



**Research Article**

**RESEARCH PROGRESS ON LIVER CANCER EPIDEMIOLOGY**

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**ABSTRACT**

The newest researches and data about liver cancer epidemiology available now were collected, and the current status and progress on the research of liver cancer epidemiology were systematically reviewed. It was found that liver cancer was still one of the common cancers, the top 7 and 2 incident cancer, respectively in the world and China in 2012. With very poor prognosis and low survival, it posed big threat to people's life and health. Its incidence was high in underdeveloped areas, basically with the same geographical distribution for its mortality, but a little difference for its prevalence. Its male incidence, mortality, and prevalence were much higher than the female rates. Recently, its incidence and mortality remained stable in the world, but decreased slightly for its incidence, mortality, and prevalence, and rose slightly for its survival in China. The DALYs of liver cancer accounted for 54.6% of the DALYs caused by all cancers in China in 2016, and China was the country with the highest DALYs caused by liver cancer globally. It suggested that the control and prevention of liver cancer should be enhanced.

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**INTRODUCTION**

Liver cancer was one of the common cancers, and the top 2 death cancer worldwide in 2012[1]. As with very low survival and great harm to people's life and health[2-5], its control and prevention was very important and urgent. For establishing effective counter-measures, we must first master the current status and characteristics of liver cancer epidemic, found out what was not doing enough and should be improved right now. Hence, we thoroughly reviewed the current status and progress on the research of liver cancer epidemiology in this paper.

**Incidence**

**General status**

GLOBOCAN2012 estimated that 782 451 new liver cancer cases occurred globally in 2012, which accounted for 5.6 percent of all new cancer cases worldwide in the same year. Liver cancer was the top 7 incident cancer worldwide in 2012, whose ASR-W (Age standardized rate by world standard population) was 10.1/10<sup>5</sup>. Its incidence was high in underdeveloped areas (ASR-W 12.0/10<sup>5</sup>), where 83 percent of all new liver cancer cases worldwide in 2012 occurred, and whose incidence was 2.22 times higher than the rate of developed areas (ASR-W 5.4/10<sup>5</sup>) [1]. 394 770 new liver cancer cases was estimated to occur in China in 2012, which accounted for 12.9 percent of all new cancer cases in China

and 50 percent of all new liver cancer cases worldwide in the same year. Liver cancer was the top 2 incident cancer in China in 2012, whose ASR-W (22.3/10<sup>5</sup>) was 2.21, 1.86, 1.07, and 0.29 times higher than the rates of the world, underdeveloped areas, Eastern Asia (the subcontinents with the highest liver cancer incidence in 2012), and Mongolia (the country with the highest liver cancer incidence worldwide in 2012), respectively in 2012 (Table 1) [1].

**Geographical distribution**

GLOBOCAN2012 data revealed that liver cancer incidence were the highest in Eastern Asia (ASR-W 20.9/10<sup>5</sup>) and South-Eastern Asia (14.2/10<sup>5</sup>), the lowest in South-Central Asia (2.9/10<sup>5</sup>) and Northern Europe (3.1/10<sup>5</sup>) in the subcontinents of the world in 2012 (Figure 1), and the highest in Mongolia (78.1/10<sup>5</sup>), Lao (52.6/10<sup>5</sup>), and The Gambia (52.6/10<sup>5</sup>), the lowest in Nepal (0.9/10<sup>5</sup>), Tunisia (1.1/10<sup>5</sup>), and Morocco (1.2/10<sup>5</sup>) in 184 countries and regions in 2012. The highest rate (in Mongolia) was 86.8 times of the lowest (in Nepal). The rate of China ranked 8<sup>th</sup> in 184 countries and regions in 2012, and was only 0.29 times of the rate of Mongolia, the country with the highest liver cancer incidence worldwide in 2012[1].

CI5 (Cancer Incidence in Five Continents) volume XI data showed that the male highest liver cancer incidence were seen in Yanting (69.1/10<sup>5</sup>), Qidong (60.9/10<sup>5</sup>), and Xianju (50.0/10<sup>5</sup>) of China, respectively, the lowest in Kingston and St Andrew of Jamaica (0.8/10<sup>5</sup>), Setif of Algeria (1.4/10<sup>5</sup>), and Batna of Algeria (1.5/10<sup>5</sup>), respectively, and the female highest incidence were seen in Yanting (28.2/10<sup>5</sup>), Qidong (21.5/10<sup>5</sup>), and Xiping (17.2/10<sup>5</sup>) of China, respectively, the lowest in

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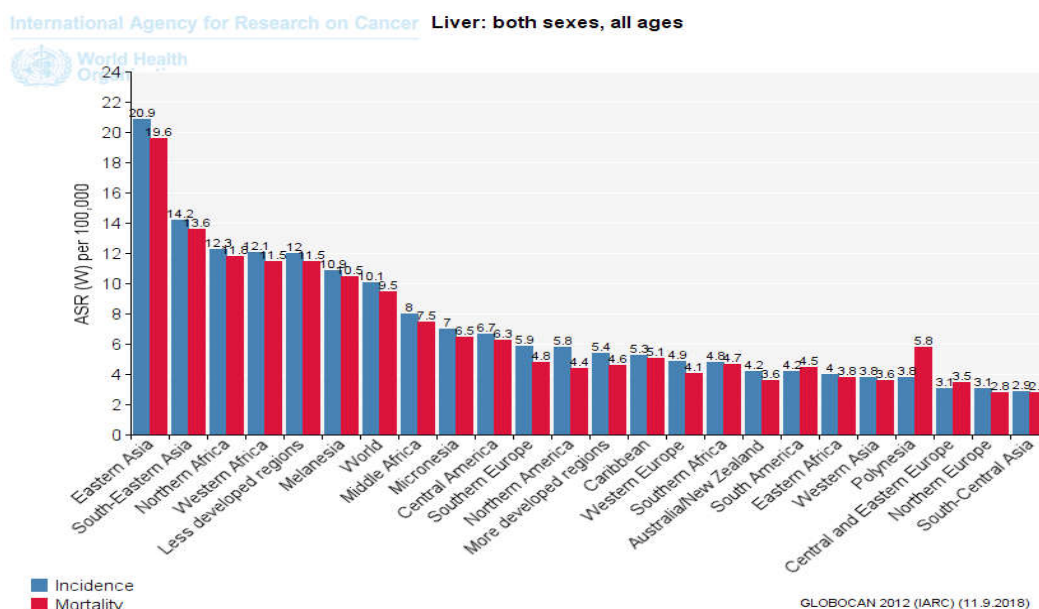
Ahmedabad of India ( $0.2/10^5$ ), Pocos de Caldas of Brazil ( $0.3/10^5$ ), and Dindigul, Ambilikkai of India ( $0.5/10^5$ ), respectively in 345 population-based cancer registries of 65 countries in 2008-2012. The male and female top 20 incident areas all located in China, Thailand, and Korea, 13 of them in China. For both male and female, 4 of the top 5 incident areas located in China, Yanting and Qidong of China were the top 1 and 2 incident areas, respectively in the 345 population-based cancer registries in 2008-2012. Beijing, Shanghai, and Sheyang of Jiangsu province were the registries with the lowest incidence among the 36 Chinese cancer registries received by CI5 volume XI[6].

incidence of liver cancer was the highest globally in 2012[1]. The ratios was 3.02 in China in 2014<sup>[7]</sup>, and 3.19 in 36 Chinese cancer registries received by CI5 volume XI[6].

GLOBOCAN2012 data revealed that the age specific incidence of liver cancer in the world, developed and underdeveloped areas, Eastern Asia, Northern Africa, and China in 2012 increased from age 40 years, quickly from age 65, peaked at age 75+. Its age specific incidence in China was close to that in Eastern Asia, much higher than those in the world, developed and underdeveloped areas, and Northern Africa[1].

**Table 1** The incidence, mortality, and prevalence of liver cancer by areas in the world, 2012 ( $1/10^5$ )

Areas	Incidence			Mortality			5-years prevalence		
	No. (N)	Prop. (%)	ASR-W	No. (N)	Prop. (%)	ASR-W	No. (N)	Prop. (%)	ASR-W
World	782451	5.6	10.1	745517	9.1	9.5	633170	1.9	12.2
Developed area	134302	2.2	5.4	123061	4.3	4.6	163807	1.0	15.8
Underdeveloped area	648149	8.1	12.0	622456	11.7	11.5	469363	3.0	11.3
Eastern Asia	466336	11.3	20.9	443948	16.1	19.6	405303	5.1	31.2
Northern Africa	19653	8.9	12.3	18704	13.0	11.8	11792	2.5	8.2
Mongolia	1518	37.5	78.1	1345	43.1	70.3	905	16.9	44.1
China	394770	12.9	22.3	383203	17.4	21.4	290910	5.8	26.3



According to the data of 339 population based cancer registries in China in 2014, NCCRC (National Central Cancer Registry of China) estimated that 365 000 new liver cancer cases occurred in China in 2014, which accounted for 9.59 percent of all new cancer cases in China in the same year. Liver cancer was the top 4 incident cancer in China in 2014, whose crude rate(CR) and ASR-W were  $26.67/10^5$  and  $17.81/10^5$ , respectively, with the ASR-W higher in rural ( $19.99/10^5$ ) than in urban areas ( $16.09/10^5$ ), higher in Western Areas ( $21.45/10^5$ ) than in Middle Areas ( $19.56/10^5$ ), higher in Middle Areas than in Easter Areas ( $16.54/10^5$ ). Among the seven administrative areas in China, the incidence of liver cancer in 2014 was the highest in Southern China and lowest in Northern China[7].

**Age and gender distribution**

Male incidence of liver cancer was much higher than that of female. GLOBOCAN2012 estimated that the ratios of its male to female incident ASRs-W in the world, developed areas, underdeveloped areas, and China in 2012 were 2.83, 3.19, 2.48, and 3.09, respectively, and 1.60 in Mongolia, whose

NORDCAN (Cancer statistics for the Nordic countries) data showed its age specific incidence in Northern Europe in 2105 increased from about age 40 years, peaked at age 80-84 for male and 75-79 for female, with the male rates much higher than the female, and the incidence lower than its mortality from age 75 for male and 70 for female[8]. NCCRC data demonstrated its age specific incidence in China in 2014 was low before age 30, increased quickly from age 30, peaked at age 80-84, with the male rates much higher than the female, the age when the incidence began to up younger for the male than the female, the incidence lower than the mortality from age 75-79, and the age specific incident pattern the same in urban and rural areas [7]. Its age specific incident pattern in China in 2014 was similar to that in 36 Chinese cancer registries received by CI5 volume XI[6], and also basically the same in different Chinese areas, only with slight difference for the peaking age, such as its peaking age was at age 60-64 in Qidong of Jiangsu province in 1972-2011[10].

**Trend**

There were no obviously increasing or decreasing trend for liver cancer incidence in the world in 1999-2012, although it rose slightly in 1999-2008 (Table 2) [1,11-13]. NORDCAN data showed that its incidence rose 145.0% for male and 73.8% for female in Northern Europe in 1960-2015, but increased for male and decreased for female in Sweden in the same period, and increased remarkably for both gender in Norway in 1953-2015[8]. ECIS (European Cancer Information System) data revealed that the incidence of liver cancer increased in Belgium and Ireland, stable in Austria and Ukraine, increased for male but stable for female in Croatia in 2000-2013[9]. Otherwise, GLOBOCAN2012 data demonstrated that its incidence increased slowly in some Europe countries such as in Denmark, Finland, France, Slovak, Spain, and British, and in some America and Oceania countries such as in Australia, Canada, Colombia, Costa Rica, New Zealand, and America, decreased in some Asia countries such as in China, Singapore, and Philippine, rose remarkably before 1995 and down obviously thereafter in Japan, and up slightly in India in 1975-2010[1]. As of the application of HBV vaccine, its incidence decreased in some high-risk areas such as in Taiwan [14].

22.07%, 21.45%, and 21.89%, respectively compared with the figures in 2012[1]. NCCRC estimated there will be 245 000, 87 000, and 332 000 new liver cancer cases for male, female, and both gender, respectively in China in 2020, and its ASRs-W will be  $23.7/10^5$  for male and  $14.2/10^5$  for female, down obviously compared with the rates in 2012.

**Death**

**General status**

GLOBOCAN2012 estimated that 745 517 liver cancer cases died globally in 2012, which accounted for 9.1 percent of all cancer death cases worldwide in the same year. With very poor prognosis, liver cancer, whose death ASR-W was  $9.5/10^5$ , was the top 2 death cancer worldwide in 2012. With similar geographical distribution as its incidence, its death ASR-W in underdeveloped areas ( $11.5/10^5$ ) was obviously higher (2.50 times) than that in developed areas ( $4.6/10^5$ ). It was estimated there were 383 203 liver cancer death cases in China in 2012, which accounted for 17.4 percent of all cancer death cases in China in the same year, its ASR-W was  $21.4/10^5$  [1]. Liver cancer was the top 3 and 2 death cancer in China in 2012 [1] and 2014 [7], respectively.

**Table 2** Incidence and mortality of liver cancer by areas, sex, and calendar Years (ASR-W,1/105)

Calendar year	Incidence				Mortality			
	World		China		World		China	
	Male	Female	Male	Female	Male	Female	Male	Female
1999	14.7	4.9	35.8	-	14.2	4.9	-	-
2002	15.7	5.8	37.9	14.2	14.9	5.7	-	-
2008	16.0	6.0	37.4	13.7	14.6	5.7	34.1	13.1
2012	15.3	5.4	33.7	12.5	14.3	5.1	32.3	10.7

**Data comes from GLOBOCAN**

GLOBOCAN data showed that liver cancer incidence in China decreased obviously from 1980s to the early 21<sup>st</sup> century and slightly recently [1,11-13]. NCCRC data also demonstrated its incidence down gradually in China recently, whose ASRs-W were  $21.35/10^5$ ,  $19.48/10^5$ ,  $19.44/10^5$ ,  $18.15/10^5$ , and  $17.81/10^5$ , respectively in 2010, 2011, 2012, 2013, and 2014[7,15-18]. One research revealed its male CR increased but ASR-W decreased, its female CR and ASR-W both down in Chinese urban areas, and both female and male CR and ASR-W decreased in Chinese rural areas in 1998-2007. Its incident patterns in different age groups and birth cohorts were similar, and its age specific incidence was low at age 20-35 year, and high at age 60+ years[19]. Another study also indicated although its CR up in China, its ASR-W down 1.8% annually in 2000-2011[20]. Its incidence was stable in Beijing, down slightly in Shanghai, and up with fluctuation in Linzhou of Henan province and Qidong of Jiangsu province in 1988-2007[21]. CI5 Plus data showed liver cancer incidence decreased 34.0% and 45.1% for male and female, respectively in 3 Chinese cancer registries ( Hong Kong, Shanghai, and Jiashang of Zhejiang province), and also decreased in each of the above 3 registries in 1993-2007 [22]. The incidence in Qidong of Jiangsu province decreased 37.2% in 1972-2011[10], but up 181.9% in Zhongshan of Canton in 1970-2010 [23].

**Prediction**

GLOBOCAN2012 predicted that there will be 676 633, 277 008, and 953 741 new liver cancer cases for male, female, and both gender, respectively worldwide in 2020, increased by

**Geographical distribution**

GLOBOCAN2012 data revealed that liver cancer mortality were the highest in Eastern Asia ( $19.6/10^5$ ) and South-Eastern Asia ( $13.6/10^5$ ), the lowest in South-Central Asia ( $2.8/10^5$ ) and Northern Europe ( $2.8/10^5$ ) in the subcontinents of the world in 2012 (Figure 1), and the highest in Mongolia ( $70.3/10^5$ ), Lao ( $50.9/10^5$ ), and Egypt ( $24.5/10^5$ ), the lowest in Nepal ( $0.9/10^5$ ), Tunisia ( $1.0/10^5$ ), and Morocco ( $1.2/10^5$ ) in 184 countries and regions in 2012. The highest rate (in Mongolia) was 78.1 times of the lowest (in Nepal). The rate of China ranked 8<sup>th</sup> in 184 countries and regions in 2012, and was only 0.30 times of the rate of Mongolia, the country with the highest liver cancer mortality worldwide in 2012. No matter men and women, Mongolia and Lao were the top 2 countries for the incidence and mortality of liver cancer in 184 countries and regions in 2012 [1].

WHO data showed that liver cancer mortality were the highest in Thailand ( $24.5/10^5$ ), Korea ( $23.1/10^5$ ), and Hong Kong of China ( $17.2/10^5$ ) for male, and in Guatemala ( $12.3/10^5$ ), Thailand ( $9.0/10^5$ ), and Nicaragua ( $6.7/10^5$ ) for female globally in 2013[24]. As different countries and regions were included in the database of WHO and GLOBOCAN2012, some difference existed between the above two database.

It was estimated there were 383 203 liver cancer death cases in China in 2012, which accounted for 17.4 percent of all cancer death cases in China in the same year. Liver cancer was the top 2 death cancer in China in 2012, whose ASR-W ( $21.4/10^5$ ) was 2.25, 1.86, 1.09, and 0.30 times of the world, underdeveloped areas, Eastern Asia (the subcontinent with the highest liver cancer mortality in 2012), and Mongolia (the country with the

highest liver cancer mortality globally in 2012), respectively[1].

NCCRC estimated that 319 000 liver cancer cases died in China in 2014, which accounted for 13.88 percent of all cancer death cases in China in the same year. With the rate higher in rural (ASR-W  $17.45/10^5$ ) than in urban areas ( $13.60/10^5$ ), the highest in Chinese Western Area ( $17.23/10^5$ ) and lowest in Eastern Area ( $14.44/10^5$ ), liver cancer was the top 2 death cancer in China in 2014, whose CR and ASR-W were  $23.31/10^5$  and  $15.29/10^5$ , respectively. Among the seven administrative areas in China, its mortality was the highest in Southern China and lowest in Northern China in 2014 [7].

#### **Age and gender distribution**

Male liver cancer mortality was much higher than that of female. GLOBOCAN2012 estimated that in 2012, the ratios of its male to female ASRs-W in the world, developed and underdeveloped areas, and China were 2.80, 2.84, 2.42, and 3.01, respectively, and 1.65 in Mongolia, whose liver cancer mortality was the highest globally in 2012[1]. The ratio in China was 3.02 in 2014 [7], but were a little lower in 1990-1992 (2.59) and 2004-2005 (2.60) [9-13].

GLOBOCAN2012 data showed that the age specific mortality of liver cancer in the world, developed and underdeveloped areas, Eastern Asia, Northern Africa, and China in 2012 increased from age 40 years, quickly from age 65, peaked at age 75+. Its age specific mortality in China was close to that of Eastern Asia, much higher than those in the world, developed and underdeveloped areas, and Northern Africa[1]. NORDCAN data indicated its age specific mortality in Northern Europe in 2105 increased quickly from about age 40 years, peaked at age 85+, with the male rates much higher than the female, and the mortality higher than its incidence from age 75 for male and 70 for female[8]. NCCRC data revealed that its age specific mortality in China in 2014 was low before age 30 years, increased quickly from age 30, peaked at age 80-84, with the male rates much higher than the female, the age for the rate began to up for the male younger than the female, the mortality higher than its incidence from age 75-79, and the age specific death patterns similar in urban and rural areas [7]. Its age specific death pattern were also basically the same in different Chinese areas, only with slight difference for its peak age, such as the peak age was at age 60-64 in Qidong of Jiangsu province in 1972-2011[10].

#### **Trend**

There were no obviously increasing or decreasing trend for liver cancer mortality in the world in 1999-2012 [1,11-13] (Table 1). Its mortality decreased in Europe In 1990-2008, down 0.4% for male and more than 2% for female annually, and its trend tend to be the same in different European countries recently, but the mortality of intra-liver duct cancer in most Europe countries up remarkably [25]. NORDCAN data showed that liver cancer mortality in Northern Europe rose 27.74% for male, but down 106.11% for female in 1953-2015. It decreased slightly for male but obviously for female in Sweden in 1960-2015, increased remarkably for male but decreased for female in Norway in 1953-2015[8]. ECIS data revealed that liver cancer mortality remained stable in Austria, Ukraine, Ireland, Croatia, and Belgium in 2000-2013, except slightly up for its female mortality in Croatia and Belgium [9]. WHO data showed that its death trend varied in countries and regions with high risk of liver cancer, its death rates increased

in some countries and regions, such as in Egypt, Maldives, Nicaragua, Romania, Singapore, Portugal, Canada, Italy, England, and United States, decreased obviously in some countries and regions, such as in Hong Kong of China, Philippine, and Armenia, increased first and decreased later in some countries and regions, such as in Korea, Japan, and Thailand, down first and up later in some countries and regions, such as in Spain, up or down with fluctuation in some countries and regions, such as in Croatia[24].

GLOBOCAN data showed that liver cancer mortality in China decreased obviously from 1980s to the early 21st century and slightly recently [1,11-13]. NCCRC data also revealed its mortality down gradually in China recently, whose ASRs-W were  $18.43/10^5$ ,  $17.48/10^5$ ,  $16.84/10^5$ ,  $15.65/10^5$ , and  $15.29/10^5$ , respectively in 2010, 2011, 2012, 2013, and 2014 [7,15-18]. One research demonstrated that its CR increased 0.7% but ASR-W decreased 2.3% annually in China in 2000-2011[26].

The data from the three Chinese national death causes surveys showed that from 1972-1973 to 2004-2005, liver cancer mortality increased 22.72%, 85.77%, and 57.84% in Chinese urban, rural, and whole China, respectively, rose 68.41% for male and 48.39% female, respectively, up more in rural areas and for male than in urban areas and for female. But it mainly increased before 1990s, thereafter only up slightly. Moreover, although its CR up continuously, its ASR by Chinese standard population rose obviously only before 1990s, thereafter it up for rural but down slightly for urban areas [27-30].

#### **Prediction**

WHO estimated that from 2009-2013 to 2034-2038, the death CR and ASRs-W of liver cancer for both gender in Japan and for male in Korea would down continuously, and the female CR down slightly and ASR-W remarkably in Korea, but the male CR and ASR-W and the female CR in Romania would increase, and the female ASR-W stable[24].

#### **Prevalence**

##### **General status**

GLOBOCAN2012 estimated that there were 633 170 liver cancer cases diagnosed in previous 5 year and still alive at the end of 2012 globally, which accounted for 1.9 percent of all cancer cases diagnosed in previous 5 year and still alive at the same time worldwide. Liver cancer, whose 5 year prevalence was  $9.5/10^5$ , was the top 15 prevalent cancer worldwide in 2012, its 5 year prevalence was much higher (2.50 times) in underdeveloped areas ( $11.5/10^5$ ) than in developed areas ( $4.6/10^5$ ). Its geographical distribution was a little different from that of its incidence and mortality. There were 290 910 liver cancer cases diagnosed in previous 5 year and still alive at the end of 2012 in China, accounted for 5.8 percent of all cancer cases diagnosed in previous 5 year and still alive at the same time in China. Liver cancer was the top 7 prevalent cancer in China in 2012, whose 5 year prevalence was  $26.3/10^5$ [1].

##### **Geographical distribution**

The prevalent geographical distribution of liver cancer was a little different to that of its incidence and mortality. GLOBOCAN2012 data revealed that its 5 year prevalence were the highest in Eastern Asia ( $31.2/10^5$ ) and Southern Asia ( $16.2/10^5$ ), the lowest in South-Central Asia ( $1.7/10^5$ ) and

Micronesia ( $2.1/10^5$ ) in the subcontinents of the world in 2012, and the highest in Japan ( $68.9/10^5$ ), Korea ( $53.9/10^5$ ), and Mongolia ( $44.1/10^5$ ), the lowest in Maldives ( $0/10^5$ ), Nepal ( $0.50/10^5$ ), and Morocco ( $0.7/10^5$ ) in 184 countries and regions in 2012. The 5 year prevalence of China ranked 6<sup>th</sup> in 184 countries and regions in 2012, and was only 0.38 times of Japan, the country with the highest 5 year prevalence of liver cancer in 2012. No matter men and women, Japan and Korea were the top 2 countries with the highest prevalence of liver cancer in 184 countries and regions in 2012[1].

The prevalence of liver cancer was higher in Chinese urban than in rural areas, whose 5 year prevalence were  $30.4/10^5$  and  $23.5/10^5$ , respectively in 2011[31].

#### **Age and sex distribution**

Male prevalence of liver cancer was much higher than that of female. The ratios of its male to female 5 year prevalence in the world, developed and underdeveloped areas, and China were 2.54, 2.37, 2.63, and 2.96, respectively in 2012<sup>[1]</sup>. The ratio in Japan, whose 5 year prevalence of liver cancer was the highest in 2012 globally, was 2.08 in 2012<sup>[1]</sup>, and the ratio in China were 3.41 and 2.66, respectively in 2008 and 2011 [31-32].

The prevalence of liver cancer were the highest at age group 40-64 years, followed by the age group 65+ and 0-39, which accounted 62.3%, 31.6%, and 6.1% of all liver cancer prevalent cases in China in 2011, respectively[31].

#### **Trend**

The 5 year prevalence of liver cancer increased from  $0.69/10^5$ ,  $0.55/10^5$ , and  $0.62/10^5$  in 1980 to  $12.75/10^5$ ,  $5.89/10^5$ , and  $9.31/10^5$  in 2015 for male, female, and both gender, respectively in Nordic Europe, increased by 1747.83%, 970.91%, and 1401.61%, respectively[8]. The 5 year prevalence of liver cancer in China decreased slightly, which were  $40.2/10^5$ ,  $38.8/10^5$ , and  $38.8/10^5$ , respectively for male, and  $14.6/10^5$ ,  $14.6/10^5$ , and  $13.1/10^5$ , respectively for female in 2008, 2011, and 2012 [1,31-32].

#### **Survival**

With very poor prognoses, the survival rate of liver cancer was very low, much lower than the rates of other common cancers[2-5]. Concord-3 data showed that its 5 year age standardized net survival rates of 290 population based cancer registries in 60 countries and regions in 2000-2014 were at 5%-30%, more than 30% in 2010-2014 in Jordan (40%) and Japan (30%), between 20-30% in Korea, Qatar, Singapore, Belgium, Italy, and Taiwan of China, less than 10% in Denmark, Slovenia, Thailand, Czech, Russia, India, Colombia, and Estonian, between 10%-20% in all other 60 countries and regions, 14.1% for all 21 Chinese population based cancer registries who participated Concord-3 project. Its net survival rates remained stable in most and increased only in a few of the above mentioned 60 countries and regions in 1995-2014, it increased more than 10% in Korea, Singapore, and Norway, between 5%-10% in Taiwan, Holland, Sweden, and New Zealand, less than 5% in United State, Japan, Italy, Portugal, and Australia[2]. NORDCAN data showed that except the female rate of Norway, its 5 year age standardized relative survival rates in Nordic Europe countries all were lower than 20%, with the male rates highest in Iceland and the female highest in Norway in 2011-2015. Its male and female 5 year

age standardized relative survival rates in Nordic Europe increased at different degrees in 1966-2015. Except in Iceland, its male and female 5 year age specific relative survival rates in Nordic European countries were the highest at age 0-49 years, lowest at age 80-89, the older the age, the lower the survival rate[8]. But its male and female 5 year age standardized relative survival rates for adult (Aged 15+ years) was the highest at age 15-44 years, lowest at age 75+ in European in 2000-2007<sup>[9]</sup>.

In China, the 5 year age standardized relative survival rate of liver cancer was obviously lower than the rates of other cancers, only higher than the rate of pancreas in 2003-2015. Its female rate (13.1%) was slightly higher than the male (12.2%), and the rate in urban area (14.0%) higher than in rural areas (11.2%) in 2012-2015. Although its male (0.7%) and female (0.9%) survival rates increased slightly from 2003-2005 to 2012-2015, its rate decreased in Chinese urban areas (-0.7%) and rose in rural areas (1.6%)[5].

SURCAN-1 (Cancer survival in developing countries) assessed cancer survival of 10 population based cancer registries in Costa Rica, China, Cuba, India, Philippine, and Thailand in 1982-1991[33]. SURCAN-2 (Cancer survival in Africa, Asia, the Caribbean and Central America) evaluated the survival of 40 cancers in 27 population based cancer registries in 14 countries during 1990-2001[34,35]. SURCAN-2 data showed that the five years relative survival rates (RS) of liver cancer in 27 cancer registries in 14 countries ranged between 0-25.4% in 1990-2001, with the highest in Tianjin (25.4%) and Hong Kong (22.4%) of China, the lowest in Barshi of India (0%) and Kampala of Uganda (1.1%), and most of them lower than 10%. For male, the highest five years RS were in Tianjin (27.0%) and Hong Kong (21.5%) of China, for female, the highest in Hong Kong (21.8%) and Tianjin (20.8%) of China. Hong Kong and Tianjin were the top 2 areas with the highest male and female 5 year RS of liver cancer in 27 cancer registries of 14 countries and at each age group in all above 27 registries in 1990-2001. Its 5 year RS rose from 2.7% in 1973-1977 to 4.9% in 1993-1997, 10 year RS rose from 2.2% in 1978-1982 to 3.1% in 1993-1997, 15 year RS rose from 2.1% in 1983-1987 to 3.4% in 1993-1997 in Singapore by period method, but its 5 and 10 year RS down slightly by cohort method[34]. The 5 year RS of liver cancer in Korea increased from 10.7% in 1993-1995 to 32.8% in 2010-2014[36].

The survival rate of liver cancer increased obviously in Shanghai. Its 5 year RS increased from 2.0% and 2.70% in 1972-1976 to 16.62% and 15.65% in 2002-2005 for male and female, respectively, with the male 1-5 year RS all higher than the female. And its 5 year RS varied with ages, the older the age, the lower the 5 year RS[37]. The 1, 3, 5, 10, and 15 year RS of liver cancer in Qidong of Jiangsu province were 15.47%, 6.60%, 4.69%, 3.41%, and 3.29%, respectively in 1972-2011. Its RS increased remarkably during the period, its 5 year RS up from 1.07% in 1972 to 6.26% in 2003-2007, and 10 year RS up from 0.36% in 1972 to 2.95% in 1998-2002. The older the age, the lower the observe survival rate, but the higher its 5 and 10 year RS [10].

#### **Disease Burden**

DALYs (Disability adjusted life years) can be used for comparing the burden of different diseases, and was increasingly paid more attention for evaluating cancer burden.

Research showed that the DALYs caused by the liver cancer in China in 2016 was 11.54 million person-years, accounted for 54.6% of the DALYs caused by the liver cancer in the world in the same year. The standardize DALYs rate in China in 2016 was  $844.1/10^5$ , 3.0 times higher than that of the world, and its male rate was 3.4 time of the female. YLLs (years of life lost) and YLDs (years lived with disability) accounted for 98.9% and 1.1% of the DALYs caused by liver cancer in China in 2016, respectively, suggesting premature death was the major cause of DALYs of liver cancer in China.

DALYs caused by liver cancer accounted for 20% of the DALYs caused by all cancers in China in 1990-2016, and was always the top 2 DALYs caused by cancers. The standardize DALYs rates of liver cancer in China in 1990-2016 increased (ARC=0.57%), especially in recent 5 year (ARC=1.75%), quicker than in the world. DALYs caused by liver cancer in China in 2050 would be 14.37 million person-years, increased by 20.0% compared with the figure in 2017. As population aging more seriously, DALYs caused by liver cancer in China would continue to increase in the future. Although its male standardize DALYs rates in China in 1990-2016 increased (ARC = 0.77%), its female rates decreased (ARC =-0.11%), suggesting the gap between the male and female DALYs of liver cancer in China would continue to increase. Although the peak age(65-69) of its standardize DALYs rate in China remained basically stable during the period, its peak age of DALYs changed from age 55-59 years in 1990 to 60-64 years in 2016, suggesting that the middle-old population was with the highest DALYs caused by liver cancer in China[37].

Viral hepatitis B (HBV) was the first attributing risk factor of liver cancer (accounted for 57% of all), and the DALYs rate caused by the HBV infection gradually increased (ARC=0.43%). Although alcohol liver disease was the third attributing risk factor of liver cancer, the DALYs rate caused by alcohol liver disease increased the most (ARC=1.1%), and female was the population with the DALYs caused by alcohol liver disease up the most. Hence, female alcohol intake in China should be controlled [38].

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