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Do increases in mortality from intrahepatic cholangiocarcinoma reflect a genuine increase in risk? Insights from cancer registry data in Scotland

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Abstract

The mortality from intrahepatic cholangiocarcinoma has increased recently in England and Wales and elsewhere. This study aims to examine recent trends in the incidence of intrahepatic cholangiocarcinoma in Scotland, to assess the extent to which changes in diagnostic practice may be influencing the observed trends, and to consider whether the results are compatible with a genuine increase in the risk of this cancer. Cancer registration (intrahepatic cholangiocarcinoma and anatomically adjacent cancers) data from Scotland 1968–1997 were analysed, including examination of trends in the percentage of cases recorded as being microscopically-verified. Since the late 1960s, the incidence of intrahepatic cholangiocarcinoma has increased approximately eight-fold in both sexes in Scotland. However, the proportion of cases verified microscopically has decreased substantially since the late 1970s, presumably due to an increasing reliance on radiological imaging for diagnosis. Despite this change in diagnostic practice, the incidence of microscopically-verified intrahepatic cholangiocarcinoma has also increased. While changes in diagnostic practice and misclassification could explain, at least part of, the observed increase in incidence of intrahepatic cholangiocarcinoma, a genuine increase in the risk of this cancer in the Scottish population seems probable. Further work is indicated to examine international trends in incidence, and to assess whether incidence differs within countries according to characteristics such as area of residence, socio-economic status, ethnic origin or occupation.

Keywords: Cholangiocarcinoma; Epidemiology; Incidence; Risk; Scotland

1. Introduction

The suggestion that mortality from intrahepatic cholangiocarcinoma (IHCC) was increasing in the UK was first raised in 1997 [1]. More recently, both incidence and mortality from the disease have been noted to be increasing in the United States [2]. A striking increase in mortality from IHCC in England and Wales since the mid-1970s has now been confirmed in a more detailed analysis [3], and increases in mortality since the late 1970s have also been observed in several other countries, particularly Australia [4].

In Scotland, although IHCC mortality rates are consistently slightly higher than those seen in England and Wales, a similar increase has been observed [4]. Mortality data offer a long time series and, for rapidly fatal cancers, provide a reasonable estimate of incidence. However, their interpretation is constrained by known deficiencies in the accuracy of death certification (compounded by a relatively low rate of autopsy in the UK), and by a lack of information about the basis of diagnosis (unless this is achieved or confirmed at autopsy). We have therefore analysed data from the Scottish Cancer Registry to determine whether trends in incidence of IHCC in Scotland are broadly in line with mortality trends, to assess the extent to which changes in diagnostic practice may be influencing observed trends, and to consider whether the results are compatible with a genuine increase in the risk of this cancer.

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2. Patients and methods

The Scottish Cancer Registry is a national registry that aims to record all incident cases of cancer in the Scottish population. Incident cases of IHCC (and, for comparison, other primary liver cancers and liver secondaries, cancers of the gallbladder and extrahepatic bile ducts, and pancreatic cancers) for the 30-year period 1968–1997 were identified from the Registry, based on International Classification of Diseases (ICD) codes appropriate to the period of diagnosis. Note that secondary liver cancers are registered only when the primary site is not established.

When a cancer is registered, the ICD code assigned is based on the final diagnosis made by the clinical team caring for the patient. No specific diagnostic criteria or definitions are required by the ICD. Inaccurate or non-specific clinical diagnosis, or incomplete information, may therefore lead to inaccurate coding. In addition, of particular relevance when considering IHCC, is the fact that under ICD rules a final diagnosis of cholangiocarcinoma with no anatomical site specified is by default coded as IHCC. If clinicians use the term cholangiocarcinoma loosely to refer to extra- as well as intra-hepatic bile duct cancers, and do not specify an anatomical site, this will result in some extrahepatic cancers being wrongly coded as IHCCs.

Mid-year population estimates were derived from the Annual Reports of the Registrar General for Scotland. Gender-specific, age-standardised incidence rates were calculated for each major diagnostic entity, and for six consecutive quinquennia, by direct standardisation to the European standard population. Absolute and percentage changes in incidence rates between 1968 and 1997, and *P*-values for trend, were estimated by Poisson regression modelling.

For both sexes combined, and for the same six quinquennia, the percentages of cases recorded as being microscopically-verified (MV) were calculated. Under the rules governing cancer registration, if an incident case is recorded as being microscopically-verified, this indicates that the tumour has been examined by means of histopathology or cytopathology, and the findings have supported the clinical diagnosis of, for example, IHCC. Whilst pathological examination and typing of tumours is not infallible, it is generally considered the 'gold standard' diagnostic tool, and, consequently, a high degree of confidence is placed in microscopically-verified cancer registrations. Cases may not be microscopically-verified for a variety of reasons, for example, the availability of accurate imaging may be considered sufficient to confirm the diagnosis in some cases. In addition, occasionally microscopic verification may not be available to the Cancer Registry, for example, if verification is only achieved after registration has occurred.

Annual gender-specific, age-standardised incidence rates for all cases of IHCC combined, and for microscopically-verified cases only, were calculated for the period 1968–1997 by direct standardisation to the European standard population. Finally, annual gender- and age-specific incidence rates of IHCC were calculated for the period 1968–1997, using the age groups 20–44 years, 45–64 years, 65–74 years, and 75+ years.

3. Results

Table 1 shows that the age-standardised incidence rate of IHCC (referred to as intrahepatic bile duct cancers in the ICD) increased from 0.12 in males and 0.17 in females in 1968–1972 to 1.53 and 1.24 per 100 000 in 1993–1997; estimated percentage changes between 1968 and 1997 of 817 and 851%, respectively. In terms of the absolute number of cases, a total of 84 cases of IHCC were registered in Scotland in 1997, compared with just 9 in 1968. Over the same time period, the incidence of liver cell cancers (mainly hepatocellular carcinomas) and secondary liver cancers also increased, but to a relatively smaller extent. The incidence of liver cancers unspecified as primary or secondary (and mostly not microscopically-verified) showed no consistent trend.

The incidence of gallbladder cancer fell over the study period, whereas the incidence of extrahepatic bile duct cancers showed no consistent trend. Interestingly, the incidence of cancer of other parts of the biliary tract, which includes cancers that involve both the intra- and extrahepatic bile ducts, also increased significantly. Incidence of pancreatic cancer increased then decreased, with the fall being more pronounced in men.

The proportion of IHCCs verified by microscopy has declined dramatically since the late 1970s. None of the other cancer types examined has shown such a marked fall in the microscopic verification rates. Despite the fall in the microscopic verification rates for IHCC, the incidence of microscopically-verified IHCC has still increased over the study period. Fig. 1 shows the striking increase in incidence of IHCC in both sexes over time, both for all registered cases, and to a lesser extent, for cases verified microscopically only. The logarithmic plot shows that the rate of increase of all IHCC cases has been fairly constant over the last three decades, whereas the rate of increase of microscopically-verified IHCC cases has slowed somewhat since the early 1980s.

Fig. 2 shows that the rate of increase of all IHCC cases has been comparable in all age groups over 45 years, although as incidence is highest in the oldest age groups, the absolute increase in incidence has been greatest in those aged over 75 years. IHCC is exceedingly rare in persons aged less than 45 years, hence results for the 20–44 year age group have been omitted from Fig. 2 as random year-to-year fluctuation in small

Table 1
Age-standardised incidence rates[a] (and percentage of cases microscopically-verified) of malignant neoplasms of the liver, biliary tree and pancreas by diagnostic entity, during six consecutive quinquennia in Scotland, 1968–1997

Diagnostic entity	Gender	Annual age-standardised incidence rates per 100 000 person years at risk[a] (and percentage of cases microscopically-verified) by period of diagnosis						Estimated absolute change in incidence 1968–1997[b]	Estimated% change in incidence 1968–1997[b]	*P* value for trend
(ICD9/ICD10)		1968–1972	1973–1977	1978–1982	1983–1987	1988–1992	1993–1997			
Liver and intrahepatic bile duct cancers	Males	1.93	2.49	3.83	4.23	4.44	5.24	+3.80	+180.7	<0.0001
(155/C22)	Females	0.94	1.05	1.53	1.67	1.91	2.22	+1.56	+171.9	<0.0001
(% Microscopically-verified)	Both	(72.8%)	(73.3%)	(73.9%)	(67.4%)	(55.3%)	(54.2%)			
Liver cell cancers	Males	1.61	2.00	2.87	2.97	2.90	3.53	+2.08	+120.1	<0.0001
(155.0/C22.0, C22.2-C22.7)	Females	0.66	0.71	0.92	0.87	0.79	0.90	+0.22	+31.7	0.0199
(% Microscopically-verified)	Both	(80.0%)	(76.4%)	(79.8%)	(75.3%)	(67.0%)	(67.6%)			
Intrahepatic bile duct cancers	Males	0.12	0.32	0.70	0.96	1.25	1.53	+1.77	+817.3	<0.0001
(155.1/C22.1)	Females	0.17	0.23	0.43	0.66	1.02	1.24	+1.40	+851.2	<0.0001
(% Microscopically-verified)	Both	(80.5%)	(81.6%)	(75.2%)	(61.0%)	(42.0%)	(37.6%)			
Liver, unspecified	Males	0.20	0.17	0.26	0.29	0.29	0.18	+0.01	+4.9	0.8562
(155.2/C22.9)	Females	0.12	0.10	0.19	0.13	0.11	0.08	−0.04	−28.7	0.2533
(% Microscopically-verified)	Both	(14.6%)	(27.0%)	(23.8%)	(25.0%)	(32.7%)	(28.9%)			
Secondary liver cancers[c]	Males	1.83	2.76	3.40	4.03	5.31	7.24	+6.01	+331.1	<0.0001
(197.7/C78.7)	Females	0.96	1.74	2.28	2.85	3.44	4.68	+4.35	+417.7	<0.0001
(% Microscopically-verified)	Both	(30.6%)	(44.3%)	(42.8%)	(40.5%)	(38.1%)	(42.8%)			
Gallbladder and extrahepatic bile ducts	Males	1.87	2.11	2.26	2.05	2.21	2.20	+0.18	+9.0	0.3170
(156/C23-C24)	Females	2.33	2.53	2.58	2.30	2.38	2.23	−0.26	−10.2	0.1023
(% Microscopically-verified)	Both	(60.2%)	(59.5%)	(67.6%)	(67.7%)	(67.2%)	(65.2%)			
Gallbladder cancers	Males	0.63	0.64	0.76	0.80	0.61	0.45	−0.24	−30.3	0.0219
(156.0/C23)	Females	1.40	1.30	1.37	1.07	1.14	0.95	−0.59	−38.6	<0.0001
(% Microscopically-verified)	Both	(65.2%)	(66.7%)	(74.9%)	(74.2%)	(75.5%)	(78.3%)			
Extrahepatic bile duct cancers	Males	0.87	0.90	1.00	0.73	0.87	0.82	−0.13	−14.0	0.2609
(156.1/C24.0)	Females	0.66	0.85	0.81	0.81	0.65	0.60	−0.12	−15.5	0.1562
(% Microscopically-verified)	Both	(51.0%)	(47.6%)	(55.0%)	(53.0%)	(51.9%)	(44.1%)			
Other parts of biliary tract	Males	0.36	0.57	0.50	0.52	0.73	0.93	+0.55	+148.6	<0.0001
(156.2-156.9/C24.1-C24.9)	Females	0.27	0.38	0.40	0.43	0.59	0.68	+0.47	+180.9	<0.0001
(% Microscopically-verified)	Both	(64.3%)	(66.2%)	(73.8%)	(79.6%)	(73.3%)	(72.0%)			
Pancreas cancer	Males	12.32	12.91	12.94	12.57	12.14	10.96	−1.89	−14.2	<0.0001
(157/C25)	Females	7.13	8.12	9.21	8.72	8.26	8.18	+0.87	+11.1	0.0033
(% Microscopically-verified)	Both	(35.7%)	(36.3%)	(43.6%)	(42.6%)	(38.9%)	(40.7%)			

ICD, International Classification of Disease.
[a] Rates directly age-standardised to the European standard population.
[b] Absolute and percentage changes estimated by Poisson regression modeling.
[c] Secondary liver cancers are registered only when the primary site is not established.

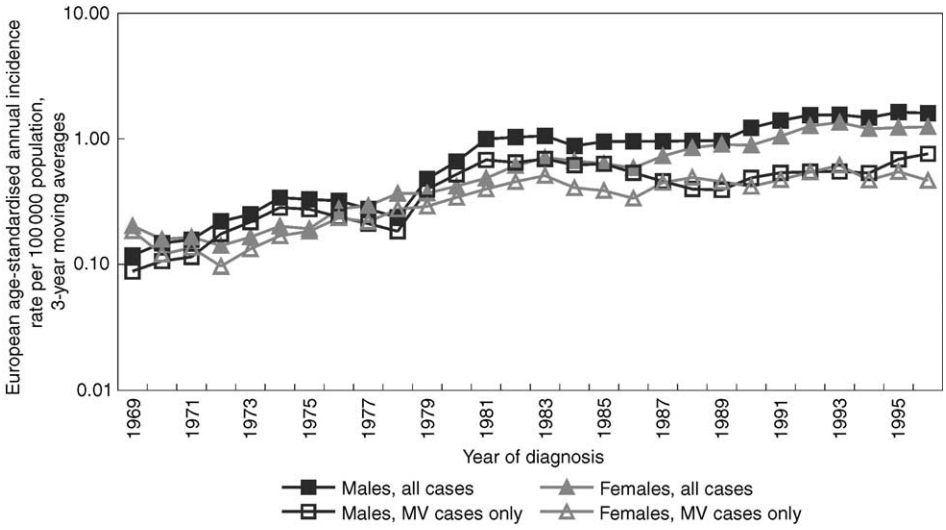

Fig. 1. Age-standardised incidence of intrahepatic cholangiocarcinoma (all registered cases and microscopically-verified (MV) cases only), Scotland 1968–1997.

numbers of cases gives very unstable annual rates for this age group.

4. Discussion

In Scotland, there has been a striking increase in the reported incidence of IHCC between 1968 and 1997. Possible explanations to consider for this observed rise in incidence include changes in the completeness or accuracy of diagnosis and registration, and/or a real increase in risk.

Diagnostic practice in relation to IHCC has changed over time. Endoscopic retrograde cholangiopancreatography (ERCP) was introduced in the United Kingdom in the late 1970s and was widely available by the mid-1980s, followed by the introduction of liver ultrasound scanning. More recently, high-resolution magnetic resonance imaging (MRI) of the biliary tree has also been developed, but this is not yet routinely available. All of these imaging techniques have facilitated the diagnosis of intrahepatic, as well as extrahepatic, bile duct tumours, although increasing reliance on imaging to diagnose IHCC may have contributed to its falling microscopic verification rates. It is important to note, however, that the increase in reported incidence of all IHCC cases started before the development of ERCP and has continued since it became widely available. In addition, the incidence of microscopically-verified IHCC has continued to increase since the introduction of ERCP, albeit at a reduced rate.

Another factor to consider is the possibility of diagnostic transfer between other cancers and IHCC. Clinically, it may be difficult to distinguish between IHCC and other cancers of the hepatobiliary system, or even pancreatic cancer, and diagnostic 'fashions' may change over time.

Neither other liver cancers, nor gallbladder cancer or extrahepatic bile duct cancers have shown decreases in their reported incidence that would be sufficient to account for the observed rise in the incidence of IHCC. Although general advances in diagnostic techniques might be expected to reduce the numbers of secondary cancers without an established primary site, the overall increase in incidence of all sites and types of cancer combined in Scotland, together with increased opportunities for detecting liver metastases, seems to have led to an increase in registrations of this diagnostic entity over time. The recent decrease in the incidence of gallbladder cancer is consistent with earlier increases in cholecystectomy rates in Scotland, which would be expected to reduce the population at highest risk of this disease [5]. Although over the whole study period, diagnostic transfer from cancers of the pancreas could theoretically account for the increase in incidence of IHCC, at least in males, trends within the study period do not support diagnostic transfer between these two cancers, as both showed increasing incidence until the late 1970s. In addition, the observed trends in the incidence of pancreatic cancer are congruent with historical patterns of smoking, a recognised risk factor for this cancer [6]. It seems unlikely therefore that diagnostic transfer alone has accounted for the observed rise in the reported incidence of IHCC.

Another potential source of data artefacts to consider relates to how precisely or not the term cholangiocarcinoma is used. As mentioned previously, a diagnosis of cholangiocarcinoma with no anatomical site specified is, under ICD rules, by default coded as an IHCC. It is possible therefore that some extrahepatic bile duct cancers are being wrongly coded as IHCCs. It is important

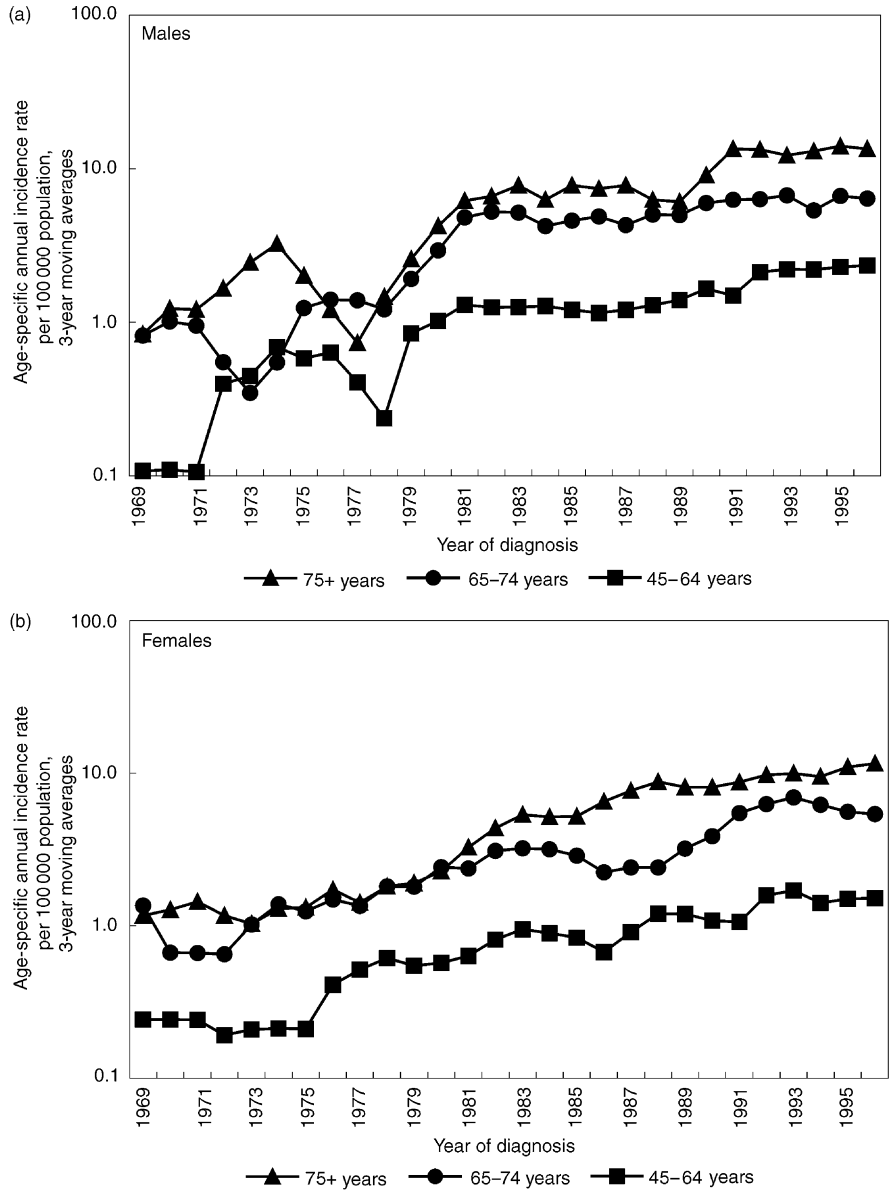

Fig. 2. Age-specific incidence of intrahepatic cholangiocarcinoma (all registered cases), Scotland 1968–1997. (a) Males, (b) females.

to note, however, that all bile duct cancers taken together have shown a marked increase in reported incidence over the study period.

With routinely collected data, it is always important to consider the possibility that observed trends could reflect problems with data quality and/or changes in data quality over time. However, available evidence suggests that the quality of Scottish cancer registration data is high, and that changes in data quality are unlikely to account for the observed increase in the incidence of IHCC [7–9].

In conclusion, it seems probable that at least some of the observed rise in the reported incidence of IHCC represents a real increase in the risk of this cancer. Traditional risk factors such as developmental abnormalities of the biliary tract, primary sclerosing cholangitis associated with ulcerative colitis, and chronic infestation with liver flukes, account for only a proportion of cases of IHCC, particularly in the West [10,11], hence the increasing incidence raises the possibility of increasing population exposure to an as yet unknown risk factor for IHCC. Possible roles for environmental carcinogens and also chronic hepatitis C infection, which is not usually associated with the development of bile duct cancers, have recently received attention [2]. Further work is indicated to increase understanding of the epidemiology and aetiology of IHCC, including examination of international trends in incidence, and studies to assess whether incidence differs within countries according to characteristics such as area of residence, socio-economic status, ethnic origin or occupation.

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