but healthy—often working from early in the morning until late in the evening, 6 days a week. To relieve daily stress, some of them resort to negative health behaviours such as smoking tobacco and getting drunk after work, or even suicide in extreme cases. Death from overwork is also a serious social problem. In the context of these demographic and social challenges, what are the best strategies for Japan to protect the health and wellbeing of its ageing population?

In this first report in the *Lancet* Series, we focus on the improvements in the health of the Japanese population after World War 2. We review and analyse the best available data and evidence for population health in Japan to explore what has made the Japanese people healthy (panel 2). We provide an overview of Japan's population health in terms of the rates and distribution of mortality, and assess possible factors that might account for the longevity of the people in Japan. We also draw attention to the future challenges for Japan in controlling risk factors and social determinants to further enhance the health status of its population. We conclude with the global lessons that can be learned from Japan's experience over the past 50 years.

Mortality rates in infants and young adults

Most of the increase in longevity in Japan in the past 60 years happened during 1950–65. Life expectancy at birth increased by 10·1 years in men and 11·9 years in women during this time, and these increases accounted for almost 40% of the total increase during 1950–2010 (table). Much of the increase in longevity during this early period was indicative of an enormous reduction in mortality rates in children younger than 5 years and young adults. In 1950, the probability of death before the age of 5 years was greater than 80 per 1000 livebirths and was very high compared with the probabilities of death in other developed countries, but fell to about 20 per 1000 livebirths by 1965 (figure 2). The probability of death in individuals aged 15–60 years was also much higher than in other developed countries, but fell and was on a par with probabilities of death in some developed countries by 1965. Consequently, in the 1950s and early 1960s, lower mortality rates in children younger than 5 years accounted for an increase in male life expectancy at birth of 4·1 years and female life expectancy at birth of 4·3 years, whereas reduced mortality rates in adults younger than 60 years accounted for increases in life expectancies of 3·1 years in men and 4·0 years in women (webappendix p 3).

The health of children younger than 5 years improved greatly in 1950–65 through the control of intestinal or respiratory infections and vaccine-preventable diseases that occurred with a drop in the number of neonatal deaths. The age-standardised mortality rate for communicable diseases, other than tuberculosis, decreased by 90% in children younger than 5 years (webappendix p 7); the age-standardised mortality rates for neonatal illnesses fell from 990 per 100 000 boys to 173 per 100 000 and from 772 per 100 000 girls to 133 per 100 000 during 1953–70 (webappendix p 7). Reduction in mortality rates for infectious diseases, other than tuberculosis, in children younger than 5 years accounted for increases of 2·2 years in male life expectancies at birth and 2·4 years in female life expectancies at birth. The reduction in the mortality rate for neonatal illnesses increased life expectancy by 1·0 year in both sexes (webappendix p 3).

The effect of a reduction in the mortality rate for tuberculosis on the extension of life expectancy at birth in young adults was equivalent to the reduction in mortality rate for other infectious diseases in children younger than 5 years. A 95% reduction in the number of deaths from tuberculosis in adults (aged 15–59 years) in 1950–65 (webappendix p 8) contributed to the increase in life expectancy of 2·4 years in men and 2·3 years in women (webappendix p 3).

See Online for webappendix

These reductions in mortality rates in 1950–65 indicated increasing investment in the public health sector during

Panel 1: Human dry dock

The Ningen Dock (or human dry dock) is a comprehensive medical check-up system that is unique to Japan.[13] The Ningen Dock started in 1954 at a hospital in Tokyo. At that time, this service could only be afforded by business and political leaders because it took 6 days of consecutive stay in hospital and cost the equivalent of 3–4 months of a civil servant's starting salary. Advances in automated blood analysers and other testing apparatus reduced the costs, and the 1-day or 1-night stay has become the main type of service. About 3 million people per year are estimated to receive the Ningen Dock at about 1500 medical institutions in the country. A key factor that underpinned the rapid growth in the use of the Ningen Dock was that several companies covered the cost for their employees to ensure their good health.

The Ningen Dock emphasises the importance of a consultation and a post-examination interview. Over 1–2 days, clients undergo a series of medical examinations, such as blood, urine and faecal tests, radiography, and ultrasonography, and a consultation with a doctor about their medical history and lifestyle habits. After the examinations, the doctor explains the results and gives lifestyle advice to the clients.

The Ningen Dock might play a part in the primary prevention of cerebrovascular and cardiovascular diseases through the control of risk factors, such as obesity, hypertension, hyperglycaemia, dyslipidaemia, and hyperuricaemia. It might also be important for secondary prevention through the detection of diseases such as the early stages of cancer. The brain dock with MRI has expanded nationwide since it started in 1988.[14] There has also been a focus on using PET scans to detect the early stages of cancer. However, the cost-effectiveness of the Ningen Dock has been questioned.

Panel 2: Data sources and methods

Mortality trends

To assess trends in mortality rates in Japan since 1950, we used life tables and individual cause of death data that were obtained from different sources (Naghavi M, unpublished).[19,20] Life tables were obtained from the human mortality database at the University of California, Berkeley, CA, USA, and the Max Planck Institute for Demographic Research, Rostock, Germany.[7] We also obtained the individual cause-of-death data for 1950–2008 from the Ministry of Health, Labour and Welfare of Japan,[19] and the Institute for Health Metrics and Evaluation at the University of Washington, Seattle, WA, USA (Naghavi M, unpublished).[20] Japan has had a complete vital registration system since 1899. Although the gold standard is cause of death information from vital registration, a potential bias could be attributable to the inclusion of ill-defined codes (eg, cardiac arrest, heart failure, and senility) and unknown causes. With the algorithm developed by Naghavi and colleagues,[21] ill-defined codes and unknown causes on death certificates were redistributed and the consistency across revisions of the International Classification of Diseases and Related Health Problems (ICD) was checked. We assessed the causes that are amenable to medical care, which was originally proposed by Nolte and McKee,[22] extracting the major causes of death from the list (webappendix p 1), because the ICD avoidable causes of death were no longer applicable to our analysis after redistribution of ill-defined and unknown causes.

Health disparities

We assessed the trend in regional disparities in longevity with data for municipal life expectancy at birth at 5-year intervals during 1985–2005.[23] Municipalities are the smallest administrative units for which life expectancy data at birth are available in Japan. Sample sizes were 3307–3354 in 1985–2000 and 1963 in 2005. The substantial drop in the sample size in 2005 was due to the municipal mergers that were undertaken after 2000. We assessed temporal trends in socioeconomic disparities in the age-standardised all-cause mortality rate in the working population (aged 30–59 years), using vital records from 1980 to 2005. We used occupational status as a measure of the socioeconomic status of individuals. We standardised death rates per 100 000 at 5-year intervals using the Japanese population in 1985 as a standard population.[24] We obtained population data according to occupational status from tables reported in the national census that is undertaken every 5 years.[3,24]

demilitarisation and democratisation in the early post-war years in Japan. 32 health laws were enacted during the first decade after the war.[25] The Japanese Government collaborated with the American occupation forces in scaling up public health interventions at the community level.[26] Water supply coverage and key interventions for maternal and child health rapidly improved after the war (webappendix p 10). The effective provision of essential interventions for child survival, such as access to safe drinking water and institutional delivery, was mediated through a high level of maternal education and health facility provision that had already been achieved before the war.[27] Moreover, free treatment for tuberculosis started in 1952,[28] and included systematic screening with chest radiography and the use of streptomycin. The incidence of tuberculosis decreased sharply at a yearly rate of 11% between 1961 and 1977.[29] Additionally, as elaborated in the second report in this *Lancet* Series,[30] health insurance coverage, which was applied to about 70% of the population before World War 2, ensured access to new interventions such as drugs and vaccines for tuberculosis.

Mortality rates for non-communicable diseases

Even after communicable diseases had been successfully tackled, life expectancy of Japanese people continued to increase steadily. Male and female life expectancies at birth, respectively, increased by 5·7 years and 5·9 years during 1965–80, 3·0 years and 4·0 years during 1980–95, and 3·3 years and 2·9 years during 1995–2008 (figure 1). The risks of people dying at the ages of 15–60 years and 60–75 years fell, becoming one of the lowest in the developed world by 1980 (figure 2).

In 1950, mortality rates for cancers and ischaemic heart disease were already quite low in Japan compared with those in other developed countries, whereas the stroke mortality rate was very high. The age-standardised mortality rates for men with cancers and other neoplasms, ischaemic heart disease, and stroke were 163·8 per 100 000, 143·4 per 100 000, and 363·1 per 100 000, respectively, and for women 137·8 per 100 000, 124·8 per 100 000, and 326·5 per 100 000, respectively (webappendix pp 11–13). The low mortality rates for cancers and ischaemic heart disease in the early post-war years is one of the features of the health transition in the Japanese people. Although it is not known why the mortality rates for non-communicable diseases, other than stroke, were already low at this time, the reasons might be a favourable lipid profile and glucose metabolism, a generally low body-mass index, and other lifestyle factors relating to diet and low to moderate alcohol intake.[31] Indeed, the results of the Ni-Hon-San study[32,33] and the Honolulu Heart Program[34] showed that Japanese Americans (first-generation immigrants) were more likely to develop ischaemic heart disease and less likely to develop stroke than were Japanese people living in Japan, drawing attention to the importance of lifestyle rather than genetic background in determining the risk of disease.[32–34] The sustained increase in life expectancy at birth after the mid-1960s was largely attributable to reduced mortality rates for non-communicable diseases (webappendix p 4). From 1965 to 1980, reduced mortality rates in adults with these diseases had a substantial effect on increasing life expectancy. Reduction in the mortality rate for stroke in people aged 60–74 years increased male life expectancy at birth by 1·1 years and female life expectancy at birth by 1·0 years (webappendix p 4). Reduced mortality rate for stroke in women aged 75 years and older also accounted for a substantial increase (0·9 years) in female longevity.

The fall in stroke mortality rates slowed during 1980–95, while ischaemic heart disease mortality rates continued to fall steadily. Although not decreasing so rapidly as that of stroke, the mortality rate for ischaemic heart disease in adults aged 60–74 years nevertheless constantly decreased in this period (webappendix p 9). Consequently, although improved stroke mortality rates continued to be a major determinant of increased life expectancy, the effect of decreased mortality rates for ischaemic heart disease became pronounced during 1980–95, particularly in elderly women (webappendix p 5). Moreover, a reduction in the mortality rate in women aged 75 years and older had the largest effect on the increase in female life expectancy at birth, accounting for a change of more than 2 years (webappendix p 5). The distribution of the effects of change in mortality rate on increased longevity by age and cause of death was similar for both sexes during 1995–2008 (webappendix p 6).

An improved stroke mortality rate coincided with a reduction in average blood pressure that started in the late 1960s.[19,35,36] The numbers of deaths from stroke associated with high blood pressure have decreased over the past three decades.[37] Two factors that might be important in contributing to the falling trend in blood pressure in the population are the increased coverage of antihypertensive drugs in patients with hypertension and improved lifestyles that include reduced dietary salt intake.[38]

A population-wide approach with easy access to primary care as a result of universal health coverage has proved to be especially successful in reducing the incidence and prevalence of stroke.[39] The national government launched a strategy for the prevention and control of hypertension and stroke in 1969 and applied the strategy nationwide in 1982. This strategy included the measurement of blood pressure for screening high-risk populations, provision of national health insurance coverage for the clinical treatment of hypertension, and population-wide health education for reduction of dietary salt intake and improvement of other lifestyle-related factors. On the basis of this strategy, occupational health acts were enacted in 1972 and community health acts in 1982 to mandate the provision of programmes for primary and secondary prevention, including annual health check-ups. More than 70% of Japanese men aged 45–54 years have some form of health check-up at least once a year.[40]

A reduction in dietary salt intake has been very important for the health improvement of the Japanese population. Average salt intake among middle-aged men decreased from 30 g/day in the 1950s to 14 g/day in the 1980s.[41] Some aspects of a westernised Japanese diet, such as the improved preservation of food might have contributed to the reduction in dietary sodium consumption.[16] These results partly support the claim that both a population-based approach and subsequent advances in modern medical technologies with the scale-up of their access have made a substantial contribution to the improved life expectancy of the Japanese population.

Cultural background

Japan's success in terms of the increased life expectancy of its population is unlikely to have resulted solely from the achievement of good access to health care. Instead, other cultural background factors might be involved. Marmot and Smith[42] hypothesised that the way Japanese people relate to each other and groups might partly account for the longevity of the Japanese population.[42] Results of previous studies have lent support to this hypothesis because strong ties in Japanese communities seem to be associated with improved outcomes in mental health, dental health, and physical functioning, while buffering against the adverse effects of income inequality.[43] More than 50 years of peace and political stability might also have contributed indirectly to Japan's success in population health.

Health inequality

The homogeneous and egalitarian nature of Japanese society is shown in terms of strong educational policies, formal and informal regulations that ensure employment security, and universal access to health care. Disparities in life expectancy at birth between prefectures had started to decrease before World War 2 and continued to decline steadily until they were very low in the 1970s.[2] Indirect evidence suggests that people living in prefectures in the northeast of Japan might have shorter life expectancies than do those living in the prefectures in the southwest.[44] This geographical gradient might be attributable to differences in risk profiles such as a higher prevalence of hypertension and diabetes in the northeastern prefectures that are related to lifestyles, health-care resources, and socioeconomic status. Our additional analysis showed that the variability in life expectancy at birth across municipalities remained low from 1985 to 2005—standard deviations of longevity changed by about 1·0 for male life expectancy and 0·8 for female life expectancy, and were small compared with 2·0–2·5 and 1·5–2·0, respectively, for counties in the USA.[45]

Gaps in all-cause mortality rates for men in different occupational groups were reduced from the early 1960s to the late 1980s, except for workers in the service industry and those working in the agriculture, fishery, and forestry industries.[2] An additional analysis we undertook showed that the downward trend in socioeconomic disparities in mortality rates continued in the early 1990s, and the mortality rates for managers and professionals rose in the late 1990s, which coincided with the Asian financial crisis in 1997 (webappendix p 14).

The rapid reduction in mortality rates in Japan might have been partly attributable to the narrowing gap in income during the period of high economic growth in the 1960s and 1970s.[42] By the 1990s, more than 90% of

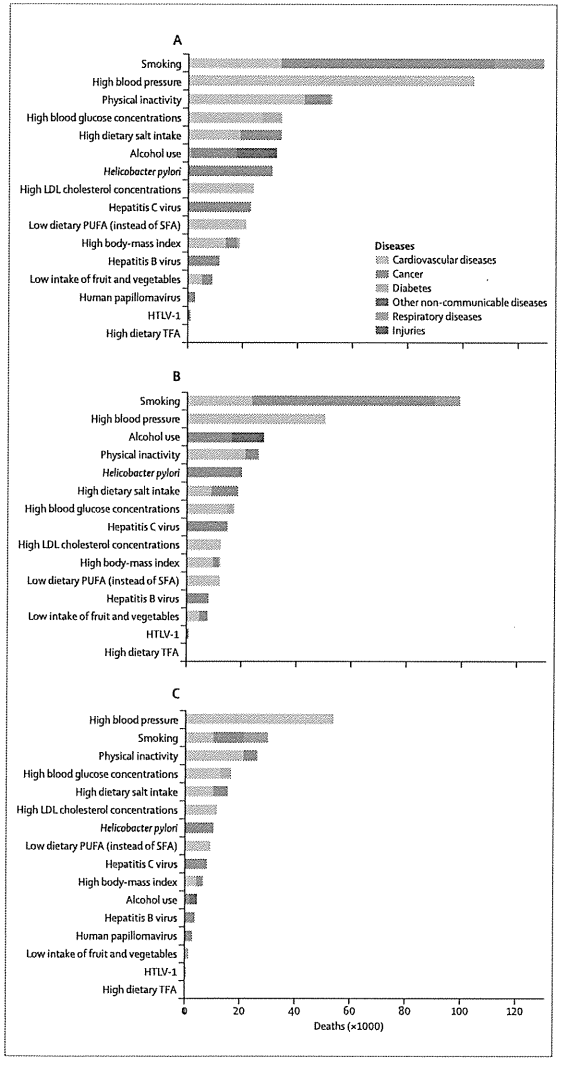

Figure 3: **Deaths from non-communicable diseases and injuries that were attributable to risk factors in Japan in 2007**
(A) Both sexes. (B) Men. (C) Women. Data from Shibuya.[37] PUFA=polyunsaturated fatty acids. SFA=saturated fatty acids. HTLV-1 =human T-lymphotropic virus type 1. TFA=trans fatty acids.

people believed that they were middle class.[46] However, this belief might no longer be applicable. During the past two decades, Japan has had economic recession. Income inequality has increased to match the average for the member countries of the Organisation for Economic Co-operation and Development,[47] which accords with reports suggesting widening health disparities in recent years,[48] despite the decreasing trend and fairly small health disparities until the 1990s.[2]

Challenges for Japanese population health

Increase life expectancy

Cancer, heart disease, and cerebrovascular disease are the three leading causes of death in Japan, accounting for more than 50% of the risk that a person at age zero will die in the course of their lifetime.[5] To strengthen the extension of Japanese life expectancy, mortality from these non-communicable diseases must be prevented. Although the use of advanced medical technology is a promising strategy for improving survival, modifying the profile of the underlying population risk factors is also important to ensure a long-term increase in population health.

A comparative assessment of preventable risk factors in Japan showed that tobacco smoking and high blood pressure were the two distinctive determinants of adult mortality from non-communicable diseases in 2007 (figure 3).[37] Of 834 000 deaths from non-communicable diseases and injuries, the exposure to tobacco smoking in terms of smoking impact ratios accounted for 129 000 deaths, whereas high blood pressure accounted for 104 000 deaths. A similar estimate of the number of avoidable deaths from tobacco use was reported in a pooled cohort study of the current smoking status.[49] The comparative risk assessment also showed that male life expectancy at birth would have been extended by 1·8 years and female life expectancy at birth by 0·6 years if all adults abstained from smoking; and by 0·9 years for both sexes if the systolic blood pressure was reduced to a pressure that resulted in minimum harmful effects in the population.

Tobacco smoking has a striking effect on population health in Japan. Despite its well known harmful effects, smoking is still commonplace—about 50% of young men smoke—and the rate has been gradually increasing among young women.[18] The Health Promotion Law was enacted in 2003 to support the prevention of smoking and passive smoking in public places. Although compliance with this national tobacco control legislation has improved, disparities still exist in the progress of tobacco control policy across local governments,[50] and no mandatory clean air law has been passed nationally. The retail price of the most popular brand of cigarettes was only US$3·3 in 2008, much lower than the average price in high-income countries ($5·0).[51] These circumstances, favouring smokers, show to some extent that tobacco tax was one of the most important sources of revenue for the government in the past.[52] Further, the rate of mortality attributable to this risk factor has increased in recent decades because of the accumulation of negative health effects in the older population.[37] Without effective policy interventions, the rate of mortality from tobacco smoking will continue to rise in the coming decades. A renewed emphasis on tobacco control, especially through its pricing mechanism, is necessary to discourage the consumption of tobacco products and promote smoking cessation.

Despite the decline in population blood pressure in the past four decades, the management of blood pressure is still not satisfactory in Japan. Blood pressure is effectively controlled with drugs in less than a fifth of the population with hypertension.[37] Additional efforts in the community and clinical practice in terms of early detection, lifestyle modification, and the effective treatment coverage of high blood pressure have the potential to extend life expectancy through a reduction in the mortality rates for cardiovascular diseases. In relation to this, strengthening adherence to standard clinical guideline recommendations[53] in general practice through continued medical education could be the key to increasing the effective coverage of outpatient services and to ensure the compliance of patients, as discussed in the third report in this Series.[54]

A large improvement in population health is still possible through the reduction of several risk factors for non-communicable diseases, such as high concentrations of blood glucose, physical inactivity, alcohol use, overweight and obesity, and high dietary salt intake. The control of several cardiovascular risks could also increase longevity for both sexes by reducing the risk of death.[37] A comprehensive prevention package is needed to lower the combined effects of several risk factors or metabolic syndrome, including the improvement of lifestyles and diet, and to increase the coverage of antihypertensive drugs. This package would be particularly relevant in the current obesity-friendly environment in Japan because, although lifestyle changes generally seem to matter more than do genetic factors, evidence suggests that the Japanese might be genetically more susceptible to being overweight or to developing diabetes mellitus.[55,56] Since 2008, in response to soaring health costs, the government has made it obligatory for people aged 40–74 years to have an annual check-up and a health education intervention that is focused on the prevention of metabolic syndrome,[57] although the effectiveness of health check-ups is not known in Japan.

Japan, similar to other east Asian countries, has many cancer-associated deaths from infectious causes.[58] Infections with hepatitis C virus and *Helicobacter pylori* account for many of the deaths from cancer.[37] In 2007, *H pylori* infection was the cause of 31 000 deaths from gastric cancer. Infection with hepatitis C virus was associated with 23 000 deaths from liver cancer, with clustering in people aged 70–79 years—ie, individuals born in the 1930s. Chronic infection with hepatitis C virus plays a major part in the cause of hepatic carcinoma in Japan.[59] A decreasing prevalence of infections with hepatitis C virus after the birth cohort of about 1935 suggests that the disease burden of this virus will decrease in the future. The fairly high prevalence of *H pylori* is similar to that of stomach cancer.[58] However, a fall in the prevalence of *H pylori* infection has been noted in people born after 1955,[60] which indicates a future reduction in the burden of gastric carcinoma attributable to this risk factor in Japan.

Prevention of suicide

Suicide prevention is another challenge for population health in Japan. Suicide rates contribute to premature mortality rates and profoundly affect society—by 2006, an estimated 3 million people had lost a loved one to suicide in Japan.[61] The number of suicides has been greater than 30 000 every year since 1998, when a sharp rise was recorded from the previous year (figure 4).[62] Roughly 70% of people who commit suicide are men and 50% are unemployed, and 40% of suicides in men are in individuals aged 45–64 years.[63] Major motives for suicide among working age men include psychiatric disorders such as depression, business failure, unemployment, and debts.[64]

The trends in suicide mortality rates might be associated with the increasing economic and social insecurity resulting from a stagnating Japanese economy since the beginning of the 1990s, especially in response to the Asian financial crisis in 1997.[65] The unemployment rate in the working age male population rose from 2·0% in 1991 to 3·4% in 1997 and then up to 5·5% in 2003.[66] Additionally, the work environment has greatly changed because of the easing in employment contract regulations in the late 1990s.[67] The employment pattern has shifted from the permanent employment that underpinned high economic growth in the past. The percentage of non-regular workers among male employees has increased from 9% in 1991 to about 19% in the late 2000s.[66] The government has responded to the suicide epidemic with a comprehensive strategy (ie, the Comprehensive Suicide Prevention Initiative[68]) that follows on from the Basic Act for Suicide Prevention, which was enacted in 2006, although its effect is not yet notable.

Reduction in morbidity and disability

Do Japanese people not only live longer but better in terms of their physical and psychological functioning? Globally, evidence suggests an increasing prevalence of morbidity in accord with the ageing population, while disability has been falling.[69] In Japan, research suggests that trends in disability prevalence differ between the young elderly (65–74 years) and the oldest old (≥85 years). For example, falling disability rates for those aged 65 years and older were recorded during the 1990s in a nationally representative sample of the Japanese elderly

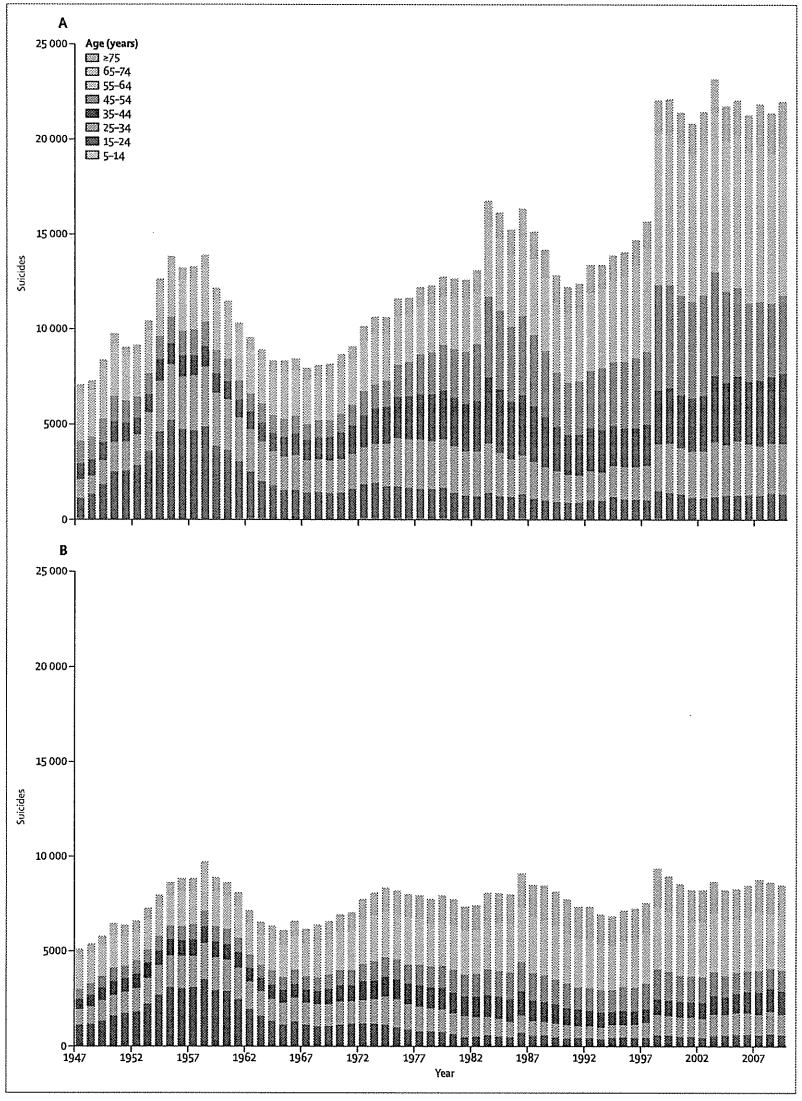

Figure 4: **Deaths from suicide by age in Japan, 1947–2009**
(A) Men. (B) Women. Data from the Ministry of Health, Labour and Welfare.[62]

population,[70] whereas increasing rates were reported for centenarians in other studies.[71,72] National health interview survey data have been used in studies to show that the functional health status of the Japanese people deteriorated during 1995–2004;[73] and morbidity rates decreased from 1984 until 1995, but the trend reversed in the late 1990s until 2004.[74] However, self-reported data were used for a few of the health domains in these studies. The survey questions and response categories are not detailed enough to obtain a reliable measure of the non-fatal health status of the population. Therefore, the national information infrastructure needs to be urgently improved to gather valid, reliable, and comparable data for the rates of disability and morbidity in the Japanese population.

Medical and long-term care

An unprecedented and unexpectedly steep reduction in mortality rates in older age groups[75] is contributing to the rapid increase in remaining life expectancy in Japan. The country has shown the most rapid increase in remaining life expectancy over the past six decades. For Japanese women, life expectancy at age 60 years increased from 16·4 years in 1950 to 28·1 years in 2007 (webappendix p 2), while life expectancy at age 80 years also increased substantially from 5·5 years to 11·4 years (webappendix p 2). The stagnating rate of increase in remaining life expectancy in other developed countries during the past two decades draws attention to Japan's exceptional improvement in life expectancy at older ages.

The nature of health care is also changing in this ageing society. The proportion of deaths resulting from illnesses that are no longer amenable to medical care, and Japanese society's concern about health have been increasing. A close link between medical care and long-term care should be further promoted to enhance population wellbeing and will be elaborated further in the fourth report in this Series.[76]

Global lessons

The experience of post-war Japan suggests that countries with low socioeconomic development can achieve progress in terms of their population health. Japan's national income was low in the beginning of the 1950s, when a tremendous increase in life expectancy at birth started largely as a result of the scale-up of the coverage of essential child survival interventions and provision of free treatment for tuberculosis. The main driving force for improved population health during this period was undoubtedly the strong stewardship of the new Japanese Government in implementing major structural reforms in the health sector and placing priority on investment in key interventions for public health in the early phase of economic growth.

The path towards universal coverage should be encouraged globally. Stroke mortality reduction was a major determinant of the sustained extension of the longevity of the Japanese population after the mid-1960s. The control of blood pressure improved with population-based interventions such as salt reduction campaigns and an increased availability of anti-hypertensive drugs through universal health insurance coverage. A reduction in mortality rates can be brought about by the interplay of improvements in both medical care and other societal factors (eg, income, education, nutrition, and sanitation). In turn, this reduction can vary by individual, place, and disease type.[77,78] A recent assessment of worldwide adult mortality rates[79] identified three important factors—socioeconomic development, increased access to health care and the progress in health technologies, and the diseases of affluence. Universal coverage is one of the most important factors and is essential in enhancing access to cost-effective health care at affordable prices that has indirectly contributed to the longevity through reduced cardiovascular-associated mortality rates in Japan. The lessons learned from the challenges and successes of population health in Japan lend support for the implementation of the current global health strategies to develop domestic health financing and risk-pooling mechanisms through health insurance and to scale up cost-effective interventions.[80]

Health disparities across regions and socioeconomic groups are quite small in this egalitarian society and have narrowed over time with increasing average population health. The establishment of free compulsory primary education early in the 20th century, a social insurance system before the war, and universal health insurance coverage in 1961 enabled the provision of equal opportunities for health promotion. These experiences confirm that working on population averages is not enough. Countries that have the least regional or socioeconomic disparity in longevity tend to be those in which the populations enjoy the longest life expectancies in the world.[69] Globalisation and rising economic disparity contribute to health inequalities and are increasingly causes for concern in many countries, and Japan is no exception. The goals of a health system include not only improvement of the averages but also reduction of health inequalities to a minimum.[81] By doing so, countries could accomplish what Japan has achieved.

Japan now has challenges for population health that many other countries will have soon. Further progress in terms of longevity in Japan is dependent on the prevention of major risk factors for non-communicable diseases such as tobacco smoking, high blood pressure, and metabolic syndrome. Prevention of premature mortality from suicide is another major issue requiring a comprehensive societal response that involves, for example, stabilisation of the labour market, and improvement of the promotion and provision of mental health services.[82] The rapidly ageing population as a result of improved survival also challenges financing and quality of care in Japan's health system.[30,54,76] The tsunami and nuclear crisis caused by the

magnitude 9·0 Great East Japan Earthquake on March 11, 2011, might also affect future population health, which will need to be monitored and assessed. How should Japan respond to these challenges? Policy options to tackle the challenges are addressed in the other five reports in this *Lancet* Series on Japan, which we hope will serve as a guide that will help other countries to develop policies that fit their specific circumstances. Indeed, this Series will draw attention to how Japan is unique in overcoming different and changing population health challenges in the past 50 years to achieve population longevity, and how the country's experience can be an important resource for the global health community and could transcend geographical, social, cultural, and political boundaries for understanding and helping enhance population health worldwide.

Contributors

All authors contributed to the study concept, design of the report, data analysis, and interpretation of the results. NI, ES, NK, and KS wrote the first draft. MI, HI, and ME did a systematic review. NI, ES, NK, HI, SI, TS, AS, and KS contributed to drafting and critical revision. All authors contributed to the discussion and have seen and approved the final version of the report.

Conflicts of interest

We declare that we have no conflicts of interest.

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Original Article

Demonstration of quality of care measurement using the Japanese liver cancer registry

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Aim: Despite advances in medical therapy, studies have reported gaps between current evidence and actual practice in many areas of medicine. Process-of-care quality indicators (QIs) are tools to measure the evidence–practice gap. This study aims to examine the feasibility of applying QIs for liver cancer care to the national registry database operated by the Liver Cancer Study Group of Japan.

Methods: Prior research developed a set of process-of-care QIs developed on the basis of the Japanese Clinical Practice Guidelines for hepatocellular carcinoma. Each QI describes target patients and care processes indicated for such patients. Among the 25 developed QIs, six appeared scorable using the information contained in the dataset from the 17th Nationwide Survey of Primary Liver Cancer.

Results: In total, 16 187 patients were eligible for the six QIs for 34 599 times, among which the indicated care was provided 83.9% times. The scores ranged from 64.4% (surgical therapy in patients with HCC 3–5 cm in diameter) to 91.1% (indocyanine green checkup before surgical resection). The information was generally available to determine eligibility (78.3%–100%) and pass/fail (91.9%–99.9%) for the QIs.

Conclusions: Applying QIs to the liver cancer registry, the quality of hepatocellular carcinoma care can be measured. In future, providing feedback regarding the results to the participating society may improve the quality of liver cancer care nationwide.

Key words: cancer registry, hepatocellular carcinoma, quality indicators, quality of health care.

INTRODUCTION

LIVER CANCER IS the third leading cause of cancer deaths worldwide.[1] Eastern countries generally exhibit higher incidences of liver cancer, but many Western countries have experienced a steady increase.[2,3] Liver cancer is prevalent in Japan, and it was the fourth leading cause of cancer deaths in 2009.[4] Despite recent advances in diagnostics and therapeutics, the 5-year survival rates based on population-based cancer registries remains relatively low at 23.1%.[5]

To improve survival, both medical therapeutic advances and their dissemination into clinical practice are necessary. To distribute current knowledge and facilitate clinical decision making for liver cancer treatment, the first evidence-based Clinical Practice Guidelines for Hepatocellular Carcinoma in Japan were published in 2005 with financial support from the Ministry of Health, Labor, and Welfare.[6,7] A follow-up survey of specialists and generalists involved in liver cancer care demonstrated successful outreach and acceptance of these guidelines among frontline practitioners of hepatocellular carcinoma (HCC) care.[8]

The next step in monitoring the effectiveness of the HCC clinical practice guidelines is the assessment of the quality of care. Although the quality of care can be assessed by structure, process, and outcome,[9] an evaluation of the process best fits the context of guideline implementation. Quality assessments that examine the processes of care compare the actual care provided to the patient against the pre-specified standards of care. Although standards may not exist for all aspects of care, examining how well the standards are incorporated into daily practice in those areas that do exist can reveal aspects of quality and create a basis for improvement. In addition, gaps in the process quality highlight areas for the guideline committee to focus on in the next round of revisions. Accordingly, we developed a set of process quality indicators (QIs) that describe standards for HCC patient care.[10,11] Although the QIs were designed to be implemented through the review of medical records, some QIs can be used on the Nationwide Survey of Primary Liver Cancer – the liver cancer registry operated by the Liver Cancer Study Group of Japan. This provided a unique opportunity to pilot test the QIs and examine certain aspects of the quality of care of some liver cancer patients in Japan.

METHODS

Development of the QIs

THE QIS WERE developed using Japanese HCC guidelines, adopting the RAND/University of California, Los Angeles appropriateness methods.[12] Details of processes and results were previously reported in Japanese.[11] Briefly, we first created candidate QIs based on the recommendations of the Japanese HCC guidelines and the medical literature. Each QI described the care standards defining target patients and indicated the care processes. From a literature review, we summarized the rationale for each candidate QI.

Next a nine-member multidisciplinary panel was convened that consisted of two hepatobiliary surgeons, three hepatologists, a gastrointestinal surgeon, a general internist, and two interventional radiologists. The panel members were nationally recognized clinicians from various practice settings, including the university and general hospital settings. The geographic distributions of the clinical practices were also taken into account.

The panel examined candidate QIs by following the modified Delphi process that consisted of two rounds of anonymous rating of the validity (scale of 1–9; 1 = definitely invalid, 9 = definitely valid) coupled with a face-to-face group discussion between rounds. During the process, the panel was allowed to modify the QIs. As per prior studies, QIs that had a median rating of 7 or higher and were rated 3 or lower by two or fewer panelists in the second ratings were accepted.[12,13]

Liver cancer registry database

The Liver Cancer Study Group of Japan operates the Nationwide Survey of Primary Liver Cancer in Japan, which is a cancer registry specifically for liver cancer.[14] Biannually, it collects 178 data items from the newly treated primary liver cancer patients and 46 items for following the previously registered patients. Participation is voluntary and is estimated to cover approximately 20% of all primary liver cancer patients in Japan.[15] We used data on patients receiving therapy for liver cancer at 645 participating institutions during 2002 and 2003. The data consisted of detailed clinical information and included the patients' baseline conditions, imaging findings, treatment modality, and pathological findings. Here, we have limited our analysis to HCC patients ≥20 years of age and have excluded patients who lacked age or diagnosis information.

Quality scores

The expert panel process resulted in 25 QIs,[11] which targeted a wide range of care processes including the pre-therapeutic evaluation, treatment choice, patient explanation of the treatment and results, and follow-ups. Of the 25 QIs, six could be scored using the information in the Liver Cancer Registry Database (Table 1). Patients were eligible for QIs if they met the criteria described in the denominator, and they were considered to have "passed" the QI if they received the care processes stated in the numerator. The quality score was calculated for each QI as the percentage of "passed" patients among those eligible. For example, the first QI in Table 1 was scored as the percentage of the patients whose alpha-phetoprotein (AFP) and protein indiced by vitamin K absence -2 (PIVKA-2) levels were measured before treatment (numerator) among those who were diagnosed with hepatocellular carcinoma (denominator). When necessary information was unavailable (i.e. either missing or coded as "unknown" in the dataset),

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Table 1 Quality indicators (QIs) applied to the liver cancer registry, quality scores, and data completeness

Denominator (target patients)	Numerator (standard care processes)	*n*	Quality score (%)	Data availability (%)	
				Denominator	Numerator
Tumor marker before initiation of therapy					
Patients who were diagnosed with hepatocellular carcinoma (HCC)	AFP and PIVKA-2 levels were measured before treatment†	16 187	82.3%	100%	94.3%
ICG check-up before surgery					
Patients who underwent surgical resection of HCC for the first time	15-min ICG retention rate was measured before treatment†	4 802	91.1%	99.2%	94.6%
Local therapy for new HCC (≤3 cm)					
HCC patients with liver damage class A, having three or less tumors of 3 cm or smaller in diameter	Surgical resection or percutaneous local ablation therapy (PEI, MCT, or RFA) was performed.	3 934	76.9%	78.3%	99.5%
Surgical therapy for new HCC (3–5 cm)					
HCC patients with liver damage class A having a solitary tumor of 3–5 cm in diameter	Surgical resection was performed.	1 029	64.4%	78.3%	99.9%
TACE indication					
HCC patients with Stage IVa or earlier, Vp 0–2 and Child–Pugh class A or B, in whom surgery and percutaneous local ablation therapy were not possible (patients who did not receive surgery or percutaneous local ablation therapy within 3 months after diagnosis)	TACE was performed.	3 741	84.5%	82.0%	99.9%
Documentation of after surgical resection					
HCC patients who received surgical resection	Medical record (including pathological report) documented the degrees of vascular invasion‡ and tumor differentiation was postoperatively determined.	4 906	81.4%	99.5%	91.9%

†Timing of the measurement was uncertain because the date of the test was not present in the registry.
Whether surgical resection was the first-line therapy was unclear because the registry did not distinguish the first-line therapy from subsequent therapies. ‡Includes invasion to the portal vein (vp), hepatic vein (vv), hepatic artery (va), and bile duct (b).
HCC, hepatocellular carcinoma; ICG, indocyanine green; MCT, microwave coagulation therapy; PEI, percutaneous ethanol injection; RFA,radiofrequency ablation; TACE, transarterial chemoembolization.

we treated the patients as follows: if QI eligibility information (applicability to the denominator) was missing, we excluded the patients from the denominator; if the information needed to determine the "pass" or "fail" status (the numerator) was unavailable, we considered that the care was not provided, and thus, the patient was counted as "fail" on the QI.

To evaluate the feasibility of applying these QIs to the liver cancer registry, we examined the completeness of the data to determine patient eligibility (the proportion of patients having all data items necessary to examine the denominator criteria [i.e. target patients]) and pass/fail (the proportion of patients having all necessary data items among all eligible patients) for QIs. Because the analysis revealed that the liver damage classification of the Liver Cancer Study Group[16] was the most frequently missing information, we further evaluated the usability of Child–Pugh classification to substitute for the liver

damage classification by examining the agreement between the two classification systems among patients with both sets of data. Because the QIs that target treatment choice focused on patients with class A liver damage, we calculated the sensitivity and specificity of the Child–Pugh class A in predicting liver damage class A. All of the statistical analyses were performed using STATA 11.1 (College Station, TX, USA). The study protocol was approved by the institutional review board of the National Cancer Center of Japan.

RESULTS

Sample characteristics

IN TOTAL, 16 187 patients were included. Table 2 presents the sample characteristics. The mean age of patients was 67 years (71.6% male). Approximately 50% of patients had liver damage of class A and 50% had solitary tumors. Similar numbers of patients underwent surgery, percutaneous local ablation, and transcatheter arterial chemoembolization (TACE).

Table 2 Sample characteristics

	n (%)
Age, mean (SD)	67 (SD = 9.4)
Male *n* (%)	11 592 (71.6%)
Liver damage class	
A	8089 (50.0%)
B	4439 (27.4%)
C	1058 (6.5%)
Unknown/No response	2601 (16.1%)
Child–Pugh class	
A	10 585 (65.4%)
B	3444 (21.3%)
C	867 (5.4%)
Unknown/No response	1291 (8.0%)
Number of tumors	
1	8970 (55.4%)
2	2727 (16.9%)
3	1198 (7.4%)
>3	3733 (15.7%)
Unknown/No response	757 (4.9%)
Tumor diameter (cm), mean (SD)	4.1 (4.0)
Primary treatment modality	
No treatment	1238 (7.7%)
Surgical resection, transplantation	4895 (30.2%)
Percutaneous local ablation	4733 (29.2%)
TACE	4423 (27.3%)
Systemic chemotherapy	718 (4.4%)
Other treatment	110 (0.7%)
No answer	70 (0.4%)

SD, standard deviation; TACE, transarterial chemoembolization.

Table 3 Cross-tabulation of Child–Pugh and Liver damage classes

CP	LD				
	A	B	C	Unknown	Total
A	7729	1813	35	1008	10 585
B	131	2445	290	578	3 444
C	6	56	693	112	867
Unknown	223	125	40	903	1 291
Total	8089	4439	1058	2601	16 187

CP, Child–Pugh classification; LD, liver damage.

Quality scores

On average, quality indicators had 5767 patients applicable, and overall the indicated care processes were provided 83.9% of the time. Table 1 presents quality scores and data completeness for each QI. The score was lowest for the QI "Surgical therapy in patients with HCC 3–5 cm in diameter" (64.4%) and highest for the QI "Indocyanine green (ICG) checkup before surgical resection" (91.1%). Although the availability of data for denominators ranged from 78.3% to 100%, information for numerators was available for more than 90% of patients for all QIs. QIs that use liver damage classification, tumor number, and tumor size were least commonly available for the denominator (78.3%). Liver damage classification, tumor number, and tumor size were missing or unknown for 2601 (16%), 757 (4.7%), and 1134 patients (7.0%), respectively.

Distribution of liver damage and the Child–Pugh classification

Table 3 presents the analysis of the concordance between Child–Pugh and liver damage classifications. These two classification systems agreed in 82.3% of patients for whom sufficient data were available. Child–Pugh A could predict liver damage class A with 98.3% sensitivity and 65.3% specificity.

DISCUSSION

WE HAVE DEMONSTRATED that certain aspects of the quality of care for patients with liver cancer can be measured using the liver cancer registry operated by the Liver Cancer Study Group of Japan. To our

knowledge, this was the first study to measure the quality of care for HCC. Standardizing the care process is challenging given the complexity of HCC care, as a range of treatment modalities from surgical resection to percutaneous and transcatheter therapy exists. The choice of treatment is influenced not only by the cancer stage but also by the baseline liver function. The QIs in this study, developed by the consensus of clinical experts, examined the actual care provided against the standards of pretherapeutic evaluation, the collection of pertinent tumor information, and treatment choice. The quality scores were high for most of the QIs, but there was also room for improvement. Although not all of the QIs developed were used for this analysis, we believe that the identification of a focus for improvement is an important initial step.

The information available in the registry was sufficiently complete for quality measurements to be made. Although information required to determine eligibility for QIs was occasionally missing, the information required to assign each QI a "pass" or "fail" status was generally available, which indicated little ambiguity in the scoring of the eligible patients. Among the missing information, the liver damage classification was the most frequently missing, presumably due to the lack of the ICG test. Although the liver damage classification was used for the QIs that focused on treatment choice in accordance with the Japanese Clinical Practice Guidelines, alternative criteria would be necessary to review actual practices. The comparison of the Child–Pugh class and liver damage class, however, revealed that the former underestimated the liver damage. For example, the Child–Pugh class A includes patients with more severe disease and is broader than liver damage class A. This result was expected, as the prothrombin criteria threshold is lower for the Child–Pugh classification.[16] Furthermore, this is consistent with a previous report that reviewed the medical records of the HCC patients.[17] If the Child–Pugh classification is used in place of the liver damage classification for the patients whose liver damage classification data are missing, the QIs targeting patients with liver damage class A would also include a broader group of the patients with liver damage class B or C. Thus, caution should be exercised when using these liver function classifications interchangeably.

For other types of cancer, we have a predecessor on using the national database for quality measurements and feedback. In the National Cancer Database, the Commission on Cancer of the American College of Surgeons measured six QIs (three for breast cancer and three for colorectal cancer) and provided feedback regarding the scores of the individual participating facilities and the distribution of these scores among other facilities.[18] This program is now developing the Rapid Quality Reporting System, in which the facilities submit and update the information continuously and the quality of care is monitored in real time. Our study indicates that the same service is theoretically possible in Japan using the liver cancer registry.

Some limitations must be considered when interpreting the results of the current study. First, the QIs that examined the appropriate documentation of vascular invasion and tumor differentiation were scored based on the availability of data in the dataset rather than on the actual medical records. This may underestimate or overestimate the quality scores for these QIs. Underestimation occurs when physicians keep appropriate documentation but fail to enter that information into the dataset, and overestimation occurs when physicians enter the information into the dataset but fail to document it in the medical record. Accordingly, caution must be exercised while interpreting these scores. Second, quality assessment requires the consideration of exceptional cases. For example, in some cases where a QI indicated surgery, surgery may not be appropriate due to compromised cardiac or respiratory functions. As the database does not contain information on the reasons why surgery was not performed, it is possible that patients who were appropriately excluded from surgery may be labeled as having received poor quality care. Hence, the results of the measurements of quality from the database should be regarded as starting points for discussions of quality and not as the final conclusions about quality. Third, the fact that the facilities participated in the registry voluntarily must be taken into account, as they are motivated and likely to be more specialized than the average Japanese hospitals. Therefore, the quality scores from these facilities may be higher than those provided by typical hospitals in Japan. Fourth, the QIs were based on the clinical practice guidelines issued in 2005, [6] but our study was comprised of patients diagnosed in 2002 and 2003. Thus, the guidelines used may have already improved some of the aspects of care scored in this analysis, but our study has demonstrated that the Liver Cancer Registry Database can be a useful data source for analyzing quality of care. Finally, the timing of the evaluation and the start of treatment for each patient was uncertain. Although the QIs targeting pretherapeutic laboratory tests (tumor markers and ICG retention) require knowledge of whether these tests were performed before the treatment was initiated, the test dates were not available in the registry. Thus, we assumed that the tests were performed before the start of the therapy and we therefore overestimated the quality scores.

Despite these limitations, we have demonstrated that the Liver Cancer Registry Database can be a tool for quality measurement. To date, cancer registries have primarily focused on clinical and epidemiological research, and the examination of the quality of care is a new area of research. Professional societies, however, have the responsibility to promote improved quality of patient care. Because the ultimate goal is to improve patient outcome, the role of these societies should not be limited to the discovery of new knowledge but should also include the monitoring of the extent to which the new knowledge is applied to patient care nationwide. This study serves as an initial step for the future growth of such activities.

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APPENDIX

The list of the quality indicators (QIs) approved by the expert panel

	Denominator (target patients)	Numerator (standard care processes)
Pre-treatment work-up		
1	Patients who were diagnosed with hepatocellular carcinoma (HCC)	AFP and PIVKA-2 levels were measured before treatment
2	HCC patients who underwent surgical resection, percutaneous local ablation therapy and transarterial chemoembolization (TACE) therapy	Dynamic CT/MRI study was performed before treatment
3	Patients who were diagnosed with HCC and received treatment	The medical records documented the clinical stage (TNM or TNM factors) and liver function level (the Child–Pugh class or the liver damage class)
4	Patients who underwent surgical resection of HCC for the first time	15-min ICG retention rate was measured before treatment
Treatment choice of local therapy		
5	HCC patients with liver damage class A, having three or less tumors of 3 cm or smaller in diameter	Surgical resection or percutaneous local ablation therapy (PEI, MCT, or RFA) was performed.
6	HCC patients with liver damage class A having a solitary tumor of 3–5 cm in diameter	Surgical resection was performed.
7	HCC patients with liver damage class A or B and three or fewer tumors smaller than 3 cm who had surgical resection or percutaneous local ablation therapy	The advantages and disadvantages of each therapy were explained and documented in the medical records
8	HCC patients with liver damage class C who underwent surgical resection, percutaneous local ablation therapy or TACE	The risks and benefits of the treatments received were explained and documented in the medical records
9	HCC patients receiving percutaneous ethanol injection (PEI) as the initial treatment	Medical records documented the reasons why RFA was not performed
10	HCC patients with Stage IVa or earlier, Vp 0–2 and Child–Pugh class A or B, in whom surgery and percutaneous local ablation therapy were not possible (patients who did not receive surgery or percutaneous local ablation therapy within 3 months after diagnosis)	TACE was performed.
11	Recurrent HCC patients with liver damage class A and a solitary tumor of 3–5 cm in diameter	Surgical resection was performed, or the medical record documented the reasons for not performing surgery
12	Recurrent HCC patients with liver damage class A and solitary tumor of 3 cm or smaller in diameter	Surgical resection or percutaneous local ablation therapy (PEI, MCT or RFA) is performed or the medical record documents the reasons for not performing these therapy
13	Recurrent HCC patients with liver damage class A and two or three tumors of 3 cm or smaller in diameter	Surgical resection, percutaneous local ablation therapy (PEI, MCT or RFA), or TACE was performed, or the medical record documented the reason for not performing these therapies.
14	HCC patients who received TACE	Lipiodol was used in the procedure
15	HCC patients with liver damage class C who satisfied Milan criteria	The option of liver transplantation was explained and documented
Documentation and explanation		
16	HCC patients who underwent surgical resection	Medical record (including pathological report) documented the degrees of vascular invasion and tumor differentiation was postoperatively determined.
17	HCC patients who underwent surgical resection	The medical record documented the physician's judgment on the postoperative risk of recurrence
18	HCC patients who underwent surgical resection	The pathological findings after surgery were explained to patients and were documented in the medical record

	Denominator (target patients)	Numerator (standard care processes)
Systemic therapy		
19	HCC patients who received systemic chemotherapy	Medical records documented the explanation to patients that surgical resection, percutaneous local ablation therapy or TACE could not be performed and that evidence for the efficacy of chemotherapy was lacking.
20	Patients who received treatment for HCC	Hormone therapy was avoided
Follow-up monitoring		
21	HCC patients who underwent surgical resection or percutaneous local ablation therapy	AFP and PIVKA-2 were monitored for at least 4-month intervals for 2 years after the curative treatment
22	HCC patients who received TACE	CT/MRI and tumor marker tests were performed within 2 months after TACE
23	HCC patients who received TACE	Image studies (contrast-enhanced CT/MRI, if not contraindicated) were performed at least every 3 months
24	HCC patients who received TACE	Tumor marker tests (AFP, PIVKA-2) were monitored at least every 3 months
25	HCC patients who received TACE and who showed elevated tumor marker levels, increases in the tumor size from diagnostic imaging or the appearance of new tumors with rich blood flow	TACE was repeated, or the medical record indicates the TACE was considered

AFP, Alpha-fetoprotein; CT, computed tomography; HCC, hepatocellular carcinoma; ICG, indocyanine green; MCT, microwave coagulation therapy; MRI, magnetic resonance imaging; PEI, percutaneous ethanol injection; PIVKA-2, protein induced by vitamin K absence-2; RFA, radiofrequency ablation; TACE, transarterial chemoembolization.