RESEARCH ARTICLE

Cohort Analysis of Incidence/Mortality of Liver Cancer in Japan through Logistic Curve Fitting

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Abstract

Incidence/mortality of liver cancer follow logistic curves because there is a limit reflecting the prevalence of hepatitis virus carriers in the cohort. The author fitted logistic curves to incidence/mortality data covering the nine five-year cohorts born in 1911-1955 of both sexes. Goodness-of-fit of logistic curves was sufficiently precise to be used for future predictions. Younger cohorts born in 1936 or later were predicted to show constant decline in incidence/mortality in the future. The male cohort born in 1931-35 showed an elevated incidence/mortality of liver cancer early in their lives supporting the previous claim that this particular cohort had suffered massive HCV infection due to nation-wide drug abuse in the 1950s. Declining case-fatality observed in younger cohorts suggested improved treatment of liver cancer. This study demonstrated that incidence/mortality of liver cancer follow logistic curves and fitted logistic formulae can be used for future prediction. Given the predicted decline of incidence/mortality in younger cohorts, liver cancer is likely to be lost to history in the not-so-distant future.

Keywords: Liver cancer - incidence - mortality - cohort analysis - logistic curve

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Introduction

Liver cancer follows unique age- and cohort-specific pattern in incidence/mortality different from other types of cancer. Age-specific incidence/mortality of most types of cancer shows exponential increase with age. However, because most liver cancer is caused by chronic infection of hepatitis viruses, the age-specific incidence/mortality of liver cancer will level off once a certain limit is reached and is therefore highly predictable for the future trend. Such limit is determined by the prevalence of hepatitis virus carriers and varies considerably among cohorts reflecting the different risk of infection of each cohort (Tsukuma et al., 2005).

Such self-limiting pattern is expected to follow logistic curve instead of exponential curve and the author fitted logistic curves to the incidence/mortality data of liver cancer in Japan. If logistic curves fit well with the observed incidence/mortality, it will provide a good prediction for the future. Also, it will illustrate difference in incidence/mortality among different cohorts.

Materials and Methods

Mortality data were obtained from the vital statistics. Site-specific cancer mortality of five-year age groups at 13 points of five year interval (1950, 1955, 1960, 1965, 1970, 1975, 1980, 1985, 1990, 1995, 2000, 2005 and 2010) was used for the purpose of cohort analysis (five-year age group at five year interval is equivalent to cohort analysis).

Incidence data were obtained from the estimates by the National Cancer Center (Matsuda et al., 2011) for five-year age groups covering seven points (1975, 1980, 1985, 1990, 1995, 2000 and 2005).

The incidence/mortality data were collated for nine cohorts (born in 1911-15, 1916-20, 1921-25, 1926-30, 1931-35, 1936-40, 1941-45, 1946-50 and 1951-55) covering 12 five-year age groups (age 30-34, 35-39, 40-44, 45-49, 50-54, 55-59, 60-64, 65-69, 70-74, 75-79, 80-84 and 85-89).

The logistic curve for incidence/mortality (**y**) of $\mathbf{x^{th}}$ age group (x=1, 2, 3...12) is expressed as;

$$\mathbf{y=K/[1+\exp(-ax+b)]}$$

Where **K** is the limit of incidence/mortality of liver cancer of a given cohort. Coefficient of **K**, **a** and **b** were estimated for each sex-cohort by optimization method using Excel Solver to minimize the sum of squares of the difference between the observed (**Y**) and fitted (**y**) incidence/mortality of $\mathbf{x^{th}}$ age group (x=1, 2, 3...12);

$$\mathbf{\Sigma(y_x-Y_x)^2}$$

The goodness-of-fit was evaluated by R^2 between observed (**Y**) and fitted (**y**) incidence/mortality for each sex-cohort.

The fitted logistic curves were used to predict the future incidence/mortality of each cohort.

For example, the male cohort born in 1946-50 has observed incidence up to the age group of 55-59 (6^{th} age group) and observed mortality up to the age group of 60-64 (7^{th} age group). The future incidence/mortality of this cohort will be predicted by the following logistic curves).

$$\mathbf{Incidence=90.3/EXP(-0.78*x+4.26)}$$
$$\mathbf{Mortality=61.8/EXP(-0.83*x+4.42)}$$

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Then their incidence in the age group of 60-64 is predicted to be 69.7 per 100,000 and their mortality in the age group of 65-69 is predicted to be 79.5 per 100,000 respectively.

Results

An example of the male cohort born in 1916-20 is presented in (Figure 1) (other graphs are omitted). The results of fitted logistic curves are summarized in (Table 1). The goodness-of-fit is strikingly good: all of the R^2 was close to one.

The observed and predicted mortality of liver cancer is presented in Figure 2. The different mortality pattern in male cohorts between those born before/after 1936 is clearly visible in (Figure 2A). Gradual and dramatic reduction of mortality of liver cancer for male cohorts

Table 1. Estimated Coefficients of Logistic Curve

	Male				Female			
	K	a	b	R^2	K	a	b	R^2
Incidence								
1911-15cohort	211.80	0.84	7.02	0.98	123.67	0.65	6.30	0.99
1916-20cohort	195.10	1.00	7.42	0.97	99.28	1.02	8.41	0.99
1921-25cohort	206.67	1.16	7.94	0.98	95.50	1.21	9.36	0.98
1926-30cohort	213.25	1.27	7.74	0.99	99.34	1.03	7.67	1.00
1931-35cohort	190.38	1.29	7.09	1.00	78.11	1.09	7.53	1.00
1936-40cohort	148.10	0.95	5.48	0.99	75.08	0.84	6.25	1.00
1941-45cohort	153.19	0.77	4.86	0.99	80.00	0.75	6.00	0.99
1946-50cohort	90.27	0.78	4.26	1.00	87.05	0.76	6.27	0.98
1951-55cohort	61.75	0.83	4.42	0.99	51.18	0.63	5.27	0.99
Mortality								
1911-15cohort	209.42	0.61	5.35	0.99	204.24	0.41	5.01	1.00
1916-20cohort	201.98	0.70	5.62	1.00	114.33	0.68	6.28	1.00
1921-25cohort	200.79	0.80	5.90	1.00	122.16	0.67	6.14	1.00
1926-30cohort	197.94	0.93	6.12	1.00	98.02	0.85	6.94	1.00
1931-35cohort	183.80	1.07	6.34	1.00	81.24	0.89	6.88	1.00
1936-40cohort	116.67	0.99	5.72	1.00	60.77	0.76	6.03	1.00
1941-45cohort	82.27	0.94	5.15	1.00	43.13	0.72	5.63	1.00
1946-50cohort	61.75	0.83	4.42	1.00	86.91	0.60	6.07	1.00
1951-55cohort	36.97	0.99	4.55	1.00	66.64	0.56	5.83	0.99

*logistic curve: y=K/(1+exp(-ax+b))

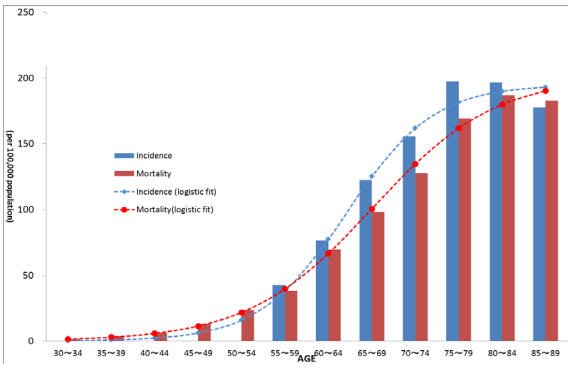

Figure 1. Cohort 1916~20 (Male). Source: Incidence: Cancer incidence and incidence rate in Japan in 2005: Based on data from the Japan (MCIJ) project. Japanese Journal of Clinical Oncology, 41, Mortality: vital statistics

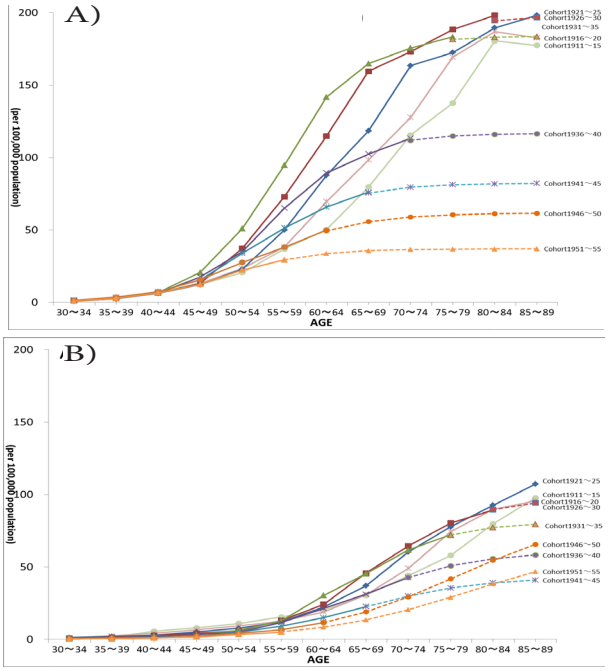

Figure 2. Age-Specific Mortality of Liver Cancer [A) Male, B) Female]. Observed (bold line) and prediction (dotted line) by logistic regression

Table 2. Observed Case-Fatality (Mortality/Incidence)

Age Group:	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85-89
Male												
Cohort1911-15							97.5%	94.8%	79.2%	89.0%	91.2%	88.2%
Cohort1916-20						89.6%	91.2%	80.4%	81.9%	85.8%	94.9%	102.8%
Cohort1921-25					86.2%	87.0%	77.9%	75.1%	77.4%	88.8%	94.6%	
Cohort1926-30				73.6%	85.1%	73.8%	73.4%	75.6%	86.1%	90.1%		
Cohort1931-35			86.8%	75.6%	83.1%	75.3%	83.7%	93.6%	91.4%			
Cohort1936-40		119.1%	72.8%	77.9%	71.5%	74.2%	84.0%	75.3%				
Cohort1941-45	79.0%	112.0%	83.0%	63.3%	74.4%	79.6%	66.5%					
Cohort1946-50	110.1%	70.7%	55.2%	71.2%	75.1%	69.2%						
Cohort1951-55	97.0%	63.5%	80.3%	73.8%	64.5%							
Female												
Cohort1911-15							110.8%	90.7%	93.2%	88.2%	86.6%	98.1%
Cohort1916-20						89.1%	85.8%	74.8%	75.2%	81.5%	93.1%	104.2%
Cohort1921-25					110.3%	86.9%	85.4%	73.2%	69.0%	92.2%	98.4%	
Cohort1926-30				79.0%	88.4%	71.6%	65.6%	70.9%	79.1%	86.6%		
Cohort1931-35			115.0%	78.7%	77.9%	61.3%	71.1%	76.1%	86.4%			
Cohort1936-40		110.3%	115.1%	82.4%	50.0%	72.4%	66.6%	66.9%				
Cohort1941-45	31.5%	128.0%	93.0%	45.9%	63.7%	69.2%	58.7%					
Cohort1946-50	107.0%	77.9%	37.7%	55.7%	75.3%	47.6%						
Cohort1951-55	119.9%	37.4%	52.1%	56.5%	60.0%							

born after 1936 is predicted as shown in dotted line in (Figure 2A).

Female cohorts show much lower mortality than male (Figure 2B) and lines appear to be condensed. Female cohorts born after 1946 show upward prediction lines but this may be due to insufficient number of observed points to make reliable predictions.

Observed case-fatality (mortality divided by incidence) is presented in (Table 2). Viewing the same age group down through cohorts, one recognizes improved treatment of liver cancer. For example, the case-fatality of male age group of 60-64 was 97.5% for the cohort born 1911-15 but improved dramatically to 66.5% for the cohort born 1941-45 (case-fatality rate is unstable in young age and cohort groups due to small sample size).

Discussion

The incidence/mortality of liver cancer was demonstrated to follow logistic curves in Japan with remarkable goodness-of-fit (R^2 close to one). The same goodness-of-fit was also reported in China (0.9885 for male, 0.9912 for female) and it appears plausible that logistic curve fitting is applicable to liver cancer generally (Qiao et al., 1989). The same cohort analysis on liver cancer incidence was also conducted in the U.S. using the SEER(Surveillance, Epidemiology and End Results) registries covering the same period with this study (1975-2005; Altekruse et al., 2009). The pattern of age-specific incidence of different cohorts presented in the study appears to be part of logistic curves but the author stopped short of applying any mathematical models.

Not only did this study established a mathematical model for predicting the incidence/mortality of liver cancer, it also provided statistical evidence to the claim by Tsukuma that "the extremely high incidence among birth cohorts around 1931-35 was related to an endemic of HCV infection among those generations in Japan. It was an outbreak of parenteral amphetamine use in the devastated society after World War II. People born in 1931-35, who were aged early twenties then, seem to have had a greater chance of HCV infection" (Tsukuma et al., 2005).

It is noteworthy that the coefficient, a, was largest in mortality (and male incidence) of the cohort born in 1931-35 in both sexes. The large coefficient, a, meant that those in this cohort died of liver cancer earlier in life. Figure 2A illustrates that both male cohorts born in 1911-1915 and 1931-35 reached the almost same mortality in their 80s (nearly 200 per 100,000). But when they were in the age of 55-59 (the most responsible and productive phase of life), the cohort born 1931-35 had more than twice the mortality of their 20 years seniors (94.7 vs 36.9 per 100,000). It is highly likely that many men born in 1931-35 were infected with HCV when they were in their twenties and later developed liver cancer when they grew older. In early 1950s, even professionals were not aware of the risk of infection through needle sharing.

The wide-spread abuse of methamphetamine, called "hiropon", in the 1950s and the government's desperate efforts against it is amply described by an American historian in a recent article (Alexander, 2013). Eventually, the abuse was controlled and men born after 1936 escaped from HCV infection. Good fitting of logistic curves means that there is a limit to incidence/mortality of liver cancer and it is possible to predict the future with good accuracy.

Viewing (Figure 1), one can tell that men born in 1936 or later will see their incidence/mortality much lower than men born before 1936 and decline further with the cohorts. When men born in 1951-55 become in their 80s, their liver cancer mortality will be close to 1/10 of the men born before 1936. By then, sex difference will be narrowed to be negligible.

Vaccination for babies born to HBV positive mothers starting in 1986 all but eradicated mother-child infection of HBV and prevalence of HCV carriers is also declining among young generations (Tanaka et al., 2011). It is likely that incidence/mortality of liver cancer will decline further than the level predicted in this study.

Historians might describe liver cancer as "a disease lost in the history" in a not-so-distant future.

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