

Mortality from primary liver cancer in Switzerland from 1975 to 1994

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Summary

Background/Aims: The aim of the present study was to analyze the mortality from primary liver cancer in Switzerland over a 20 year period and compare our results with the mortality data from Germany, France, Italy and Austria.

Methods: Absolute and age-standardized mortality rates for primary liver cancer from 1975 to 1994 were obtained from the Swiss Federal Office of Statistics. The corresponding figures (1980–1994) for Germany, France, Italy and Austria were extracted from the World Health Organization mortality database.

Results: The average age standardized mortality rate from primary liver cancer in Swiss men increased by 33% over the last twenty years from 3.9 to 5.2/100'000 people, whereas it remained unchanged on a much lower level in women

(around 1.1/100'000). A similar increase was observed in men from France (91%), Italy (44%) and Germany (52%), whereas in Austria (5%) the increase was much less pronounced.

Conclusion: The rising mortality from primary liver cancer in Switzerland is restricted to Swiss men. The changes in Switzerland are very similar to those in France, Italy and Germany. The reason for this increase remains unknown, but could be related to an increase in HCV-related primary liver cancer. Population based studies analyzing the aetiology of the underlying liver disease associated with HCCs detected are required to address this issue.

Key words: age standardized mortality rate; hepatocellular cancer; epidemiology

Introduction

Hepatocellular carcinoma (HCC) is by far the most common primary liver cancer (PLC) (80–85%), with approximately half a million new cases per year worldwide [1]. The highest HCC incidence is observed in Asia and some areas of Africa; whereas its incidence is markedly lower in industrialized countries [1]. In recent years however, a significant increase in HCC incidence, in hospitalizations due HCC and in HCC related mortality has been observed in the United States and different European countries [2–5]. In an analysis

of almost 40,000 autopsies performed in the Canton of Zurich between 1967 and 1978, the proportion of PLC among autopsies more than doubled [6]. However, a more recent formal analysis of PLC mortality in Switzerland has never been performed. The aim of the present study was therefore to analyze the changes in PLC mortality in Switzerland from 1975 to 1994 and compare these data with the mortality data from the surrounding countries Germany, France, Italy and Austria.

Material and methods

Data sources

We used the data base from the Swiss Federal Office for Statistics to analyze trends in mortality from PLC in Switzerland. Data on mortality are accumulated yearly by the Swiss Federal Office of Statistics as part of the Swiss

vital statistics data. The crude and age standardized (world population) mortality rates (ASMR) for women and men were obtained from 1975 to 1994. This time period was chosen because in the mid 1970 ultrasound and CT became widely available in Switzerland and after

1994 the coding system in Switzerland was changed to the ICD-10 code. To analyze trends in mortality from PLC in our neighbouring countries Germany, France, Italy and Austria, the corresponding ASMR were obtained from the WHO mortality database.

Diagnostic codes

We included mortality data from all patients with the diagnosis of PLC (ICD-8: 155.0 in Switzerland and ICD-9: 155.0 in the WHO mortality database). The majority of PLC represent hepatocellular carcinoma [1].

Statistical analysis

The ASMR of consecutive five year periods and the 95% confidence interval were calculated. Any two rates with not overlapping confidence intervals were considered significantly different [2].

To examine the age distribution of the patients dying from primary liver cancer, the age specific mortality rate for consecutive five year periods and the 95% confidence interval were calculated.

Results

Mortality rates in Switzerland

The absolute number of deaths due to PLC in the Swiss population increased from 250 in 1975 to 403 in 1994 corresponding to a 60% increase. This rise was especially marked in Swiss men, where the absolute numbers increased from 165 in 1980 to 318 in 1994, corresponding to a 92% increase in overall mortality. In women however, the absolute mortality rate during the same time period remained stable at 85 deaths per year.

The ASMR in the Swiss population showed a marked increase from 2.4 (95% CI 2.1 to 2.6) in 1975–1979 to 2.9 (95% CI 2.5 to 3.3) in 1990 to 1994. This rise was restricted to Swiss men, where the ASMR significantly rose from 3.9 (95% CI 3.6 to 4.1) from 1975–1979 to 5.2 (95% CI 4.5 to 5.9) from 1990–1994 (fig. 1). The respective rate for Swiss women remained basically unchanged (1.2 (95% CI 1.0 to 1.4) from 1975 to 1979 and 1.1 (95% CI 0.9 to 1.2) from 1990–1994 respectively) (fig. 2).

Mortality rates in the neighbouring countries Germany, France, Italy and Austria

To investigate whether the significant increase of the age standardized PLC mortality observed in Swiss men was an isolated phenomenon or rather part of a general increase in PLC mortality in Europe, the ASMR from the surrounding countries France, Italy, Austria and Germany were also analyzed, using the data from the WHO mortality database. A significant rise of the ASMR in men was observed in all countries except Austria (fig. 1). Surprisingly, however the ASMR from 1990–94 was significantly higher in Swiss men (5.2 (95% CI 4.5 to 5.9)) compared to German (2.6 (95% CI 2.3 to 2.8)) and Austrian men (3.7 (95% CI 3.3 to 4.1)) but lower than the ASMR of French (6.9 (95% CI 6.0 to 7.8)) and Italian men, respectively (8.1 (95% CI 7.1 to 9.1)). As in Switzerland, the ASMR of women was significantly lower in all countries (Fig. 2). Only in France and Germany a small, though significant, rise in the ASMR could be observed (5-year average ASMR rose in France from 0.7 (95% CI 0.61 to 0.78) to 1.0 (95% CI 0.85 to 1.1) and in Germany from 0.64 (95% CI 0.57 to 0.7) to 0.94 (95% CI 0.85 to 1.1)).

Age specific mortality rate in Switzerland

The age specific mortality rate from PLC in Swiss men (age groups 45–49 up to 80–84) for the respective 5 years age periods is shown in figure 3. The age specific mortality increased continuously, reaching a plateau after the age of 70 for the period from 1975 to 1979. A similar trend was observed for the more recent time period although mortality no longer peaked, but showed a steady

Figure 1

Age standardized mortality rate of primary liver cancer among men in France, Italy, Austria and Germany from 1980 to 1994 and Switzerland (1975–1994). Each point represents the average incidence for the respective 5 year period.

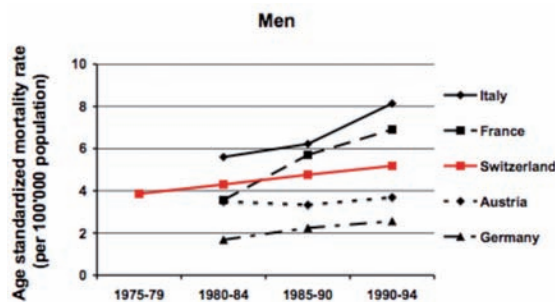


Figure 2

Age standardized mortality rate of primary liver cancer among women in France, Italy, Austria and Germany from 1980 to 1994 and Switzerland (1975–1994). Each point represents the average incidence for the respective 5 year period.

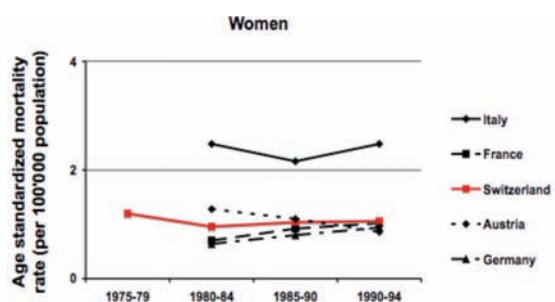
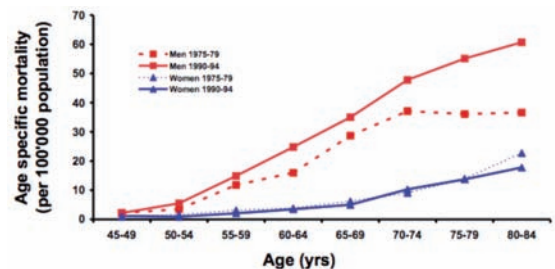


Figure 3

Age specific mortality rate of primary liver cancer among Swiss men and women from 1975 to 1979 and from 1990 to 1994 according to age. Each point represents the average incidence for the respective 5 year period. The differences between the rates for the two periods were significantly different for the ages 60 to 64 in men only.



increase up to the age of 80 to 85 years. More importantly, a shift of the mortality curve towards younger age was observed. Thus the age specific mortality rate for the age group 60–64 was significantly higher in the most recent time period from

1990–1994 (24.8 (95% CI 20.7 to 28.8)) compared to 1975–1979 (16 (95% CI 12.1 to 20)). In women again, no significant changes in the age specific mortality rate could be observed over the 20 year observation period (fig. 3).

Discussion

We found a marked increase in the absolute number of deaths (60% increase) and a significant rise in the ASMR due to PLC in the Swiss population, which rose from 2.4 per 100,000 during the period from 1975 to 1979 to 2.9 per 100,000 during the period from 1990–1994. This rise was especially pronounced in Swiss men, where the absolute number increased by almost 100% and the 5 year ASMR increased from 3.9 per 100,000 from 1975 to 1979 to 5.2 per 100,000 from 1990 to 1994. Accordingly, the men to women rate rose from 2:1 to 4:1 over the last 20 years. Older age was associated with a higher risk, but we also observed a shift towards younger age groups in the more recent years.

The last two decades witnessed the introduction of improved imaging tools for the diagnosis of liver tumours which might lead to a detection bias. Thus, the observed rise in PLC mortality may be due to better diagnostics methods, rather than to a true increase of its incidence. However the two most widely used diagnostic tools to detect PLC, namely ultrasound and alpha fetoprotein have been routinely used in Switzerland since the late 1970s. More importantly, a detection bias should also lead to an increase in the PLC related mortality in women, however no such changes could be observed in females.

We also analyzed whether the rise in PLC mortality observed in Switzerland was an isolated phenomenon or whether there is a general increase in PLC mortality in Europe. Indeed, a rise in PLC related mortality was detected in the male population in all countries except Austria. In France and Germany even in women a slight increase in PLC mortality was observed. Thus, our data are in agreement with observations from Europe and the USA, suggesting that there is indeed a real increase in mortality due to PLC, especially in men (2-5). Surprisingly the ASMR for PLC in Switzerland is markedly higher compared to that in the US, England, Germany and Austria, but lower than that in France and Italy. Whether this is due to different prevalences of cirrhosis per se or some specific underlying aetiology such as hepatitis C and B remains to be seen.

In most studies from developed countries, PLC predominantly affects the elderly. However the observed rise in PLC mortality cannot be explained by an aging population alone. All data were age standardized to control for this effect. In addition we not only observed an absolute rise in PLC mortality, but also a shift toward younger age groups.

A limitation of our study is the lack of autopsy data to confirm the diagnosis of PLC. We can therefore not completely rule out, that some cancers in our study were misclassified liver metastases from unknown primary cancers. However in an older study over 40,000 autopsy cases from the Zurich area were analyzed for the occurrence of PLC [6]. In this study, performed between 1967 and 1978, the proportion of PLC among autopsies rose significantly from 0.68% in 1967 to 1.51% in 1978. In accordance with the findings from this autopsy study, the nationwide mortality rate for the same time period also rose [6]. Therefore we believe that the increase observed in our study is caused by a real increase in PLC mortality and is not merely due to misclassification.

Our study completely relies on mortality data and one might argue, that this may underestimate the incidence of PLC. However, the fatality rate (mortality/incidence ratio) for PLC remains around 1, indicating that most patients do not survive longer than one year [1]. In addition the survival rate of HCC, the most frequent PLC, did not change significantly over the last 20 years [7]. Therefore we believe that mortality data still very closely reflect PLC incidence data.

The main issue arising from studies like ours and others [2–5] relates to the question of which factor(s) are responsible for the rise in PLC incidence. In developed countries, the main risk factors associated with the development of PLC are alcoholic liver cirrhosis and viral hepatitis B and C. In our country the mortality rate for alcoholic liver cirrhosis declined over the last 20 years (data not shown). A similar trend has been reported from the United States were alcohol related diagnosis and age adjusted mortality related to alcoholic cirrhosis decreased during the same time period [2]. In Switzerland, we have currently no reliable mortality data on hepatitis B and C related liver cirrhosis and therefore are unable to clearly show, whether the increase in mortality due to PLC is indeed related to chronic hepatitis B and C infection or whether other aetiologies might be responsible for this rise. The hepatitis C epidemic is the most likely culprit to explain this rise. Indeed, in recent studies El Serag et al. could show that in the US there was a 2 to 3-fold increase in the age-adjusted rates for PLC associated with hepatitis C virus [8, 9]. Recently, diabetes mellitus was identified as a risk factor for non-alcoholic fatty liver disease and also HCC [10]. However these studies were mostly re-

stricted to the special patient population of the US-Veteran Administration system or patients older than 65 years of age. In addition, in a large population based US study, increasing body mass index was associated with an increased risk for liver cancer in men and women [11, 12]. Which of these risk factors are responsible for the rise in liver cancer observed in Switzerland and other countries remains to be seen. Clearly more population based data on the risk factors associated with PLC but also on protective factors such as coffee consumption [13] are needed.

The long latency period after HCV infection until liver cirrhosis and PLC occur, suggests that there will be a future increase in PLC mortality in the years to come [14, 15]. Indeed, this is supported by our own modelling of the Hepatitis C epidemic for Switzerland, which predicts a rise in HCC mortality of 170% until 2015 [16]. Simi-

lar data have been reported for France and USA [17, 18].

In summary, our study shows a significant increase in absolute and age standardized PLC mortality rates in Switzerland, which is restricted to men and associated with a shift towards younger age groups. The factor(s) responsible for this increase remain to be elucidated.

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