RESEARCH COMMUNICATION

Epidemiology of Cancer of the Liver and Intrahepatic Bile Ducts in an Australian Population

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Abstract

The incidence of liver and intrahepatic bile duct cancer in Australia is low at about one third the world average but increases are evident. South Australian registry data have been used to describe: age-standardized incidence and mortality trends; and disease-specific survivals, using Kaplan-Meier estimates and Cox proportional hazards regression. The study included 1,220 incident cancers (901 hepatocellular carcinomas; 201 cholangiocarcinomas; 118 other types) and 983 deaths. Incidence and mortality rates increased by 2-3 fold during 1977-2007. Incidence increases affected males, females and all ages. There was a strong: male predominance (3 to 1); and age gradient (70+ year old incidence >30 times under 50 year old incidence). Compared with hepatocellular carcinomas, cholangiocarcinomas and other histology types more often affected females and older ages and less often the Asian born. All histology types showed similar incidence increases. Apart from recognized risk factors (e.g., hepatitis B/C infection and aflatoxins for hepatocellular carcinoma; liver-fluke infection for cholangiocarcinomas, etc.), common risk factors may include excess alcohol consumption and possibly obesity and diabetes mellitus. Five-year disease-specific survival in 1998-2007 was 16%, with higher fatalities applying for earlier periods, older patients, males, lower socio-economic groups, and cholangiocarcinomas. Aboriginal patients tended to have higher case fatalities (p=0.054). Survival increases may be due to earlier diagnosis from alpha feta protein testing and diagnostic imaging, plus more aggressive treatment of localized disease. Mortality increases require a preventive response, including hepatitis B vaccination, prevention of viral infection though contaminated blood and other body fluids, early detection initiatives for high-risk patients, aggressive surgery for localized disease, and experimentation with new systemic therapies.

Keywords: Liver cancer - incidence - mortality - prevention - control - South Australia

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Introduction

Primary cancers of the liver and intrahepatic bile ducts are generally combined in international statistics from which they are estimated to comprise about 6% of invasive cancers world-wide (Alam et al., 2009; Horner et al., 2009; Ferlay et al., 2010). They are rarer in Australia, accounting for approximately 1% of invasive cancers recorded by cancer registries (AIHW, 2010; Ferlay et al., 2010). The age-standardized incidence in Australia is estimated to be about a third the incidence world-wide and 15% or less of the incidence observed in high-risk populations in Middle Africa and East Asia (Alam et al., 2009; Ferlay et al., 2010).

Global variations in incidence correlate with prevalence of chronic viral hepatitis (Srivantanakul et al., 2004; Alam et al., 2009; Altekruse et al., 2009; Nguyen et al., 2009). Around 80% or more of hepatocellular carcinomas, the predominant histology type, are attributed to hepatitis B and C infection (Adami et al., 1996; Srivantanakul et al., 2004; Tischoff and Tannapfel, 2007; Alam et al., 2009; Altekruse et al., 2009). Other causes include ingested aflatoxins produced by *Aspergillus flavus*, a mould that can affect grain stored in hot humid conditions, together with excess alcohol consumption, fatty liver related cirrhosis and smoking (Klatsky and Armstrong, 1992; Corrao et al., 1995; Yu et al., 1997; Alam et al., 2009; Altekruse et al., 2009; Kemik et al., 2010). Approximately three quarters of liver cancers in Australia are hepatocellular carcinomas, with cholangiocarcinomas of intrahepatic bile ducts being the next most common type (SACR, 2000; CCCR, 2001). Cholangiocarcinomas are often diagnosed in migrants, especially those from South East Asia and other countries where infection with the liver flukes, *Clonorchis sinensis* and *Optisthorchis viverrini*, is endemic (Klatsky and Armstrong, 1992; Watanapa, 1996; CCCR, 2001; Watanapa and Watanapa, 2002; Alam et al., 2009). Other risk factors for cholangiocarcinoma include hepatolithiasis, primary sclerosing cholangitis, ulcerative colitis, cholecystitis, and congenital fibropolycystic liver disease (Tischoff and Tannapfel, 2007; Kahn et al., 2008; de Martel et al., 2010; Lindkvist et al., 2010).

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Compared with the Australian born, residents born in other countries have a higher incidence of cancers of the liver and intrahepatic bile ducts, particularly migrants from Asia where incidence rates have been observed to be about three or four times the rates seen in the Australian born, depending on the study (Law et al., 2000; CCCR, 2001; CCSA, 2003; Alam et al., 2009; NSW Health, 2010). As found in other populations, males have an age-standardized incidence about 2-3 times that of females and residents of socio-economically disadvantaged areas have higher incidence rates than those of less disadvantaged areas (CCSA, 2003; Alam et al., 2009; AIHW, 2010; NSW Health, 2010). Depending on locality, Aboriginal and Torres Strait Islander residents have recorded incidence rates between two and 10 times the incidence for other Australians (Wan and Mathews, 1994; SACR, 1997; Coory et al., 2000; Condon et al., 2005; Roder, 2005; Valery et al., 2006; Cottrell et al., 2007; Cunningham et al., 2008; Alam et al., 2009; AIHW, 2010).

An approximate three-fold increase in age-standardized incidence of liver and intrahepatic bile duct cancer has been observed in Australia since the early 1980s (AIHW, 2010). Corresponding increases have been reported in North America, Japan, and some but not all European countries (La Vecchia, 2000; Bosch et al., 2004; 2005; Horner et al., 2009). The increase in Australia has been attributed to increases in hepatocellular carcinoma resulting from migration from high-risk areas of Asia, Africa and Europe and to an increased prevalence of chronic viral hepatitis infection, particularly hepatitis C (CCCR, 2001; Law et al., 2003; O'Sullivan et al., 2004; Alam et al., 2009). Alcohol consumption has also increased and may be contributing, together with an increased prevalence of obesity (Oh et al., 2005; Australian Government, 2008; Alam et al., 2009).

Increases in incidence of cholangiocarcioma are also observed and attributed to migration from South East Asia and other high-risk countries and potentially from increases in prevalence of primary sclerosing cholangitis (CCCR, 2001; Alam et al., 2009; Lindkvist, 2010)). Increases in cholangiocarcinomas have been reported in Asia (Hsing et al., 1998) and other predominantly western countries, with most cases considered as sporadic and occurring in the absence of known risk factors. (Patel, 2001; Taylor-Robinson et al., 2001; Patel, 2002; Endo et al., 2008; Khan et al., 2008; de Martel et al., 2010).

Australian population-based cancer registry data are used in this study to describe: (1) incidence and mortality trends for liver and intrahepatic bile duct cancers during 1977-2007; (2) differences in secular trends and epidemiological characteristics by histology type; and (3) differences in survival post diagnosis by socio-demographic and histological characteristics, and period of diagnosis. The implications of results for health-service policy and research are indicated.

Materials and Methods

Data collection

The South Australian Cancer Registry was employed as the data source. The Registry has received statutory notifications of invasive liver and intrahepatic bile duct cancers since 1977. It covers all regions of South Australia (one of eight Australian states and territories) and invasive cancers of all types except non-melanoma skin cancers. Its procedures have been described previously (SACR, 2000). Death data are collected through routine notifications, electronic searches of official State death records and the National Death Index at the Australian Institute of Health and Welfare, and from interstate registries. Under-ascertainment has been checked through active follow-up, and with deaths reported independently, and found to be minimal (Bonett et al., 1988; SACR, 2000).

The present study included 1,220 invasive cancers of the liver and intrahepatic bile ducts (ICD-O-3: C22) diagnosed between 1977 and 2007 (Fritz et al., 2000). They comprised 901 hepatocellular carcinomas (SNOMED 81703), 201 cholangiocarcinomas of bile ducts (SNOMED 81603), and 118 other cancers, including hepatoblastomas, adenocarcinomas, sarcomas and cancers of other histology types.

Socio-demographic descriptors included age at diagnosis; sex; region of residence, classified as 20 statistical sub-divisions and as metropolitan or non-metropolitan (SACR, 2000); country of birth (World Health Organization criteria) (Ferlay et al., 2010); Aboriginal status; and relative socio-economic disadvantage, as inferred from residential postcode characteristics using the SEIFA index of relative socio-economic disadvantage (ABS, 1998).

Statistical analyses

A de-identified file was extracted and analysed in-house under provisions of the South Australian Health Care Act 2008, employing STATA 9.2 software (StataCorp, 2005).

Mean annual incidence and mortality rates were calculated by sex for all histology types combined, and separately for hepatocellular carcinomas, cholangiocarcinomas, and other histology types in aggregate, for six periods, i.e., 1977-82, 1983-87, 1988-92, 1993-97, 1998-2002, and 2003-07. Rates were directly standardized by five-year age group (with an open-ended category from 85 years) to the 2001 Australian reference population (Armitage and Berry, 1987; StataCorp, 2005). Ninety-five per cent confidence limits were calculated assuming a Poisson distribution, as described previously (Dobson et al., 1991). Rates were obtained for all ages combined and by age category (i.e., under 50, 50-59, 60-69, 70-79, and 80 years or more) to investigate time trends by age.

Differences in socio-demographic descriptors were investigated by histology type. Initially descriptors were analysed as univariate predictors, using the Pearson chi-square test for nominal variables (substituting the Fisher Exact Test when cell sizes were small) and the Kruskal-Wallis ANOVA for ordinal variables (Armitage and Berry, 1987; StataCorp, 2005).

Socio-demographic differences by histology type were further explored using multiple logistic regression analysis, with hepatocellular carcinomas as the designated reference category (Armitage and Berry, 1987; StataCorp, 2005). All socio-demographic variables were entered as

candidate predictors of histology type (the dependent variable), with backwards elimination of candidate predictors where the fit of the model did not reduce as a consequence ($p>0.05$). Assumptions underlying each analysis, including an absence of co-linearity, were found to be satisfied.

Kaplan-Meier product-limit estimates of disease-specific survival were calculated, using one-day intervals and treating dates of death from other causes prior to the end of 2007, and for people still alive, December 31st, 2007, as censoring dates (Armitage and Berry, 1987; StataCorp, 2005). Multivariable Cox proportional hazards regression was also undertaken to assess socio-demographic and histological predictors of survival from liver cancer. Parallel analyses were undertaken by histology type. The regression analysis employed the same censoring criteria as for the Kaplan-Meier analyses. All predictor variables were entered into the analysis, with backwards elimination. Assumptions underlying the analysis, including proportionality and an absence of co-linearity, were found to be satisfied (Armitage and Berry, 1987; StataCorp, 2005).

Disease-specific survival was employed, not relative survival, because the life tables needed to undertake relative survival analyses were not available for many population sub-groups. Analyses have shown very similar survival estimates in South Australia, irrespective of use of disease-specific or relative survival method (SACR, 1997), such that the disease-specific survivals presented here are regarded as a good proxy for relative survivals. For example, 5-year relative survival was found to be 6.9% in a study of liver and intrahepatic bile duct cancers diagnosed in 1977-98 (SACR, 2000), which was the same as the 6.9% 5-year disease-specific survival calculated for that period.

Results

Trends in incidence and mortality

Liver and intra-hepatic bile duct cancers comprised 0.6% of all invasive cancers recorded on the Registry for 1977-2007, 0.8% of those in males and 0.4% of those in females. The proportion ranged from 0.5% in 1977-83 to 0.8% in 1998-2007. Almost three quarters (71.3%) occurred in males. The most common type was hepatocellular carcinoma (73.9%), followed by cholangiocarcinomas (16.5%), and other types such as hepatoblastomas, adenocarcinomas, and sarcomas (9.7%).

Liver and intrahepatic bile duct cancers accounted for 1.1% of cancer deaths recorded on the Registry for 1977-2007, comprising 1.4% of cancer deaths in males and 0.8% of those in females. The proportion ranged from 0.8% in 1977-83 to 1.5% in 1998-2007. Almost three quarters (70.9%) occurred in males. The histology types responsible for these deaths were hepatocellular carcinomas (73.4%), cholangiocarcinomas (17.3%) and other types (9.3%).

The mean annual age-standardized incidence (95% confidence limits) per 100,000 for all cancers of the liver and intrahepatic bile ducts increased by 155.6% from 1.8 (1.5, 2.2) in 1977-82 to 4.6 (4.1, 5.0) in 2003-07, with increases occurring in both sexes (Table 1). An increase was evident in each age group, ranging from 79.8% for 60-69 year olds to 174.2% for those aged 80 years and over. Increases applied to all histology categories between 1977-82 and 2003-07, namely, 142.9% for hepatocellular carcinomas, 157.6% for cholangiocarcinamas and 128.6% for other histology types, with both males and females showing increases (Table 2).

The male to female age-standardized incidence ratio was 3.0:1 for 1977-2007 (Table 1). There was a steep incidence gradient with age in that the mean annual incidence per 100,000 during 1977-2007 was 0.4 (0.4, 0.5) for 0-49 years, 3.9 (3.4, 4.5) for 50-59 years, 7.7 (6.8, 8.6) for 60-69 years, 13.7 (12.4, 15.2) for 70-79 years and 12.9 (11.1, 14.8) for 80 years and over.

Univariate analyses by histology type indicated no difference by diagnostic period (KWp=0.254), but differences by age at diagnosis (KWp<0.001), sex (KWp<0.001), and whether born in an Asian country (KWp=0.010). Differences were not observed by region of residence, Aboriginal status or relative socio-economic

Table 1. Annual Incidence and Mortality Rates (95% confidence limits) of Invasive Cancers of the Liver and Intrahepatic Bile Ducts per 100,000 Population by Calendar Year and Sex* – Age-Standardised (Australia 2001 Reference Population)

	Period						
	1977-82	1983-87	1988-92	1993-97	1998-02	2003-07	Total 1977-2007
Incidence	(n=124)	(n=92)	(n=139)	(n=188)	(n=266)	(n=411)	(n=1,220)
Males	2.89	2.06	3.27	3.80	5.24	7.12	4.02
(n=871)	(2.32, 3.56)	(1.58, 2.65)	(2.66, 3.97)	(3.18, 4.51)	(4.53, 6.02)	(6.32, 7.98)	(3.76, 4.30)
Females	1.01	0.93	1.04	1.35	1.51	2.29	1.34
(n=349)	(0.71, 1.40)	(0.63, 1.31)	(0.74, 1.43)	(1.02, 1.75)	(1.18, 1.91)	(1.90, 2.75)	(1.20, 1.49)
Total	1.84	1.43	2.02	2.46	3.19	4.56	2.56
(n=1,220)	(1.53, 2.20)	(1.15, 1.75)	(1.70, 2.39)	(2.12, 2.84)	(2.82, 3.60)	(4.13, 5.02)	(2.42, 2.71)
Mortality	(n=106)	(n=90)	(n=113)	(n=162)	(n=205)	(n=307)	(n=983)
Males	2.54	2.09	2.66	3.30	3.89	5.32	3.28
(n=697)	(2.00, 3.18)	(1.61, 2.67)	(2.12, 3.30)	(2.71, 3.97)	(3.28, 4.58)	(4.64, 6.07)	(3.04, 3.53)
Females	0.83	0.81	0.83	1.19	1.27	1.70	1.10
(n=286)	(0.56, 1.19)	(0.53, 1.18)	(0.56, 1.18)	(0.89, 1.56)	(0.97, 1.63)	(1.23, 1.92)	(0.97, 1.24)s
Total	1.57	1.40	1.64	2.12	2.43	3.36	2.07
(n=983)	(1.29, 1.90)	(1.13, 1.72)	(1.35, 1.97)	(1.81, 2.47)	(2.11, 2.79)	(2.99, 3.76)	(1.94, 2.21)

*Confidence limits based on Poisson distribution; Data source: South Australian Cancer Registry

Table 2. Annual Incidence (95% Confidence Limits) of Invasive Cancers of the Liver and Intrahepatic Bile Ducts per 100,000 Population by Histology Type, Calendar Year and Sex*– Age-Standardised (Australia 2001 Reference Population)

	Period						
Histology type	1977-82	1983-87	1988-92	1993-97	1998-02	2003-07	Total 1977-2007
Hepatocellular carcinoma	(n=89)	(n=75)	(n=109)	(n=141)	(n=199)	(n=288)	(n=901)
Males	2.24	1.71	2.69	3.07	4.29	5.42	3.20
(n=693)	(1.74, 2.84)	(1.27, 2.25)	(2.15, 3.33)	(2.51, 3.72)	(3.65, 5.01)	(4.73, 6.18)	(2.97, 3.45)
Females	0.61	0.71	0.67	0.85	0.83	1.28	0.82
(n=208)	(0.38, 0.93)	(0.45, 1.06)	(0.43, 0.99)	(0.60, 1.18)	(0.59, 1.14)	(0.98, 1.64)	(0.71, 0.94)
Total	1.33	1.16	1.57	1.85	2.39	3.23	1.90
(n=901)	(1.07, 1.64)	(0.91,1.45)	(1.29, 1.89)	(1.56, 2.18)	(2.07, 2.75)	(2.87, 3.63)	(1.78, 2.03)
Cholangiocarcinoma	(n=20)	(n=9)	(n=20)	(n=29)	(n=44)	(n=79)	(n=201)
Males	0.39	0.09	0.39	0.51	0.60	0.96	0.49
(n=102)	(0.19, 0.72)	(0.02, 0.26)	(0.19, 0.70)	(0.30, 0.82)	(0.38, 0.91)	(0.68, 1.31)	(0.40, 0.59)
Females	0.29	0.19	0.27	0.29	0.48	0.77	0.38
(n=99)	(0.14, 0.54)	(0.07, 0.41)	(0.12, 0.51)	(0.15, 0.51)	(0.30, 0.73)	(0.55, 1.05)	(0.31, 0.46)
Total	0.33	0.15	0.30	0.39	0.52	0.85	0.42
(n=201)	(0.20, 0.51)	(0.07, 0.28)	(0.18, 0.46)	(0.26, 0.56)	(0.38, 0.70)	(0.67, 1.06)	(0.36, 0.48)
Other	(n=15)	(n=8)	(n=10)	(n=18)	(n=23)	(n=44)	(n=118)
Males	0.33	0.30	0.23	0.22	0.35	0.74	0.36
(n=76)	(0.16, 59.0)	(0.12, 0.62)	(0.08, 0.50)	(0.13, 0.35)	(0.19, 0.60)	(0.50, 1.60)	(0.28, 0.45)
Females	0.11	0.02	0.11	0.21	0.20	0.24	0.15
(n=42)	(0.03, 0.28)	(0.00, 0.11)	(0.03, 10.24)	(0.10, 0.40)	(0.10, 0.37)	(0.13, 0.40)	(0.11, 0.20)
Total	0.21	0.13	0.15	0.22	0.27	0.48	0.24
(n=118)	(0.11, 0.35)	(0.06, 0.26)	(0.07, 0.28)	(0.13, 0.35)	(0.17, 0.41)	(0.35, 0.64)	(0.20, 0.29)

*Confidence limits based on Poisson distribution; Data source: South Australian Cancer Registry

Table 3. Relative Risk (95% Confidence Limits) of Case Fatality from Invasive Cancer of the Liver and Intrahepatic Bile Ducts, 1977 to 2007*

Predictors	Relative risk
Age at diagnosis (yrs.):	
Under 50 (reference) (n=132)	1.00
50-59 (n=202)	1.73 (1.33, 2.26)
60-69 (n=302)	1.80 (1.40, 2.31)
70-79 (n=391)	2.30 (1.81, 2.94)
80+ (n=193)	3.08 (2.35, 4.04)
Sex:	
Male (reference) (n=871)	1.00
Female (n=349)	0.84 (0.73, 0.97)
SES:**	
1 quartile lower (n=1,220)	1.06 (1.00, 1.11)
Histology type:	
Other (reference) (n=1,019)	1.00
Cholangiocarcinoma (n=201)	1.20 (1.01, 1.42)
Diagnostic period:	
1977-90 (reference) (n=296)	1.00
1991-97 (n=247)	0.57 (0.48, 0.69)
1998-2007 (n=677)	0.39 (0.33, 0.45)

*Multivariable proportional hazards regression (see text); **SEIFA Index of Relative Socio-economic Disadvantage; Data source: South Australian Cancer Registry

disadvantage (p>0.150). Socio-demographic differences by histology type confirmed in multiple regression analysis were as follows:

- Cholangiocarcinomas were more likely than hepatocellular carcinomas to be: (1) diagnosed in patients aged age 70-79 years (relative odds: 1.63 (1.14, 2.33)) and 80 years or more (relative odds: 1.93 (1.25, 2.97)) than in those under 70 years; and (2) diagnosed in females than males (relative odds: 3.13 (2.26, 4.43)). Conversely patients with these cancers were less likely than those with hepatocellular carcinomas to have been born in Asia (relative odds: 0.19 (0.07, 0.52)).
- Other histology types were generally more likely than hepatocellular carcinomas to be: (1) diagnosed in patients aged 80 years or more (relative odds: 1.76 (1.06, 2.91)) than in those under 70 years; and (2) diagnosed in females than males (relative odds: 1.72 (1.13, 2.60)). Conversely patients with these cancers were less likely than hepatocellular carcinoma cases to have been born in Asia (relative odds: 0.39 (0.15, 0.97)).

Mortality data showed similar trends to incidence data, with the mean annual age-standardized rate per 100,000 increasing by 112.5% from 1.6 (1.3, 1.9) in 1977-82 to 3.4 (3.0, 3.8) in 2003-07, with increases in both sexes (Table 2). The male-to-female age-standardized mortality ratio was similar to the corresponding incidence ratio at 3.0:1 (Table 2).

Survival

Survivals from liver and intrahepatic bile duct cancers reduced with period from diagnosis during 1977-2007 from 30.0% at one year to 14.8% at three years, 11.2% at five years, 8.1% at 10 years and 6.7% at 15 years. The five-year survival (± standard error) was higher at:

- 27.7(±4.5)% for patients diagnosed under 50 years of age, compared with 15.2(±3.1)% at 50-59 years; 10.0(±2.2)% at 60-69 years ; 7.9(±1.6)% at 70-79 years; and 3.0(±2.4)% at 80 years or more.
- 12.7(±2.0)% for females compared with 10.5(±1.3)% for males.
- 16.2(±1.9)% for 1998-2007 compared with 7.3(±1.7)% for 1991-97, 3.9(±1.7)% for 1984-90, and 5.6 (±2.1)% for 1977-83.

Table 4. Relative Risk (95% Confidence Limits) of Case Fatality from Invasive Cancer of the Liver and Intrahepatic Bile Ducts by Histology Type; 1977-2007*

	Hepatocellular carcinoma (n=901)	Cholangiocarcinoma (n=201)	Other histology (n=118)
Age at diagnosis (yrs.):			
Under 50 (reference) (n=132)	1.00 (n=94)	1.00 (n=17)	1.00 (n=21)
50-59 (n=202)	1.69 (1.24, 2.30) (n=159)	1.13 (0.58, 2.17) (n=31)	2.32 (0.91, 5.90) (n=12)
60-69 (n=302)	1.68 (1.25, 2.24) (n=246)	1.33 (0.66, 2.66) (n=31)	2.89 (1.29, 6.51) (n=25)
70-79 (n=391)	2.02 (1.51, 2.69) (n=283)	2.11 (1.16, 3.83) (n=76)	3.23 (1.44, 7.26) (n=32)
80+ (n=193)	2.68 (1.93, 3.72) (n=119)	3.28 (1.73, 6.20) (n=46)	5.69 (2.53, 12.78) (n=28)
Sex:			
Male (reference) (n=871)	1.00 (n=693)	1.00 (n=102)	1.00 (n=76)
Female (n=349)	0.84 (0.71, 1.00) (n=208)	0.92 (0.67,1.26) (n=99)	0.55 (0.34, 0.89) (n=42)
SES:**			
1 quartile lower (n=1,220)	1.04 (0.98, 1.11) (n=901)	1.10 (0.96,1.25) (n=201)	1.09 (0.89, 1.34) (n=118)
Diagnostic period:			
1977-90 (reference) (n=296)	1.00 (n=224)	1.00 (n=42)	1.00 (n=30)
1991-97 (n=247)	0.60 (0.49, 0.74) (n=190)	0.37 (0.23, 0.61) (n=36)	0.83 (0.41, 1.67) (n=21)
1998-2007 (n=677)	0.39 (0.33, 0.47) (n=487)	0.31 (0.21, 0.46) (n=123)	0.37 (0.21, 0.66) (n=67)

*Multivariable proportional hazards regression (see text); **SEIFA Index of Relative Socio-economic Disadvantage; Data source: South Australian Cancer Registry

No differences were observed in survivals by socio-economic status, place of residence or Aboriginal status ($p>0.15$), whereas higher survivals were observed in the Asian born ($p<0.001$).

Multivariable Cox proportional hazards regression confirmed that risk of case fatality from these cancers was higher in older patients, males, earlier diagnostic periods, and potentially lower socio-economic localities, with an elevated case fatality applying for cholangiocarcinomas compared with hepatocellular carcinomas and other histology types (Table 3). Aboriginal status was also associated with higher case fatality if retained in this model, although statistical significance was marginal ($p=0.054$). Similarly, non-Asian country of birth was associated with increased case fatality, but statistical significance was not achieved ($p=0.080$).

Multivariable models also showed for each histology category, increased case fatality with increased age and a decrease in case fatality for more recently diagnosed cases (Table 4). While males tended to have higher case fatalities than females, only the difference for "other histology types" was statistically significant ($p=0.016$). In no instance did socio-economic status gain statistical significance ($p>=0.159$).

Discussion

Cancers of the liver and intrahepatic bile ducts are comparatively rare cancers in Australia (AIHW, 2010; Ferlay et al., 2010), but marked increases in incidence have occurred, as reported in North America, Japan and a number of European countries (La Vecchia et al., 2000; Bosch et al., 2004; Bosch et al., 2005; Horner et al., 2009; AIHW, 2010). The 2-3 fold increase in incidence observed in this study was a little lower than recorded Australia wide, but may have been an under-estimate. It is possible, for example, that a number of metastatic lesions were misclassified as primary cancers of the liver in the initial years following commencement of the Registry in 1977, due to the absence of historic data on primary sites. This may explain the decrease in recorded incidence and mortality observed between 1977-82 and 1983-87, despite a pronounced increase in 1977-2007.

The scale of increase in incidence was similar by histology type, which may have causal implications. It is likely that increases in prevalence of chronic viral hepatitis infection would have been an important factor in the increase in hepatocellular carcinomas (Tischoff and Tannapfel, 2007; Alam et al., 2009; Altekruse et al., 2009). Although there is inconclusive evidence of a link between hepatitis C infection and risk of cholangiocarcinoma (Kobayashi et al., 2000), this infection would not explain the similar increases seen for other histology types (Kaczynski et al., 1998). Conversley, liver fluke infection likely contributed to the increase in cholangiocarcinomas, but this would not explain the increases for other histology types (Shin et al., 1996; Watanapa, 1996; Watanapa and Watanapa, 2002; Alam et al., 2009). Increased migration from high risk countries would tend to have increased the incidence of hepatocellular carcinoma and cholangiocarcinoma, but seems to be an unlikely explanation for the increased incidence of other histology types (Law et al., 2000; CCCR, 2001; CCSA, 2003; Alam et al., 2009; NSW Health, 2010).

While advances in screening from alpha feta protein testing and diagnostic imaging may have led to artificial increases in incidence, it is clear from the equivalent increases in mortality rates that the reported increases are real (Altekruse et al., 2009). The questions arise whether other factors of broad aetiological relevance have contributed. For example, is the obesity and diabetes mellitus epidemic increasing vulnerability to cancers of the liver and intrahepatic bile ducts irrespective of histological type and sub-site? (Adami et al., 1996; Oh et al., 2005; Ioannou et al., 2007; Kita et al., 2007; Wong et al., 2007; Australian Government, 2008). Diabetes is more common in males than females, and in lower than upper socio-economic groups, which is similar to the pattern seen for these cancers (AIHW, 2008). Further research is warranted to determine factors responsible for these marked increases in incidence rates as they are not easily explained by known risk factors.

Male to female ratios for these cancers of 3.0 to one were similar to the ratios seen in national Australian data and USA SEER data (Horner et al., 2009; AIHW, 2010). The male predominance was stronger for hepatocellular carcinomas than other histology types, which may reflect a higher prevalence of viral hepatitis infection in males and perhaps stronger contributions from excess alcohol consumption and smoking in males than females (CCCR, 2001; Amin et al., 2008). Compared with other histology types, hepatocellular carcinomas were more strongly associated with migration from Asia, where endemic hepatitis infection would be an important factor (Alam et al., 2009).

Survival from cancers of the liver and intrahepatic bile ducts remains low, irrespective of population (Faivre, 1998; AIHW, CA, AACR, 2008; Horner et al., 2009), with a five-year figure of 16% applying to the 1998-2007 diagnostic period. This represents an increase, however, over the corresponding 4-7% applying for 1977-97. Corresponding USA SEER data are similar, indicating a five-year survival of 14% for 1999-2005, compared with 4-6% for 1978-95, and an intermediary figure of 9% for 1996-98 (Horner et al., 2009).

It is likely that recent increases in survival have been affected by earlier diagnosis from alpha feta protein screening and gains in diagnostic imaging, together with treatment gains from more aggressive resection of localized disease and other hepatic directed therapies such as radio-frequency ablation and trans-arterial chemotherapy embolisation (Endo et al., 2008; Altekruse et al., 2009; Toso et al., 2010). Liver transplantation also may be contributing for the sub-set of cases so treated (Altekruse et al., 2009). Although targeted therapies for hepatocellular carcinoma hold promise, it is probably too early for survival benefits from these treatments to show in population statistics and it is unlikely that standard chemotherapy has had an impact, given its inactivity with hepatocellular carcinoma (Altekruse et al., 2009). Nonetheless it is possible that the use of platinum based chemotherapy may have had some impact on survival from cholangiocarcinoma (Williams et al., 2010). Further research is needed into early detection, the surgical management of localized disease, liver transplantation and targeted adjuvant therapies.

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