# Liver cancer mortality over six decades in an epidemic area: What we have learned

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## Introduction

25      Liver cancer is one of the most dominant malignant tumors in the world. According to

26 GLOBOCAN 2018 [1], it was estimated that the incident cases of liver cancer was 841,080,

27 which accounted for 4.65% out of 18,078,957 malignant tumors in the world every year, ranking

28 sixth in the world (fifth in men and ninth in women). Among 9,555,027 deaths with cancer,

29 781,631 cases (8.18%) died of liver cancer, ranking fourth in the world (second in men and sixth

30 in women) [1]. In 2017, incident cases of liver cancer in China were about 441,200, and the

31 number of deaths were 395,200 [2], implying that the proportion of incident cases and death

32 cases of liver cancer in China accounts for 52.46%, and 50.56%, respectively, of the global

33 burden. In particular, liver cancer has among the poorest prognosis of all cancers. For instance,

34 according to data of 291 cancer registries in 61 countries and regions in the CONCORD 3 Study

35  [3], the 5-year survival rate of liver cancer was 5%-30% in 2000-2014, and only 10%-19% in

36  Europe and America; while the 5-year survival rates in China in 2006-2008, 2009-2012, 2013-

37  2015 were 10.1%, 9.8% and 12.1%, respectively [4]. In another research report in 2017, it was

38  estimated that the global disability-adjusted life years (DALYs) was 20.8 million, of which 99%

39  was years of life lost (YLLs) due to early death and 1% was years lived with disability (YLDs)

40  [5]. Thus, liver cancer constitutes a serious disease burden both in the whole world and in China,

41  and the study of liver cancer in China is of great significance for global cancer control.

42      Since the 1970s in China, a series of systematic studies on the epidemiology, etiology and

43  prevention of liver cancer have been carried out, and great progress has been made. Among

44  them, the prevention and treatment of liver cancer in Qidong, formerly a county and now a city

45  in Jiangsu Province, has been most representative [6,7]. This paper summarizes the trend of liver

46  cancer mortality over the past 60 years in Qidong according to a death retrospective survey and,

47  subsequently, a cancer registration report system, and makes an analysis and evaluation on the

48  related challenges and progress in the study of the etiology and prevention of this disease. As

49  such, it demonstrates that the age-standardized trajectories of dominant, often fatal cancers can

50  be attenuated dramatically with better understandings of underlying etiologies and

51  implementation of cancer control programs.

## Materials & Methods

53      *Retrospective survey of death*

54      During the period of July to August 1972, a 14-year retrospective survey (1958-1971) of

55  cancer was organized among the 1.03 million residents in Qidong in order to understand the

56  prevalence of liver cancer in this area [6]. At that time, the investigation teams were composed of

57  cadres of brigade (village) doctors, barefoot doctors (grassroots medical staff), county hospital

58  doctors, and medical team members (from hospitals / research institutes / universities in

59  Shanghai and Jiangsu, Province). The investigation was carried out in the form of an

60  investigational forum, usually with 3-5 "old" peasants and cadres in each brigade (village) [8].

61  The information in the questionnaire included address, name, gender, age at/and the date of

62  death, cause of the death and/or the main symptoms (if any), and the diagnosis. For suspected

63  cancer deaths, especially liver cancer, double checking of the cause would be performed with

64  their family members or relatives. The survey showed that most of the cases were diagnosed and

65  treated before death. In 1971, for example, 31.25% of the cases with liver cancer were diagnosed

66     by the Shanghai Cancer Hospital and/or other provincial and municipal hospitals; 50.20% of the

67     cases were diagnosed by the Qidong People's Hospital or the Affiliated Hospitals of Nantong

68     Medical College; 14.17% were diagnosed in district and/or commune (township) hospitals; only

69     4.38% were not identified in diagnosis units (unknown).

70        ***Cancer registration report***

71        The Qidong Cancer Registry was established in 1972, covering the whole Qidong area and

72     all of the registered population. All malignant tumors, including brain and central nervous

73     system tumors, have been included and registered [8]. The International Classification of

74     Diseases (ICD) 8th edition (ICD-8) was used for cancer cases before 1979, ICD-9 was used for

75     the years 1979-2000, and ICD-10 was used for coding after 2000. Liver cancer was 155.0-155.9

76     in ICD-8 and ICD-9, and C22.0-22.9 in ICD-10. All data used in this database have been recoded

77     as C22.0-22.9 according to ICD-10.

78        In 1990, the Qidong Cancer Registry was admitted to the International Cancer Registration

79     Association (IACR) as a voting member unit. Some of data after 1983 were published in "Cancer

80     Incidence in Five Continents (CI5)" by the International Agency on Cancer Research (IARC)

81     [9,10], or "Annual Report on Cancer of China" by the National Cancer Registry Center of China

82     [11,12]. Most of the liver cancer cases in Qidong were diagnosed by alpha-fetoprotein (AFP) and

83     / or B-ultrasound (85.81%), and were verified by histology (12.36%). Almost all cases (98.17%)

84     were defined by at least one of the three diagnostic criteria; classification by death certificate

85     only (DCO) were only 0.34%.

86        ***Population information***

87        Information regarding the population of Qidong has come from the Residents Household

88     Annual Report of the Qidong Public Security Bureau. The population size in Qidong has

89     exceeded 1 M since the 1970's; and reached a level of 1.12M in 2017. The age structure of the

90     Qidong population in the years after 1972 have come from several sources: sampling survey in

91     1976 (ps1976), the third (national) census in 1982 (ps1982), the fourth census in 1990 (ps1990),

92     the fifth census in 2000 (ps2000) and the sixth census in 2010 (ps2010). Hence, the population

93     numbers of the age-groups from 1972 to 1976 were extrapolated according to the population

94     structure of ps1976; the population age-group from 1982 to 1990 was extrapolated according to

95     the population structure of ps1982 and ps1990; and the same method was used to extrapolate the

96     population numbers of age-groups by period through the structures of two adjacent censuses.

97      *Statistical methods*

98      For the period of 1958-1971, the Qidong death retrospective survey data [6] were used to

99      calculate the natural death rate, cancer mortality and liver cancer mortality. For the period of

100     1972-2017, the natural death rate came from the Qidong Vital Registry. The other statistical

101     indicators were calculated based upon the registered data, which included the crude mortality

102     rate (CR), age-specific mortality rate, sex-specific mortality rate, truncated rate of 35-64,

103     cumulative rate 0-74, and cumulative risk; and birth cohort analysis was performed. The age-

104     specific mortality rate was calculated as an average level for each five-year period (following the

105     period compiled in CI5 [9,10]). The age-standardized rates were calculated by the China

106     population in 1964 (ASRC) and by the world population in 1960 (ASRW), respectively. The

107     growth rate of the two years (y, y-1) at the end of the period compared with the two years (x, x +

108     1) at the beginning of the period was evaluated by the percentage change (PC) of the rate (r):

109     $PC_{x-y}=\{[(r_y+r_{y-1})-(rx+r_{x+1})]/ (r_x+r_{x+1})\}\times100$ [13]. The Joinpoint Regression Program 4.7.0.0

110     (2019) was used to estimate the annual percent change (APC), average annual percent change

111     (AAPC) and APC of each age group, allowing for the average increasing/decreasing trends of

112     the rates to be evaluated [14,15].

## Results

114     *Natural death rate, mortality rates of cancer and liver cancer in Qidong*

115     According to the data from this period of six decades, the natural mortality rates in Qidong

116     residents have experienced progressions from high to low, and then from low to high; the

117     mortality rate between 1958 and 1960 was about $900/10^5$ (9‰), which dropped to its lowest of

118     $540/10^5$ (5.4 ‰) in the middle and late 1970s, and then slowly increased back to about $900/10^5$

119     (9‰) at the end of the period (2015-2017). Mortality rates of cancer combined increased slowly

120     from $57/10^5$ in 1958 to $200/10^5$ in 1995 now exceed $300/10^5$. The mortality rate of liver cancer

121     increased from $20/10^5$ in 1958 to about $50/10^5$ in the 1970s, then fluctuated towards about $70/10^5$

122     in the late 1990s and then at the beginning of this century, moved towards $80/10^5$ in 2008, before

123     decreasing continuously, now approaching $52/10^5$ (Figure 1).

124     *Liver cancer mortality, cumulative mortality and truncated rate*

125     Cancer registration data after 1972 were used to evaluate accurately the proportion of liver

126     cancer hazard within total cancer deaths. The average crude mortality rate of liver cancer was

127     $58.86/10^5$, while deaths due to liver cancer accounted for 30.53% (31,261/102,390 total cases),

128 and the truncated mortality rate of 35-64 years old was $104.06/10^5$, the cumulative mortality rate

129 of 0-74 years old was 4.79%, and the cumulative risk of liver cancer was 4.68%. The mortality

130 rates and other evolution indicators over the years for liver cancer in Qidong are shown in Table

131 1.

132 ***Trend of liver cancer mortality***

133 From 1972 to 2017, the crude mortality rate of liver cancer in Qidong increased by

134 +17.78% in PC, and +0.88% in APC; But, the ASRC and ASRW decreased by -61.25% and -

135 51.43% in PC, and -1.80% and -1.35% in APC, respectively, showing a clear downward trend.

136 Analysis using the Joinpoint Regression Program showed that the average annual percent change

137 (AAPC) of ASRW was -1.3% (95% CI: -1.6%, -1.1%), in which -1.5% (95% CI: -1.7%, -1.2%)

138 was for men and -1.0% (95% CI: -1.3%, -0.7%) was for women, as shown in Figure 2 and Table

139 2.

140 Turning point analysis of multiple models showed that the trend in ASRW of liver cancer

141 during the 45 years of registration in Qidong could be divided into three joinpoints (four

142 periods), i.e., 1972-1992, 1992-1995, 1995-2006 and 2006-2017. Each of the APCs was -1.39%,

143 +4.50%, -1.42% and -4.66%, respectively. For men, it was one point (2 periods): 1972-2005 and

144 2005-2017, APCs were -0.48% and -4.51%, highlighting a significant downward trend. For

145 women, four joinpoints (5 periods) were identified: 1972-1986, 1986-1989, 1989-1994, 1994-

146 2008 and 2008-2017, APCs were -0.42%, -11.52%, +7.68%, -1.13% and -4.74%, respectively,

147 indicating that the APC of the last period had a significant downward trend (Figure 3). The

148 results given by the multiple models showed that the AAPCs for men, women and both sexes

149 were -1.8% (95% *CI*: -2.2%, -1.5%), -1.4% (95% *CI*: -3.5%, 0.7%) and -1.8% (95% *CI*: -2.8%, -

150 0.8%), respectively, as shown in Table 2.

151 ***Crude mortality, standardized mortality of liver cancer by gender***

152 The mortality rates of liver cancer over time in Qidong have been relatively stable; gender

153 differences always higher in males than in females. From 1972 to 2007, the crude mortality rate

154 of liver cancer was $91.86/10^5$ in men and $29.92/10^5$ in women, with a sex ratio of 3.07:1. For

155 ASRC and ASRW, the sex ratio was 3.48:1 and 3.32:1, respectively. The crude mortality rates

156 by sex and by year are listed in Table 3.

157 ***Age specific mortality and mean age of death***

158      The mortality rate of liver cancer increased with age. At the age group of 35-39, the rate

159    $(67.59/10^5)$ exceeded the average mortality level $(58.86/10^5)$ in the population. Mortality rates at

160    all age groups over 40 remained at levels of around $110/10^5$, and dropped to less than $90/10^5$ at

161    the age group of 80-84. Rates in all age groups were also higher in men than in women. From

162    1972 to 2017, the average age of death of liver cancer in Qidong was 53.71 years old, but

163    showing a 5-year difference by gender: men 52.41 and women 57.58. It was observed that the

164    average age of death for both sexes was under 50 years each year before 1993 (reaching a low of

165    48); since 1993, age of death of liver cancer has increased rapidly from 50, to 55 in 2004, and

166    then over 60 after 2012 (Figure 4).

167    *Mortality trend of liver cancer by period*

168    Taking 1972 as the first period, every 5 years as the next increments, 9 more periods

169    covered the following 45 years in order to analyze the mortality rate of each age group. The

170    results show that the mortality rate of liver cancer in the age group ≥ 75 years fluctuated in the

171    range of 50-70 per $10^5$ before the 1990s, and then gradually increased to more than $100/10^5$, and

172    by 2013-2017, it had exceeded $200/10^5$. At age groups of 55-64 and 65-74 the rates have swayed

173    around the range of 100-150 per $10^5$. A slight upward trend in the later period was found in the

174    55-64 age group, while a slight downward trend was seen at 45-54 age group. There were

175    significant declining trends in all age groups under 54 years old, particularly at 35-44, 25-34, and

176    15-24 (Figure 5).

177    The analysis with the Joinpoint Regression Program showed that the mortality rate at age

178    group ≥ 75 years had a significant upwards trend in 1972-2017, with an AAPC of +3.69%; and at

179    age group of 65-74 years, AAPC was +0.95%. The younger the age, the more significant the

180    trend for declining mortality from liver cancer: AAPCs at 55-64, 45-54, and 35-44 were -0.85%,

181    -1.73% and -3.58%, respectively (Figure 6).

182    *Liver cancer mortality in the birth cohorts*

183    Birth cohort analysis demonstrated that the mortality of liver cancer in age groups of 15-19,

184    20-24, 25-29, 30-34, 35-34 and 40-44 displayed downward trends. At age groups of 45-49 and

185    50-54 the mortality began to show a downward trend in the later period of the birth cohort. In

186    general, in the cohorts of "1953" and later births, clear cohort effects have been observed with

187    respect to reduction of liver cancer mortality. However, in the cohort of before "1938", i.e., at

188    age groups of 70-74, 75-79, 80 and over, the mortality rates showed rising trends (Figure 7).

## Discussion

190  The premise of cancer control is to understand the prevalence and trends of cancer. Therefore,

191  long-run monitoring data on incidence or mortality are particularly of importance. Since the

192  1970s, Qidong City, Jiangsu Province has carried out a series of cancer research programs on

193  prevention and treatment, such as retrospective survey of death, cancer registration reporting,

194  studies of cancer etiology and prevention [6-8] that provide detailed information for the

195  evaluation of long-term trends and comprehensive prevention effects of liver cancer mortality in

196  Qidong, and in China as well.

197         Data over the past 60 years (Figure 1) show that the natural death rate in the Qidong

198  population experienced an evolutive course from higher to lower, and then from lower back to

199  higher, truly reflecting the dynamic characteristics of the local population due to substantial

200  change of population structure [8,16] and control of diseases: the slow decline of mortality rate

201  (such as infectious diseases) in the general population in the early period, and the increase of

202  mortality rate (such as chronic diseases) due to aging in the recent decades. That the trend of

203  cancer mortality has increased likely reflects the synergetic effects of two factors: an increase of

204  risk factors and the aging of the population. It is worth noting that the trend of liver cancer

205  mortality before the beginning of this century was "synchronous" with the rate of increase of

206  cancer; after 2008, liver cancer mortality was no longer elevated in concert with the increase of

207  overall cancer mortality, but rather decreased. Other cancers such as lung cancer are now

208  exerting dominance in Qidong.

209         Our data shows that liver cancer has been the primary form of cancer in Qidong since 1958.

210  The observed crude mortality rate of liver cancer increased from $20.45/10^5$ in the 1950's to about

211  $50/10^5$ in the middle 1970's, and reached to the highest level of more than $80/10^5$ at the turn of

212  this century. Moreover, the proportion of liver cancer in all cancers was 35.49% (4428/12476) in

213  1958-1971 and 30.53% (31261/102390) in 1972-2017, meaning one in three cancer patients died

214  of liver cancer. However, the proportion of liver cancer in total cancer death has declined

215  substantively over the past decade. Table 1 shows that the proportion of liver cancer in total

216  cancer deaths has declined to 22.52% (8004/35549) in the years 2008-2017, and to 18.39%

217  (1925/10468) in just the last three years of analysis (2015-2017).

218         Based upon the data from the registration system, the overall mortality trend of liver cancer

219  was evaluated. It can be seen that the percent change (PC) of the crude mortality of liver cancer

220  during 1972-2017 was +17.78%; but the PCs of ASRC and ASRW were -61.25% and -51.43%,

221  showing a downward trend. Joinpoint Regression analysis illustrated that average annual percent

222  change (AAPC), in term of ASRW, displayed a clear declining trend, which was -1.49% in men,

223  -1.01% in women, and -1.33% for both sexes (Figure 2). According to the multiple model of

224  Joinpoint Regression (Table 2), the AAPCs of men, women and the both were -1.8%, -1.4% and

225  -1.8%, respectively, indicating that mortality from liver cancer in Qidong did show a significant

226  downward trend.

227      The similar trends have been found across China: the standardized mortality rate of liver

228  cancer, for instance, in Changning District, Shanghai during the years 1973-2013, was -2.1% in

229  men and -2.7% in women, respectively [17]. A recent study in China showed that the crude

230  mortality rate of liver cancer in China increased during 1997-2016, with an AAPC of +0.5%, but

231  the age-standardized rate was in decline [18]. Another report showed that the age-standardized

232  mortality rate of AAPC for liver cancer in China was -0.5% in men, -1.3% in women, and -0.8%

233  in both sexes from 1990 to 2017 [19]. A South Korea report showed that the age-standardized

234  mortality rate of AAPC in 1983-2012 was -1.55% in men and -0.56% in women [20]. In a recent

235  Meta-analysis report [21] that included 31 population-based studies showed that the pooled APC

236  estimates for liver cancers was +0.8%, in which +3.2% in the region of North

237  America/Europe/Australia, whereas −1.7% in several Asian countries. These di□erent patterns

238  may reflect geographical variation or changes in the ratio of liver cancers attributable to various

239  risk factors.

240      The age-specific mortality rate from this 60-year data set showed that liver cancer

241  contributed the most hazard towards disease burden in the middle-aged and elderly residents. In

242  individuals over 35 years in Qidong, the mortality rate of liver cancer (over $110/10^5$) has

243  exceeded the average level of the general population, and has been stable at the level of 110-

244  $140/10^5$ for those over 45 years old. The cumulative rate and the cumulative risk of 0-74 years

245  old (which reflects the level of lifetime mortality) reached 5.15% and 5.02%, respectively, being

246  yet another metric of this cancer epidemic. In the 1970s and 1980s, it was found that the

247  proportion of liver cancer deaths in young adults was very high, in term of the truncated rate of

248  35-64 years: between $120/10^5$ and $140/10^5$ in the 1970s-1980s, down to $100-110/10^5$ in 1990-

249  2005, to less than $100/10^5$ in the last period, and even lower than $50/10^5$ in the most recent 2

250  years. For the average death age of liver cancer, they were relatively young patients before the

251    1990s, since then the average death age increased gradually from under 50 to exceed 65 years

252    old. These changes clearly show that the mortality of liver cancer in the Qidong youth and

253    middle-aged population has exhibited a rapid downward trend.

254        Furthermore, the change of liver cancer mortality in each age group by 5-year-period was

255    investigated (Figure 5). Gradual downward trends could be found in the age groups of 15-24, 25-

256    34, and 35-44 years old; but obvious up- or down-ward trends were not observed in the age

257    groups of 45-54 and over, whilst fluctuated at high levels of mortality. However, the mortality of

258    liver cancer in the age group over 75 years has continuously increased so far. Joinpoint

259    regression analysis also shows that the AAPCs in those aged 35-44, 45-54 and 55-64 exhibited

260    significantly decreasing trends, while in those aged 65-74, 75 and over exhibited significantly

261    increasing trends (Figure 6). These results demonstrate that the high mortality rate for liver

262    cancer in the elderly population, together with the increased proportion of the elderly population

263    (aging), has had a great impact on the increasing crude mortality rate of liver cancer in this area.

264    In the United States, the largest increases were observed in persons aged 55-59 years (AAPC,

265    8.9%) and 60–64 years (AAPC, 6.4%) between 2000 and 2012 [22].

266        The encouraging elements of this situation are, however, based upon the birth-cohort

267    analysis. The cohort mortality rates in all age groups of 15-19, 20-24, 25-29, 30-34, 35-39 and

268    40-44 years old, i.e., for those born after the 1950s, have experienced weakened epidemic trends

269    (Figure 7). This outcome has given a clear signal towards the prevention and control of liver

270    cancer: the reduction of liver cancer mortality in the Qidong population has already been

271    reflected in the young generation of this area; and, this downward trend is also being transmitted

272    to the middle-aged cohort population. Thus, the key question is: what kind of causes (measures)

273    led to the change (decline) of liver cancer mortality in the young and middle-aged people in

274    Qidong?

275        Globally, there are many of risk factors contributing to liver cancer etiology, and different

276    populations have disparate risk patterns [23]. Primary prevention precisely aimed at key risk

277    factors is essential and perhaps the only realistic and sustainable approach [24]. During the past

278    decades in the Qidong region, epidemiological and etiological research on liver cancer, control

279    of risk factors, implementation of primary prevention (elimination of exposure to risk factors)

280    and secondary prevention (early diagnosis and early treatment) have been the priority goals for

281    liver cancer studies [6,8,25,26]. This effort has achieved positive results. The main measures that

282    have been targeted to the major causes of liver cancer include: prevention of hepatitis B,

283    prevention of grain-mildew leading to aflatoxin contamination and detoxification, improvement

284    of drinking water source and secondary prevention. Which of these measures has made the most

285    direct and/or significant contributions to the decrease of liver cancer mortality in Qidong?  It is

286    worth assessing the available information and evidence.

287        Hepatitis B virus (HBV) is known as perhaps the most important pathogenic factor of liver

288    cancer etiology. Experimental research on HBV, and control of hepatic diseases have been

289    undertaken since the 1970s in Qidong [6,26-28]. Most important, hepatitis B vaccination in

290    infants started in 1983: the newborns in some of townships would receive three doses of hepatitis

291    B vaccine, but the limited coverage of this program led to only a small proportion of actual

292    vaccinations in the newborns prior to 2002. Then, hepatitis B vaccination was included into the

293    Expanded Program on Immunization (EPI) in China [29,30] which made it possible to vaccinate

294    all newborns with full population (and financial) coverage in Qidong [28].  It does mean though,

295    that as of the year 2017, most of the hepatitis B vaccine recipients have been under the age of 20

296    years, who in turn did not contribute to the real changes observed in the mortality curve. In other

297    words, it is obvious that the curve on the right side of the "1983" birth cohort as in Figure 7 is not

298    enough to affect the downtrend of mortality rate of liver cancer in the Qidong population. But, if

299    one focuses on the period results in Figure 4 one would speculate that the decline curve in the

300    age group of 15-24, for instance, is likely due to vaccination. Obviously, the cross-sectional

301    results (Figure 5) obscure the real effects within the cohort results (Figure 7). An early report

302    from Taiwan proffered a conclusion that the incidence of hepatocellular carcinoma in children

303    has declined due to the hepatitis B vaccination [31]. But, we have noted that even in the figure of

304    their paper, the major decline of incidence for the children of 6-14 years in fact occurred before

305    1984 when the vaccination had not yet been introduced.  In a later paper [32] from a 20-year

306    follow up, it was concluded that the prevention of hepatocellular carcinoma by this HBV vaccine

307    extends from childhood to early adulthood. Accordingly, the decrease of liver cancer

308    incidence/mortality in children/adolescence or young adults in Qidong or in Taiwan must be

309    affected by the elimination or diminution of other risk factors (other than HBV) or other

310    effective measures taken, simply because the changed panorama of liver cancer pattern in the

311    general population happened before vaccination.

312    The relationship between drinking water and liver cancer in Qidong has also attracted the

313    interest of researchers [33,34]. However, it is not clear what kind of substance or pollution in the

314    water was related to the incidence (or mortality) of liver cancer. Possible factors include

315    cyanobacteria toxin (microcystins or cyanotoxins) [35-37], some chemical mutagens [38], or

316    even inorganic arsenic [39] in the water. There have been no reports to provide any strong

317    evidence in animal experiments as to causation of liver cancer, and not enough epidemiological

318    data in the population to establish the relationship between drinking water and the incidence or

319    mortality of liver cancer. It has been reported [409] that the distribution of cyanobacteria in the

320    United States is very extensive, but incidence rate of liver cancer has not been high for decades.

321    However, a recent report, based upon an ecological study in Ohio (USA), observed that a

322    population served by bloom-impacted surface waters had 14.2% higher HCC incidence rates

323    than those served by non-bloom-impacted surface waters [41]. In a Canadian study, however, no

324    association with cyanobacterial toxin exposure in the geographic distribution of liver cancer was

325    observed, implying blue-green algae pollution may not play an important role in the etiology of

326    liver cancer in Canada [42]. Qidong has gradually changed the sources of drinking water since

327    the 1980s and vastly expanded the coverage of piped tap water since the beginning of this

328    century [43]. Yet the existing evidence related to a role of drinking water is not sufficient to

329    illuminate the inevitable relationship between the decrease of liver cancer mortality and the

330    change of drinking water source and causality in Qidong over the past decades.

331    There have been many reports on the relationship between aflatoxin and liver cancer,

332    showing that aflatoxin can be a critical etiological factor of liver cancer in some geographical

333    regions [44-46]. Corn can be easily contaminated by aflatoxin (produced by *Aspergillus flavus*)

334    and was a staple food of Qidong residents for a long time, especially in times of food shortages.

335    In the 1970s, the contamination rate of aflatoxin in corn (levels exceeding 20 ppb) ranged from

336    5.68-98.79% [6]. Animal experiments using corn harvested from Qidong fields exhibited definite

337    hepatocarcinogenic effects on rats and ducks in the 1970s [6]. Since then comprehensive

338    preventive measures to control aflatoxin contamination, so called "post-harvest management",

339    have been undertaken in Qidong [6,26]. In response to social and economic changes, from the

340    mid-1980s, Qidong residents (all age groups) completely changed their habit of eating corn to

341    rice (known to be much less contaminated by aflatoxin) [6,7,26]. These changes of habit and

342    other control measures have led to impressive results evidenced by exposure biomarkers detected

343  in historical biobank blood samples: the median levels of aflatoxin-albumin adducts in Qidong

344  residents decreased significantly from 19.3 pg/mg in 1989 to 3.6 in 1995 pg/mg, 2.3 pg/mg in

345  1999, 1.4 pg/mg in 2003, and undetected (< 0.5 pg/mg) levels in 2009 and 2012 [16]. The

346  exposure level of aflatoxin in this decade has decreased to a level of > 1/40th of the level in the

347  1980s. To date, this provides the most and perhaps only convincing evidence for the causal link

348  (association) between the elimination of risk factors and the reduction of mortality of liver

349  cancer, especially as supported by the birth-cohort analysis that demonstrates about a 50%

350  decrease of ASRW of liver cancer over the past decades. From Figure 5 and Figure 7, we also

351  noted that the trend of mortality at aged 75 and over was not decreasing but in fact increasing.

352  This outcome may reflect that the diminution of aflatoxin exposure in the late period of life was

353  too late to affect aging people or may reflect a "delayed toxicity" [46]. This interpretation is

354  plausible given the long latency period for the development of liver cancer.

355        There may be other risk factors contributing to liver cancer etiology in Qidong. Hepatitis C

356  virus, for example, is of most interest globally [24,47]. However, there has been no evidence to

357  show this virus was common in the general population, or in patients with liver cancer in Qidong

358  over the past 60 years. In our previous nested case-control study early this century, we found that

359  the prevalence of HCV infection was low (1.6% in cases *vs.* 2.1% in controls) and did not seem

360  to play a role in the etiology for liver cancer [48]. A 13.25 year follow-up study in Qidong also

361  indicated that only 6 of 119 liver cancer patients with positive HBV were coinfected with HCV,

362  contributing little to the risk of hepatocellular carcinoma [49]. Besides the major risk factors as

363  mentioned above, there may be other minor risk factors or the interaction effects of risk factors

364  from environment or from mutagens [36,48,50,51]. In recent times, diabetes mellitus (DM),

365  metabolic syndrome (MetS) and obesity or metabolic disease/obesity have been considered as a

366  growing problems for the development of liver cancer [52-54]. In a 2015 study from Jiangsu

367  province where Qidong is located, the prevalences of DM were 8.6% in men and 8.4% in women,

368  and 2.7-4.8% at ages of 18-44 and 13.2% at ages over 65 [55]. In a study of 325 patients with

369  liver cancer in our Qidong hospital [56], 31.38% had type II DM, and those who were at age of

370  over 60 *vs.* under 60, the rates were 43.14% *vs.* 13.28%, indicating a possible association

371  between DM and the risk of liver cancer in the elderly. This may also partially explain why the

372  birth cohort of age groups over 65 had increased mortality (Figure 7). However, in a Taiwan

373  study [57], it was concluded that DM, MetS and obesity were not associated with liver cancer

374    development in hepatitis virus infected groups within an epidemic area. These factors need to be

375    further observed and studied. Hence, among these mentioned factors and or the effects on liver

376    cancer, either there was insufficient evidence or a synergistic effect with aflatoxin or HBV

377    synchronously. Furthermore, the population attributable risk (PAR) for developing liver cancer

378    in the general population was limited, so it was unlikely to affect the downward trend of liver

379    cancer mortality in Qidong.

380          Secondary prevention, which involves early diagnosis and early detection, could influence

381    liver cancer mortality. In the 1970s, a series of large-scale screening programs for early diagnosis

382    and treatment of liver cancer measuring serum alpha-fetoprotein (AFP) were carried out. A large

383    number of early liver cancer patients were detected and some good outcomes achieved [6].

384    However, the mortality rates of liver cancer in Qidong at that period fluctuated at a high level

385    (Figure 1, Table 1). In a 1980's liver cancer screening program in Qidong, it was found that

386    focused screening within a high-risk population could improve the detection levels of liver

387    cancer, with a short-term effect on the change of survival rate, but no effect on mortality in the

388    long term [58]. After 2007, periodical diagnostic screening using combined methods of AFP and

389    ultrasound examination monitoring were recommended. This practice has shown the effect of

390    screening on the early diagnosis and treatment, and may improve the outcome of liver cancer for

391    some [59]. However, the proportion of patients who received the early diagnosis relative to the

392    total number of patients in Qidong was still too small, and insufficient to affect mortality

393    outcomes in the general population. Unfortunately, in general, the now substantial decrease of

394    liver cancer mortality in Qidong cannot be attributed to a change in the detection rate or to

395    improvements in treatment, but rather to changes in the matrix of risk factors in the population.

## 396  Conclusions

397          The crude mortality rate of liver cancer in Qidong experienced a dynamic flux from low to

398    high, then sustained at high levels for decades, followed by a gradual decrease in recent years.

399    After excluding the influence of the "aging" of the Qidong population, it emerged that the

400    decrease of the standardized mortality rate of liver cancer in Qidong happened earlier than that of

401    the crude rate, and the decline has accelerated since the beginning of this century. Moreover, it

402    was first reflected in the newest generation, with a higher slope of decline in men who are at 3-

403    fold higher risk than women overall. In a comprehensive investigation of the risk factors that

404    may affect the downward trends in Qidong, the most significant effect appears to be the control

405  of mildew in the staple food (corn), coupled with profound dietary changes effected by social

406  and economic mandates, to result in dramatic declines in the intake of aflatoxin. This change in

407  the exposure was documented directly with the use of analytically rigorous methods for

408  measures of biological markers in archived serum samples collected longitudinally within the

409  population. The beneficial effect of improving drinking water may not be excluded, but direct

410  positive evidence has not been obtained so far. The prevention of hepatic diseases, such as

411  hepatitis B, must not be ignored, since hepatitis B vaccination has shown effectiveness in

412  prevention of liver diseases in children [31,60], but has not yet been reflected in the prevention

413  of liver cancer in the adult populations. For certain, the present evidence regarding HBV

414  vaccination is not enough to explain or contribute to the current declining trend of liver cancer

415  mortality in Qidong. The change (reduction) of liver cancer mortality in the past six decades has

416  clearly implied that the efforts in Qidong have shown the promise of the control of liver cancer.

417  Through unremitting efforts in a landscape of social, economic, environmental and medical

418  change, liver cancer in Qidong is no longer the number one cause of cancer mortailty, having

419  been overtaken by lung cancer in the past decade [8,61]. The etiological mechanisms need to be

420  explored further, yet the rationale and appropriateness of the measures taken in Qidong area have

421  been proven, and has helped us to better understand the etiology of liver cancer in this region.

422  Six decades of monitoring the state of liver cancer mortality in Qidong coupled with rigorous,

423  longitudinal monitoring of aflatoxin biomarkers, has provided a working example that reducing

424  aflatoxin contamination can be achieved by interventions at the population level; in our case, has

425  also provided vigorous evidence that controlling aflatoxin may help reduce substantively the

426  burden of morbidity and mortality of liver cancer.

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434

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642

643

## Figure Legends

645    FIGURE 1   Natural death rate, mortality rates of cancer and of liver cancer in Qidong, 1958-2017

646    FIGURE 2   AAPC models of WASR by sex for liver cancer mortality in Qidong, 1972-2017

647    FIGURE 3   The APC of liver cancer mortality in Qidong, 1972-2017

648    FIGURE 4   The average ages of patients with liver cancer in Qidong, 1972-2017

649    FIGURE 5   Age-specific mortality rates of liver cancer by period in Qidong, 1972-2017

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651    FIGURE 7   Birth-cohort mortality rates of liver cancer in Qidong, 1972-2017

Crudemortality, truncated rate and cumulative rate of liver cancer in Qidong,1972-2017

1    **Crude mortality, truncated rate and cumulative rate of liver cancer in Qidong, 1972-2017**

| Year | No. of cancer death | No. of liver cancer death | Of total cancer (%) | Liver cancer mortality rate (per 10⁵) | Truncated rate of 35-64 (per 10⁵) | Cumulative rate of 0-74 (%) | Cumulative risk (%) |
|---|---|---|---|---|---|---|---|
| 1958 | 438 | 158 | 36.07 | 20.45 | NA | NA | NA |
| 1959 | 577 | 210 | 36.40 | 26.79 | | | |
| 1960 | 583 | 213 | 36.54 | 26.79 | | | |
| 1961 | 472 | 171 | 36.23 | 21.35 | | | |
| 1962 | 678 | 226 | 33.33 | 27.49 | | | |
| 1963 | 689 | 237 | 34.40 | 27.74 | | | |
| 1964 | 910 | 295 | 32.42 | 33.51 | | | |
| 1965 | 985 | 333 | 33.81 | 36.89 | | | |
| 1966 | 1062 | 358 | 33.71 | 38.77 | | | |
| 1967 | 999 | 322 | 32.23 | 34.13 | | | |
| 1968 | 1183 | 444 | 37.53 | 46.05 | | | |
| 1969 | 1236 | 457 | 36.97 | 46.33 | | | |
| 1970 | 1287 | 502 | 39.01 | 49.80 | | | |
| 1971 | 1377 | 502 | 36.46 | 49.02 | | | |
| 1972 | 1113 | 507 | 45.55 | 49.04 | 138.43 | 5.95 | 5.78 |
| 1973 | 1112 | 469 | 42.18 | 44.97 | 127.22 | 5.40 | 5.26 |
| 1974 | 1309 | 536 | 40.95 | 50.92 | 143.02 | 6.02 | 5.84 |
| 1975 | 1533 | 560 | 36.53 | 52.74 | 148.67 | 6.21 | 6.02 |
| 1976 | 1419 | 524 | 36.93 | 48.92 | 136.96 | 5.81 | 5.65 |
| 1977 | 1468 | 529 | 36.04 | 49.00 | 140.24 | 5.68 | 5.52 |
| 1978 | 1523 | 555 | 36.44 | 51.07 | 143.3 | 5.88 | 5.71 |
| 1979 | 1557 | 555 | 35.65 | 50.84 | 134.29 | 5.55 | 5.40 |
| 1980 | 1517 | 529 | 34.87 | 48.30 | 122.15 | 5.26 | 5.13 |
| 1981 | 1530 | 510 | 33.33 | 46.38 | 119.84 | 4.99 | 4.86 |
| 1982 | 1561 | 528 | 33.82 | 47.72 | 117.56 | 5.14 | 5.01 |
| 1983 | 1615 | 603 | 37.34 | 54.18 | 127.46 | 5.44 | 5.30 |
| 1984 | 1712 | 643 | 37.56 | 57.56 | 137.02 | 5.82 | 5.65 |
| 1985 | 1752 | 634 | 36.19 | 56.60 | 131.84 | 5.85 | 5.68 |
| 1986 | 1731 | 599 | 34.60 | 53.32 | 121.74 | 5.05 | 4.93 |
| 1987 | 1680 | 607 | 36.13 | 53.75 | 125.13 | 5.18 | 5.05 |

| 1988 | 1718 | 569 | 33.12 | 50.02 | 113.80 | 4.63 | 4.53 |
| 1989 | 1740 | 536 | 30.80 | 46.77 | 100.11 | 4.16 | 4.07 |
| 1990 | 1973 | 619 | 31.37 | 53.62 | 115.51 | 4.75 | 4.64 |
| 1991 | 1963 | 622 | 31.69 | 53.59 | 110.56 | 4.69 | 4.58 |
| 1992 | 1976 | 599 | 30.31 | 51.51 | 111.16 | 4.46 | 4.36 |
| 1993 | 2034 | 680 | 33.43 | 58.43 | 116.94 | 4.91 | 4.79 |
| 1994 | 2182 | 792 | 36.30 | 68.02 | 127.76 | 5.81 | 5.64 |
| 1995 | 2313 | 804 | 34.76 | 69.07 | 127.65 | 5.46 | 5.31 |
| 1996 | 2231 | 794 | 35.59 | 68.13 | 118.33 | 5.18 | 5.05 |
| 1997 | 2064 | 802 | 38.86 | 68.71 | 114.69 | 5.32 | 5.18 |
| 1998 | 2269 | 803 | 35.39 | 68.83 | 111.38 | 5.09 | 4.96 |
| 1999 | 2266 | 797 | 35.17 | 68.51 | 118.64 | 5.04 | 4.91 |
| 2000 | 2407 | 810 | 33.65 | 69.73 | 114.43 | 5.05 | 4.92 |
| 2001 | 2347 | 853 | 36.34 | 73.58 | 115.23 | 5.04 | 4.92 |
| 2002 | 2399 | 863 | 35.97 | 74.79 | 115.67 | 5.05 | 4.93 |
| 2003 | 2456 | 809 | 32.94 | 70.50 | 104.53 | 4.67 | 4.57 |
| 2004 | 2656 | 913 | 34.38 | 80.16 | 110.07 | 5.43 | 5.29 |
| 2005 | 2897 | 863 | 29.79 | 76.28 | 102.88 | 4.93 | 4.81 |
| 2006 | 2818 | 841 | 29.84 | 74.65 | 96.44 | 4.89 | 4.77 |
| 2007 | 2853 | 802 | 28.11 | 71.52 | 91.19 | 4.24 | 4.15 |
| 2008 | 3230 | 885 | 27.40 | 79.28 | 94.67 | 4.85 | 4.73 |
| 2009 | 3043 | 798 | 26.22 | 71.57 | 80.65 | 4.26 | 4.17 |
| 2010 | 3163 | 751 | 23.74 | 67.16 | 80.29 | 3.70 | 3.64 |
| 2011 | 3324 | 746 | 22.44 | 66.47 | 75.38 | 3.81 | 3.74 |
| 2012 | 3127 | 745 | 23.82 | 66.28 | 73.05 | 3.84 | 3.77 |
| 2013 | 3199 | 703 | 21.98 | 62.56 | 63.85 | 3.51 | 3.44 |
| 2014 | 3142 | 649 | 20.66 | 57.77 | 55.09 | 3.02 | 2.98 |
| 2015 | 3451 | 686 | 19.88 | 61.15 | 58.70 | 3.41 | 3.36 |
| 2016 | 3494 | 651 | 18.63 | 58.12 | 49.91 | 3.09 | 3.04 |
| 2017 | 3523 | 588 | 16.69 | 52.61 | 43.92 | 2.84 | 2.80 |
| **Total*** | **102390** | **31261** | **30.53** | **60.48** | **104.06** | **4.79** | **4.68** |

3      * Sum of 1972-2017 registered data.

**The APC and AAPC of liver cancer mortality bymultiple models simultaneously in Qidong, 1972-2017**

1 **The APC and AAPC of liver cancer mortality by multiple models simultaneously in Qidong, 1972-2017**

| Cohort | Trend (Segment) | Period | APC | 95% CI | Test Statistic (t) | Prob > \|t\| |
|---|---|---|---|---|---|---|
| *APC:* | | | | | | |
| Both sexes | 1 | 1972-1992 | -1.4* | -1.8 to -0.9 | -6.1 | 0.00 |
| | 2 | 1992-1995 | 4.5 | -9.9 to 21.2 | 0.6 | 0.50 |
| | 3 | 1995-2006 | -1.4* | -2.5 to -0.3 | -2.7 | 0.00 |
| | 4 | 2006-2017 | -4.7* | -5.7 to -3.7 | -9.3 | 0.00 |
| Male | 1 | 1972-2005 | -0.8* | -1.1 to -0.6 | -7.0 | 0.00 |
| | 2 | 2005-2017 | -4.5* | -5.6 to -3.4 | -8.4 | 0.00 |
| Femal | 1 | 1972-1986 | -0.4 | -1.7 to 0.9 | -0.7 | 0.50 |
| | 2 | 1986-1989 | -11.5 | -33 to 16.9 | -0.9 | 0.40 |
| | 3 | 1989-1994 | 7.7 | -1.1 to 17.2 | 1.8 | 0.10 |
| | 4 | 1994-2008 | -1.1 | -2.3 to 0.0 | -2.0 | 0.10 |
| | 5 | 2008-2017 | -4.7* | -6.8 to -2.6 | -4.5 | 0.00 |
| *AAPC:* | | | | | | |
| Both sexes | All period 1972-2017 | | -1.3* | -1.6 to -1.1 | -10.2 | 0.00 |
| | 3 Joinpoints | | -1.8* | -2.8 to -0.8 | -3.5 | 0.00 |
| Male | All period 1972-2017 | | -1.5* | -1.7 to -1.2 | -11.7 | 0.00 |
| | 1 Joinpoint | | -1.8* | -2.2 to -1.5 | -10.8 | 0.00 |
| Female | All period 1972-2017 | | -1.0* | -1.3 to -0.7 | -6.4 | 0.00 |
| | 4 Joinpoints | | -1.4 | -3.5 to 0.7 | -1.3 | 0.20 |

3  * Indicate that it is significantly different from zero at the alpha = 0.05

Crude rate, ASRC, and ASRW by sex for liver cancermortality in Qidong, 1972-2017 (per $10^5$)

1    **Crude rate, ASRC, and ASRW by sex for liver cancer mortality in Qidong, 1972-2017 (per 10⁵)**

| Year | Male | | | | Female | | | | Total | | | |
|------|------|------|------|------|--------|------|------|------|-------|------|------|------|
| | No. of Death | CR | ASRC | ASRW | No. of Death | CR | ASRC | ASRW | No. of Death | CR | ASRC | ASRW |
| 1972 | 394 | 77.76 | 75.96 | 96.73 | 113 | 21.43 | 18.01 | 23.16 | 507 | 49.04 | 45.11 | 57.34 |
| 1973 | 352 | 68.85 | 66.70 | 84.32 | 117 | 22.01 | 20.30 | 24.71 | 469 | 44.97 | 41.97 | 52.36 |
| 1974 | 390 | 75.43 | 73.34 | 91.49 | 146 | 27.26 | 23.62 | 30.33 | 536 | 50.92 | 47.02 | 58.87 |
| 1975 | 432 | 82.71 | 80.99 | 101.73 | 128 | 23.72 | 19.10 | 25.33 | 560 | 52.74 | 48.25 | 61.12 |
| 1976 | 416 | 78.88 | 77.61 | 95.54 | 108 | 19.87 | 16.98 | 21.66 | 524 | 48.92 | 45.67 | 56.42 |
| 1977 | 415 | 78.05 | 74.07 | 93.58 | 114 | 20.81 | 16.90 | 22.17 | 529 | 49.00 | 44.06 | 55.96 |
| 1978 | 415 | 77.54 | 71.85 | 90.19 | 140 | 25.38 | 22.25 | 28.11 | 555 | 51.07 | 45.93 | 57.49 |
| 1979 | 409 | 76.06 | 68.78 | 85.39 | 146 | 26.35 | 22.21 | 27.93 | 555 | 50.84 | 44.61 | 55.38 |
| 1980 | 395 | 73.42 | 63.65 | 80.27 | 134 | 24.05 | 19.29 | 24.71 | 529 | 48.30 | 40.67 | 51.30 |
| 1981 | 388 | 71.81 | 61.55 | 76.59 | 122 | 21.81 | 17.78 | 22.80 | 510 | 46.38 | 39.08 | 48.75 |
| 1982 | 411 | 75.31 | 62.37 | 78.76 | 117 | 20.87 | 16.75 | 21.47 | 528 | 47.72 | 39.01 | 49.16 |
| 1983 | 448 | 81.59 | 66.26 | 83.21 | 155 | 27.49 | 21.11 | 27.26 | 603 | 54.18 | 43.20 | 54.27 |
| 1984 | 511 | 92.69 | 74.72 | 92.64 | 132 | 23.33 | 17.41 | 22.43 | 643 | 57.56 | 45.65 | 56.93 |
| 1985 | 480 | 86.66 | 67.39 | 85.81 | 154 | 27.19 | 19.92 | 25.73 | 634 | 56.60 | 43.25 | 55.02 |
| 1986 | 459 | 82.59 | 63.28 | 78.51 | 140 | 24.66 | 17.67 | 22.79 | 599 | 53.32 | 40.15 | 50.15 |
| 1987 | 467 | 83.63 | 63.16 | 78.78 | 140 | 24.52 | 17.44 | 22.44 | 607 | 53.75 | 39.99 | 50.06 |
| 1988 | 454 | 80.64 | 59.55 | 73.50 | 115 | 20.02 | 14.32 | 18.17 | 569 | 50.02 | 36.67 | 45.37 |
| 1989 | 421 | 74.18 | 53.47 | 66.48 | 115 | 19.88 | 13.54 | 17.15 | 536 | 46.77 | 33.26 | 41.31 |
| 1990 | 495 | 86.52 | 60.88 | 76.67 | 124 | 21.29 | 14.97 | 18.44 | 619 | 53.62 | 37.55 | 46.85 |
| 1991 | 475 | 82.51 | 56.14 | 70.28 | 147 | 25.13 | 15.31 | 20.42 | 622 | 53.59 | 35.54 | 45.04 |
| 1992 | 465 | 80.54 | 53.86 | 66.95 | 134 | 22.88 | 14.63 | 18.61 | 599 | 51.51 | 34.11 | 42.56 |
| 1993 | 529 | 91.46 | 57.75 | 74.93 | 151 | 25.79 | 14.78 | 20.30 | 680 | 58.43 | 36.06 | 47.16 |
| 1994 | 594 | 102.79 | 62.82 | 81.58 | 198 | 33.77 | 19.12 | 25.64 | 792 | 68.02 | 40.78 | 53.29 |
| 1995 | 600 | 104.01 | 62.01 | 79.41 | 204 | 34.74 | 18.88 | 25.72 | 804 | 69.07 | 40.21 | 52.14 |
| 1996 | 600 | 103.78 | 59.01 | 77.45 | 194 | 33.04 | 17.24 | 23.09 | 794 | 68.13 | 37.93 | 49.88 |
| 1997 | 584 | 100.82 | 56.17 | 72.96 | 218 | 37.07 | 18.40 | 25.79 | 802 | 68.71 | 37.13 | 49.11 |
| 1998 | 600 | 103.77 | 56.67 | 73.41 | 203 | 34.49 | 17.38 | 23.77 | 803 | 68.83 | 36.77 | 48.12 |
| 1999 | 619 | 107.41 | 57.68 | 75.10 | 178 | 30.32 | 15.41 | 20.62 | 797 | 68.51 | 36.42 | 47.59 |
| 2000 | 608 | 105.58 | 54.24 | 71.40 | 202 | 34.49 | 16.46 | 22.66 | 810 | 69.73 | 35.22 | 46.80 |
| 2001 | 667 | 116.12 | 59.61 | 77.24 | 186 | 31.80 | 14.31 | 19.99 | 853 | 73.58 | 36.76 | 48.30 |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 2002 | 669 | 117.00 | 56.22 | 74.49 | 194 | 33.32 | 15.04 | 21.01 | 863 | 74.79 | 35.46 | 47.40 |
| 2003 | 605 | 106.42 | 50.16 | 67.10 | 204 | 35.23 | 15.00 | 20.94 | 809 | 70.50 | 32.45 | 43.74 |
| 2004 | 684 | 121.53 | 56.17 | 75.08 | 229 | 39.75 | 15.90 | 22.82 | 913 | 80.16 | 35.87 | 48.61 |
| 2005 | 631 | 112.98 | 49.42 | 67.38 | 232 | 40.50 | 15.63 | 22.71 | 863 | 76.28 | 32.36 | 44.66 |
| 2006 | 619 | 111.35 | 48.62 | 66.16 | 222 | 38.90 | 13.95 | 20.67 | 841 | 74.65 | 31.14 | 43.11 |
| 2007 | 590 | 106.68 | 44.41 | 61.02 | 212 | 37.30 | 13.00 | 18.95 | 802 | 71.52 | 28.58 | 39.67 |
| 2008 | 624 | 113.41 | 46.94 | 64.01 | 261 | 46.11 | 16.19 | 23.83 | 885 | 79.28 | 31.44 | 43.61 |
| 2009 | 581 | 105.87 | 41.18 | 57.89 | 217 | 38.33 | 13.75 | 20.03 | 798 | 71.57 | 27.27 | 38.50 |
| 2010 | 549 | 99.86 | 38.83 | 53.57 | 202 | 35.54 | 11.04 | 16.64 | 751 | 67.16 | 24.81 | 34.79 |
| 2011 | 545 | 98.84 | 37.76 | 52.98 | 201 | 35.21 | 10.91 | 16.54 | 746 | 66.47 | 24.16 | 34.39 |
| 2012 | 522 | 94.54 | 34.00 | 49.31 | 223 | 39.00 | 12.57 | 18.81 | 745 | 66.28 | 23.10 | 33.66 |
| 2013 | 496 | 89.93 | 32.53 | 47.47 | 207 | 36.18 | 9.78 | 15.86 | 703 | 62.56 | 20.99 | 31.30 |
| 2014 | 451 | 81.91 | 28.01 | 41.99 | 198 | 34.57 | 9.81 | 15.66 | 649 | 57.77 | 18.69 | 28.30 |
| 2015 | 494 | 89.89 | 30.76 | 46.94 | 192 | 33.55 | 9.17 | 14.68 | 686 | 61.15 | 19.69 | 30.17 |
| 2016 | 464 | 84.60 | 27.70 | 43.19 | 187 | 32.71 | 8.68 | 14.36 | 651 | 58.12 | 17.87 | 28.01 |
| 2017 | 411 | 75.13 | 24.45 | 38.88 | 177 | 31.02 | 7.86 | 13.04 | 588 | 52.61 | 15.87 | 25.27 |
| **Total** | **23428** | **91.86** | **54.55** | **71.18** | **7833** | **29.92** | **15.67** | **21.44** | **31261** | **60.48** | **34.78** | **45.71** |

# Figure 1

Natural death rate, mortality rates of cancer and of liver cancer in Qidong, 1958-2017
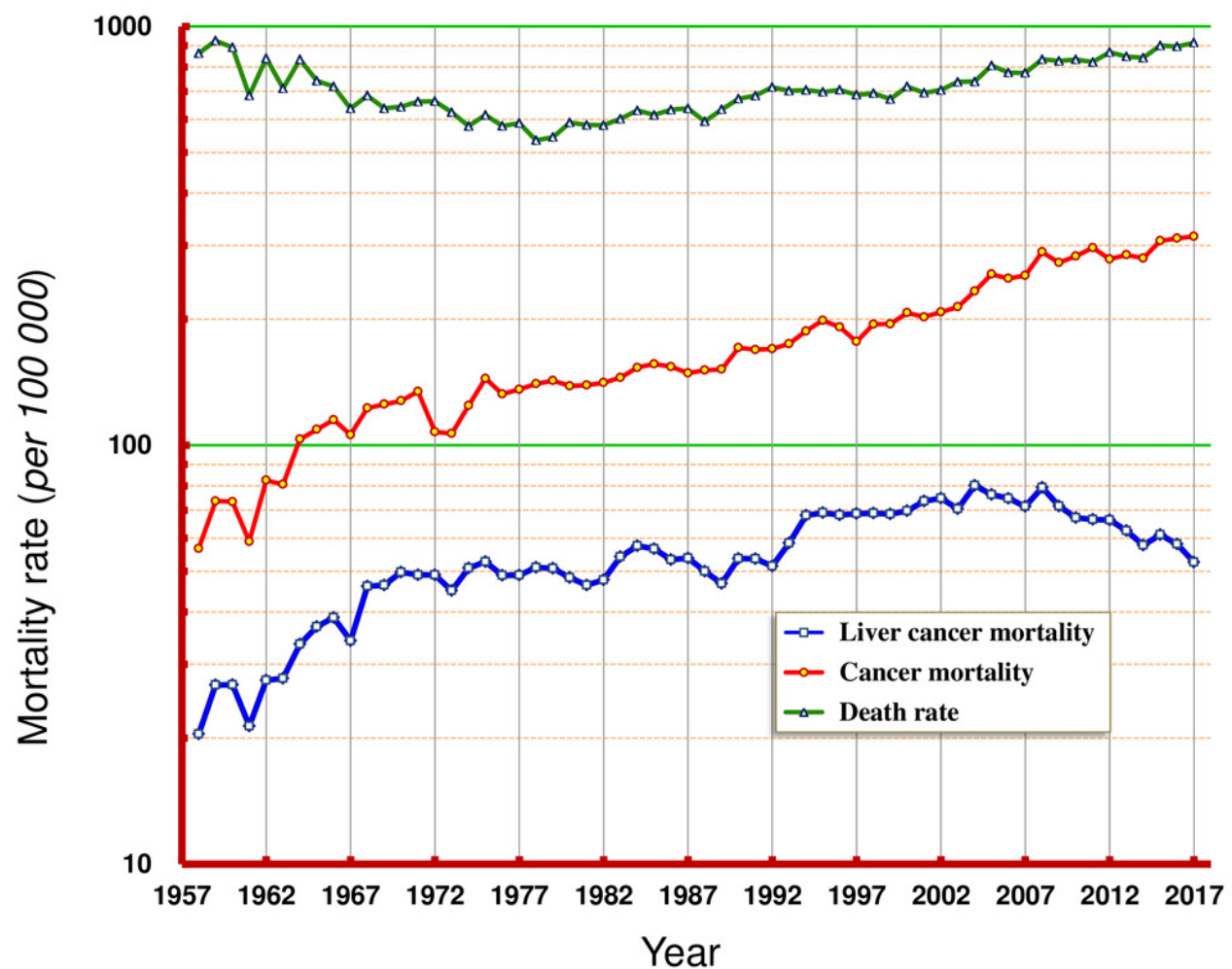
FIGURE 1

# Figure 2

AAPCmodels of WASR by sex for liver cancer mortality in Qidong, 1972-2017

AAPC models of WASR by sex for liver cancer mortality in Qidong, 1972-2017
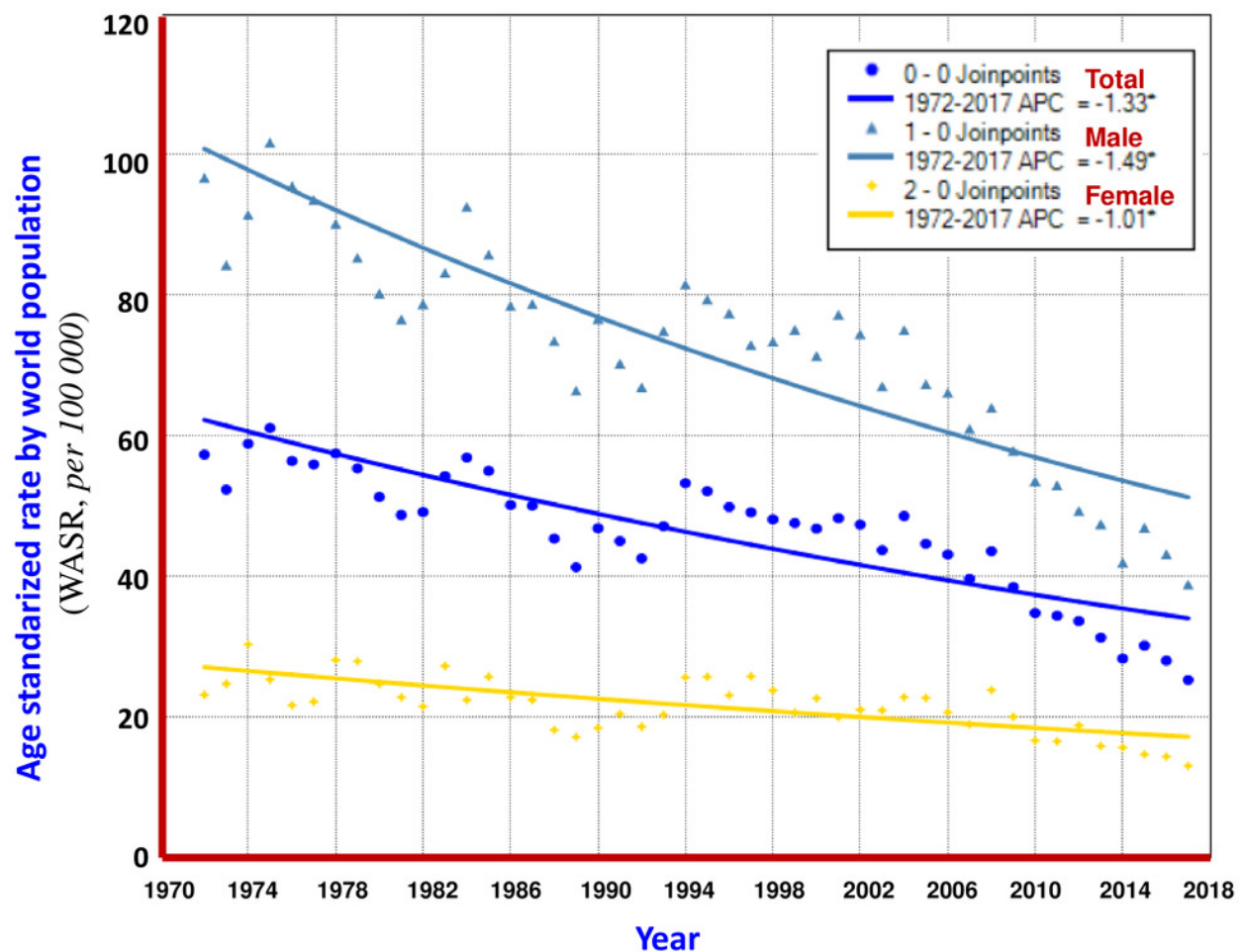
FIGURE 2

# Figure 3

The APC of liver cancer mortality in Qidong, 1972-2017
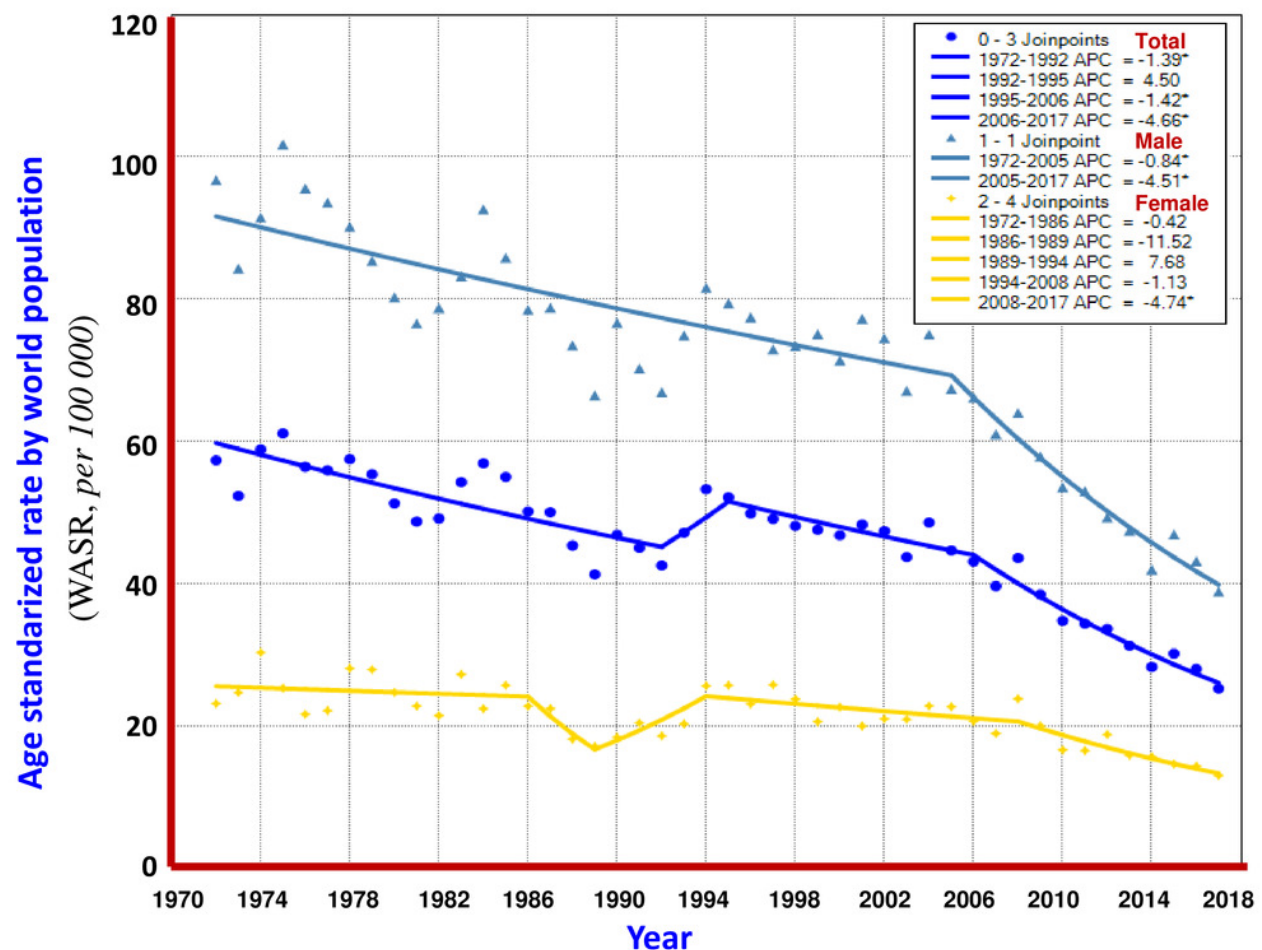
FIGURE 3

# Figure 4

The average ages of patients with liver cancer in Qidong, 1972-2017
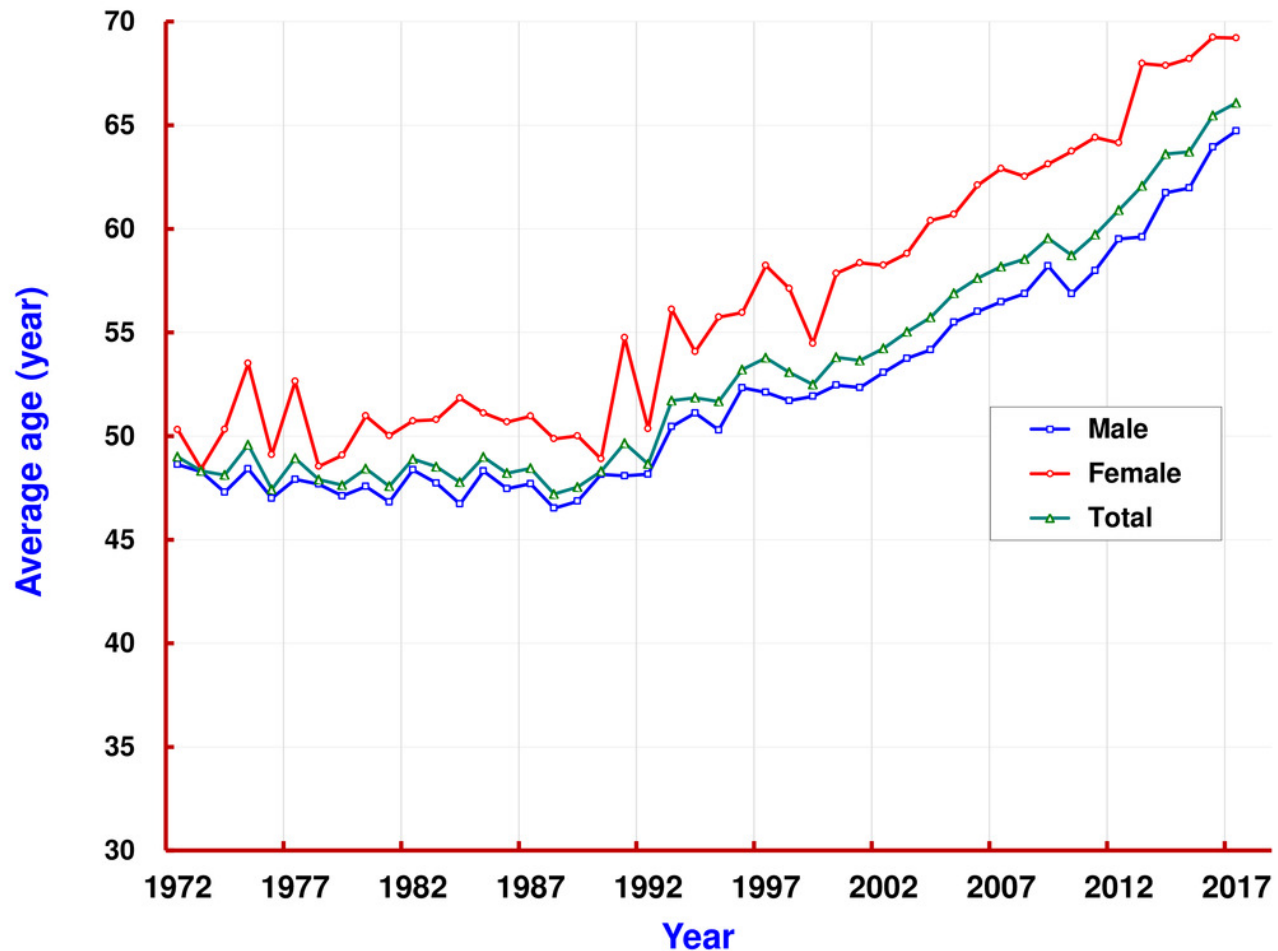
FIGURE 4

# Figure 5

Age-specific mortality rates of liver cancer by period in Qidong, 1972-2017
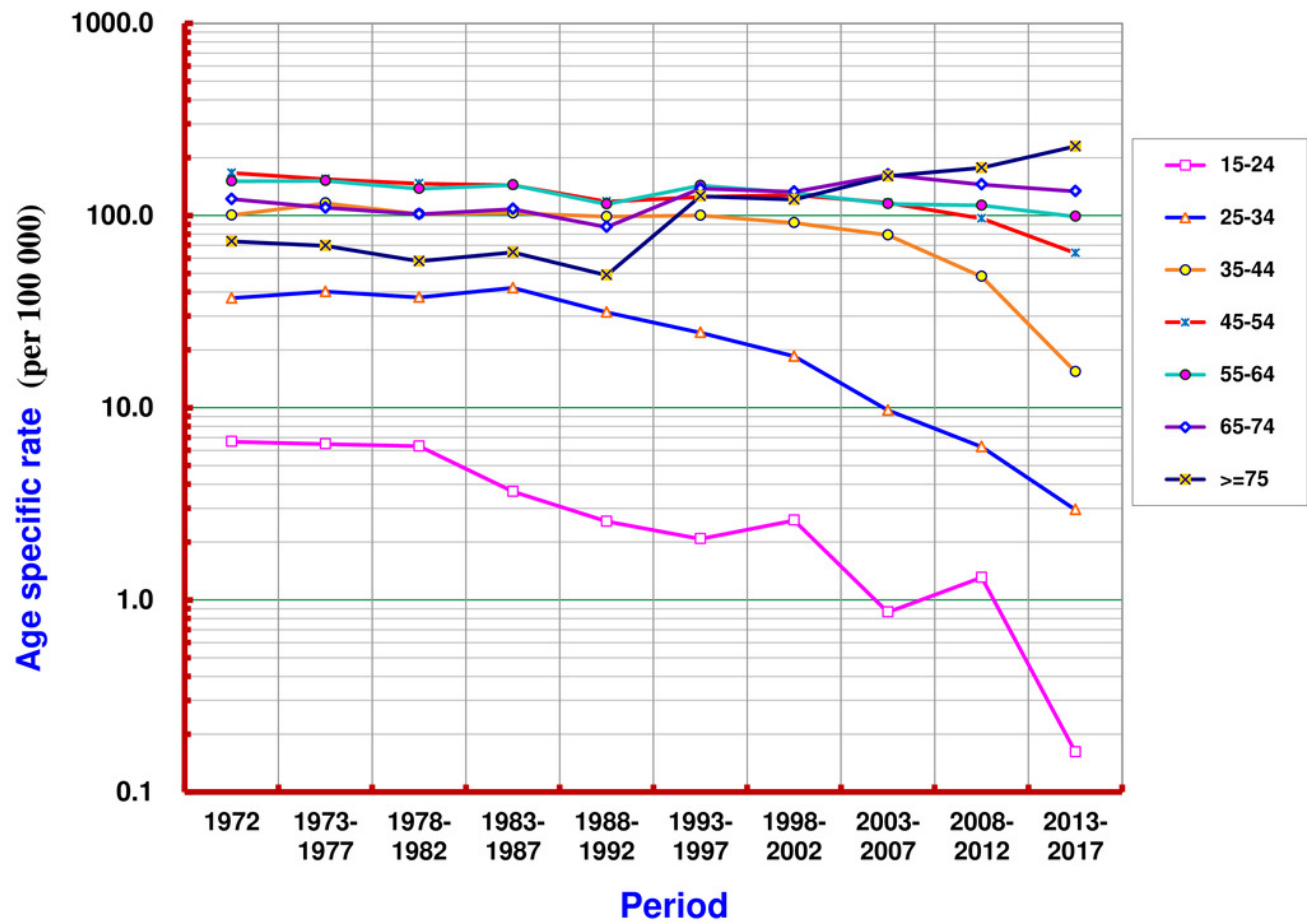
FIGURE 5

# Figure 6

AAPCs of mortality rates of liver cancer by age group in Qidong, 1972-2017
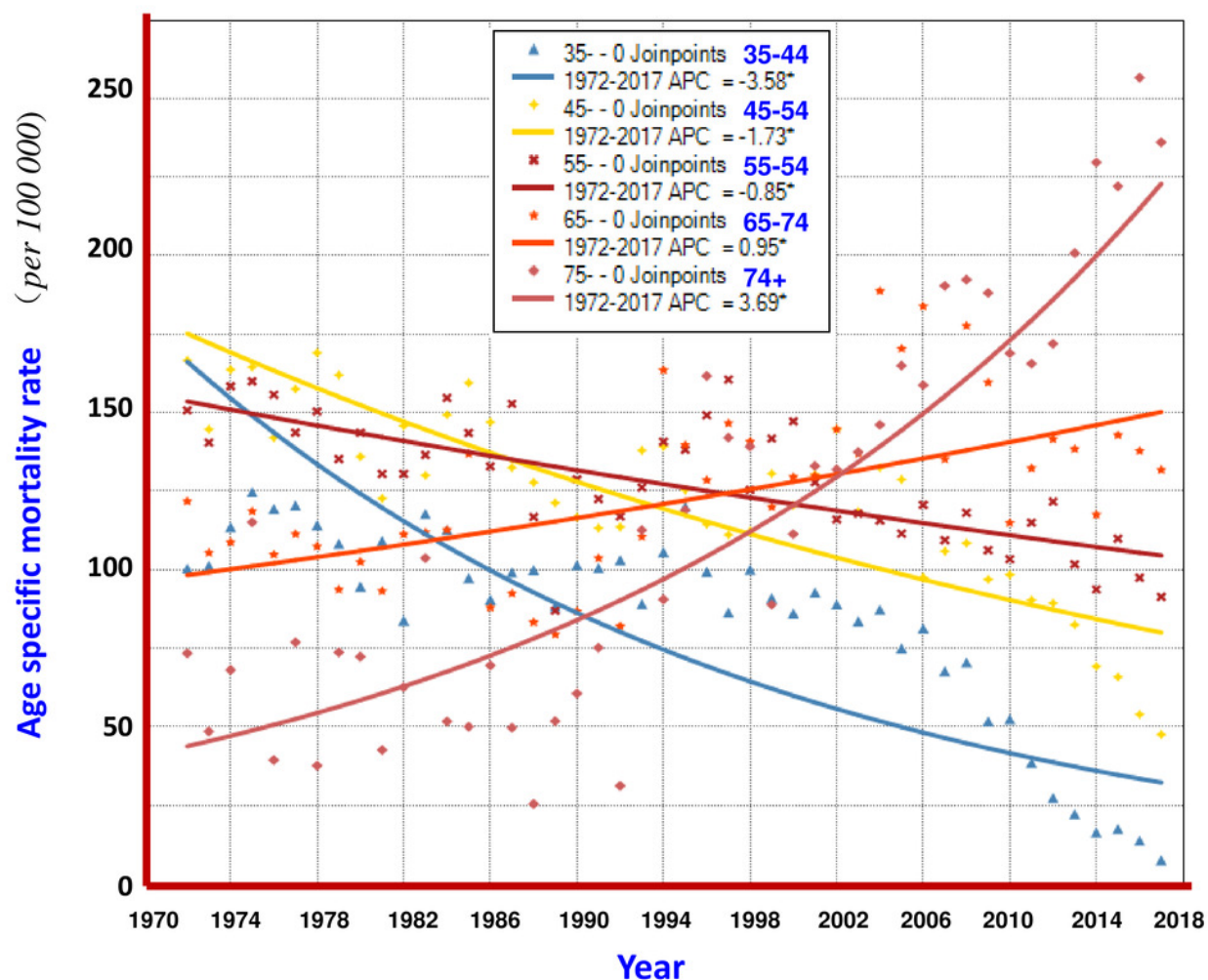
FIGURE 6

# Figure 7

Birth-cohort mortality rates of liver cancer in Qidong, 1972-2017

FIGURE 7