Increase in mortality rates from intrahepatic cholangiocarcinoma in England and Wales 1968–1998

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Abstract

***Background*—The age standardised mortality rate per 100 000 population for all causes of liver tumours (International Classification of Disease 9 (ICD-9) 155) has almost doubled in England and Wales during the period 1979–1996. We further analysed the mortality statistics to determine which anatomical subcategories were involved.**

***Methods*—Mortality statistics for liver tumours of ICD-9 155, 156, and subcategories, and for tumours of the pancreas (ICD-9 157), in England and Wales were investigated from the Office for National Statistics, London, from 1968 to 1996 inclusive. Data for 1997 and 1998 were also available on intrahepatic cholangiocarcinomas.**

***Results*—There has been a marked rise in age standardised mortality rates for intrahepatic cholangiocarcinoma. Since 1993, it represents the commonest recorded cause of liver tumour related death in England and Wales. This is evident in age groups older than 45 years. In contrast, mortality trends from other primary liver tumours, including hepatocellular carcinoma, were unremarkable.**

***Conclusions*—The observed increase in mortality from intrahepatic cholangiocarcinoma may represent better case ascertainment and diagnosis due to improved diagnostic imaging, use of image guided biopsies, or increased use of ERCP. However, the trend started before ERCP was introduced nationally, mortality rates have continued to increase steadily thereafter, and there is no clear evidence that diagnostic transfers easily explains the findings. Alternatively, these observations may represent a true increase in intrahepatic bile duct tumours. Epidemiological studies are required to determine whether there is any geographical clustering of cases around the UK.**

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Keywords: intrahepatic cholangiocarcinoma; age standardised mortality rates; age specific mortality rates

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Studies from France, Italy, and the USA suggest that the incidence of hepatocellular carcinoma (HCC) is increasing,[1 2] and this may be related to chronic hepatitis C virus (HCV) infection.[1–4] Age standardised mortality rates (ASMR) for all causes of malignant liver tumours (International Classification of Disease 9 (ICD-9) 155) have increased from 1979 to 1994 in the UK,[5] but unlike in Southern Europe, the ASMR for HCC has been reported to be relatively static over this time period while the ASMR for intrahepatic cholangiocarcinoma may have been increasing.[5]

We investigated ASMR and age specific mortality rates (ASpMR) for all liver tumours in England and Wales, starting in 1968, when comparable mortality records began, to determine when the rise in ASMR for intrahepatic cholangiocarcinoma first started and which age groups have primarily been affected.

Methods

Mortality data for 1968–1996 were obtained for the English and Welsh populations from the Office for National Statistics (ONS) in London. Information was requested on:

- ICD-9 155 (all malignant liver tumours)
- ICD-9 155.0 (primary liver tumours, mainly HCC)
- ICD-9 155.1 (intrahepatic cholangiocarcinoma)
- ICD-9 155.2 (histologically unspecified liver tumours)
- ICD-9 156 (all extrahepatic biliary system tumours)
- ICD-9 156.0 (gall bladder tumours)
- ICD-9 156.1 (tumours of the extrahepatic bile ducts)
- ICD-9 157 (pancreatic tumours).

The ICD-9 155.0 code contains information on all primary tumours of the hepatic parenchyma but is overwhelmingly composed of data on HCC. Mortality data, supplied in five year age bands, were considered to be an indicator of incidence because prognosis from liver cancer is poor. Additional mortality data for 1997–1998 were requested, once they had become available, for intrahepatic cholangiocarcinoma, the tumour of primary interest, as initial analysis indicated that the observed trends for this tumour warranted further up to date inspection.

Abbreviations used in this paper: ASMR, age standardised mortality rates; ASpMR, age specific mortality rates; ERCP, endoscopic retrograde cholangiopancreatography; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; ICD-9, International Classification of Disease 9; ONS, Office for National Statistics; OPCS, Office of Population Censuses and Surveys; WHO, World Health Organization.

NUMBER OF DEATHS

The total number of deaths attributed to each ICD category of cancers was analysed by year and sex. No deaths before 1968 are included because coding changes between ICD-7 (1958–1967) and ICD-8 (1968–1978) make it impossible to accurately trace deaths attributed to a particular category earlier than this. Coding changes between ICD-8 and ICD-9 for the tumours under study seemed to be minor, although it is recognised that any change in coding can have an impact on mortality statistics.[6] In our analysis, we mapped the change in code for "unspecified primary or secondary tumours of the liver" across ICD revisions from 197.8 to 155.2.

Two other notable changes to the collection and coding of deaths in England and Wales occurred in 1993 which may affect interpretation of trends in mortality. These include the move back by the Office of Population Censuses and Surveys (OPCS) to the internationally accepted interpretation of World Health Organization (WHO) rule 3, regarding the selection of the underlying cause of death, which was in operation before 1984.[7] In addition, until 1992 it was standard procedure for the OPCS to apply to the person certifying the death for further information regarding the underlying cause of death when the conditions mentioned on the death certificate were vague. The use of such "medical enquiries" to help assign a more definite code to the underlying cause of death was discontinued in 1993.[7]

AGE STANDARDISED MORTALITY RATES

ASMR per 100 000 population were calculated using direct standardisation with the European standard population as a reference population.[8]

AGE SPECIFIC MORTALITY RATES

Initially, ASpMR per 100 000 of the population were analysed by five year age bands but given that tumours are much less common in the younger age groups and that treatment and management may differ between middle and very old age, these were aggregated into more clinically relevant age specific groups. The following age bands were therefore chosen: 20–44, 45–64, 65–74, and 75+.

Results

ALL LIVER TUMOURS

ASMR per 100 000 population for the combined causes of malignant liver tumours increased steadily in the period 1968–1996 from 1.29 to 1.93 in females and from 2.56 to 3.70 in males (fig 1A, B). Total numbers of deaths increased from 967 (396 females; 571 males) in 1968 to 1822 (770 females; 1052 males) in 1996 (table 1).

Primary liver tumours including hepatocellular carcinomas

Data on primary liver tumours revealed fluctuations in ASMR about a stable mean between 1968 and 1978 for both sexes. However, in 1979 there was a noticeable increase in ASMR for both males and females

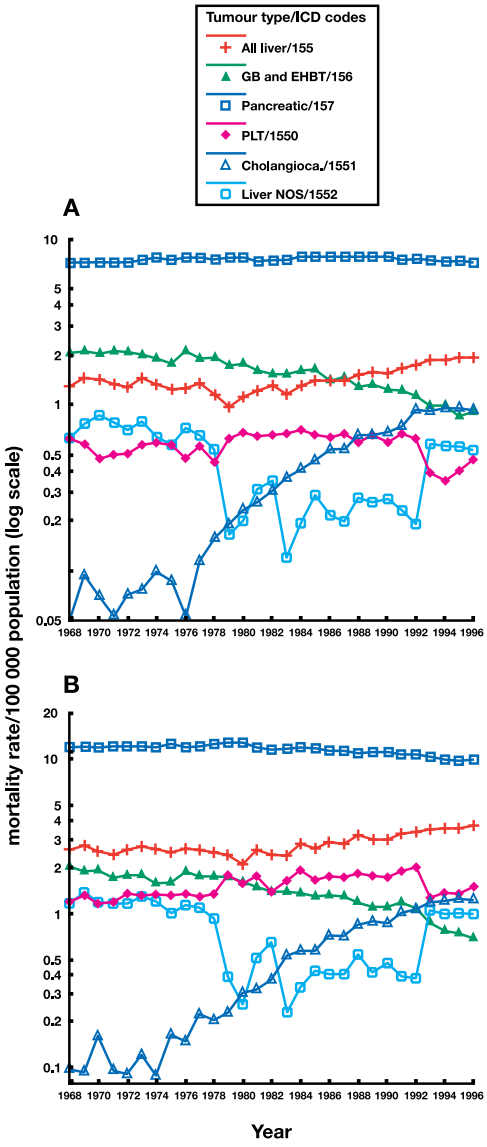

Figure 1 Age standardised mortality rates per 100 000 population of England and Wales in (A) females and (B) males for: all malignant liver tumours (ICD-9 155); primary tumours of the hepatic parenchyma which are mainly hepatocellular carcinomas (ICD-9 1550); intrahepatic cholangiocarcinoma (ICD-9 1551); unspecified liver tumours (ICD-9 1552); all tumours of the gall bladder and extrahepatic biliary tree (ICD-9 156); and all tumours of the pancreas (ICD-9 157). Mortality rates are plotted on a logarithmic scale. All liver, all malignant liver tumours; GB and EHBT, gall bladder and extrahepatic biliary tree; PLT, primary liver tumours—mainly hepatocellular carcinoma; cholangioca., intrahepatic cholangiocarcinoma; liver NOS, liver, not otherwise specified.

until 1992 (fig 1A, B). In 1993 there was a sharp decline in ASMR to levels more in common with those before 1979.

Intrahepatic cholangiocarcinoma

ASMR per 100 000 population for intrahepatic cholangiocarcinoma increased markedly for both sexes over the period 1968–1996 (fig 1A, B). There was a 15-fold increase in ASpMR per 100 000 population in ages 45 and above (fig 2A, B). The total number of deaths increased from 38 (17 females, 21 males) in 1968 to 736 (387 females, 349 males) in 1996

Table 1 Numbers of deaths by ICD-9 code in England and Wales 1968–1996

	155			1550			1551			1552			156			1560			1561			157		
Year	F	M	Total	F	M	Total	F	M	Total	F	M	Total	F	M	Total	F	M	Total	F	M	Total	F	M	Total
1968	396	571	967	180	292	472	17	21	38	199	258	457	688	437	1125	407	177	584	223	205	428	2279	2619	4898
1969	458	603	1061	180	282	462	30	20	50	248	301	549	706	412	1118	436	148	584	224	193	417	2318	2666	4984
1970	451	587	1038	147	276	423	22	35	57	282	276	558	699	415	1114	424	163	587	219	200	419	2368	2654	5022
1971	443	551	994	158	271	429	16	23	39	269	257	526	708	391	1099	420	159	579	235	159	394	2442	2757	5199
1972	424	599	1023	163	310	473	23	22	45	238	267	505	710	405	1115	413	146	559	231	198	429	2468	2778	5246
1973	478	637	1115	184	313	497	25	27	52	269	297	566	695	415	1110	391	151	542	253	195	448	2559	2780	5339
1974	449	611	1060	196	311	507	34	21	55	219	279	498	662	378	1040	376	133	509	236	177	413	2659	2797	5456
1975	418	589	1007	181	312	493	30	40	70	207	237	444	636	377	1013	334	128	462	236	186	422	2607	2963	5570
1976	433	629	1062	156	319	475	19	36	55	258	274	532	744	449	1193	387	164	551	269	220	489	2768	2853	5621
1977	453	625	1078	180	309	489	38	53	91	235	263	498	682	420	1102	360	139	499	266	227	493	2775	2920	5695
1978	398	606	1004	151	332	483	47	48	95	200	226	426	691	426	1117	371	146	517	246	213	459	2692	3008	5700
1979	336	583	919	208	434	642	66	54	120	62	95	157	634	409	1043	341	138	479	229	203	432	2809	3087	5896
1980	376	522	898	227	380	607	74	78	152	75	64	139	668	402	1070	332	140	472	262	197	459	2837	3127	5964
1981	419	628	1047	220	430	650	89	78	167	110	120	230	599	365	964	321	121	442	230	184	414	2762	2989	5751
1982	463	597	1060	230	341	571	101	91	192	132	165	297	564	354	918	326	123	449	189	177	366	2822	2898	5720
1983	396	594	990	231	409	640	123	127	250	42	58	100	576	346	922	346	125	471	170	167	337	2836	2976	5812
1984	466	713	1179	231	479	710	148	148	296	87	86	173	613	346	959	364	153	517	192	119	311	3009	3028	6037
1985	499	680	1179	220	425	645	171	145	316	108	110	218	632	329	961	359	130	489	191	146	337	3014	3063	6077
1986	514	750	1264	218	456	674	206	183	389	90	111	201	552	339	891	325	144	469	157	144	301	3093	2950	6043
1987	526	726	1252	229	437	666	206	185	391	91	104	195	575	347	922	330	148	478	164	122	286	3078	2987	6065
1988	583	837	1420	207	467	674	242	227	469	134	143	277	512	311	823	321	124	445	123	143	266	3103	2905	6008
1989	576	802	1378	220	456	676	248	239	487	108	107	215	558	294	852	311	116	427	166	115	281	3164	2952	6116
1990	570	818	1388	207	458	665	252	231	483	111	129	240	513	300	813	305	105	410	133	110	243	3149	2996	6145
1991	645	879	1524	242	501	743	301	269	570	102	109	211	486	318	804	276	129	405	132	117	249	3068	2941	6009
1992	684	919	1603	223	528	751	372	285	657	89	106	195	491	302	793	282	125	407	140	100	240	3108	2926	6034
1993	735	970	1705	142	348	490	355	329	684	238	293	531	402	248	650	233	101	334	120	93	213	3023	2853	5876
1994	781	983	1764	132	374	506	405	335	740	244	274	518	420	221	641	269	87	356	100	77	177	3029	2781	5810
1995	761	999	1760	142	366	508	402	347	749	217	286	503	373	215	588	218	106	324	112	76	188	3079	2760	5839
1996	770	1052	1822	164	416	580	387	349	736	219	287	506	380	205	585	227	90	317	106	70	176	3044	2829	5873

155, all malignant liver tumours; 1550, primary liver tumours (mainly hepatocellular carcinoma); 1551, intrahepatic cholangiocarcinoma; 1552, unspecified liver tumours; 156, tumours of the extrahepatic biliary tree and gall bladder; 1560, tumours of the gall bladder; 1561, extrahepatic cholangiocarcinomas; 157, pancreatic tumours.
F, female; M, male

(table 1). This cancer now represents the commonest primary liver tumour in England and Wales, having overtaken hepatocellular carcinoma in 1993 (table 1). Additional data for 1997–1998 showed a further marked increase in mortality rates from the 1996 statistics. ASMR increased from 0.92 and 1.22 in 1996 to 1.12 and 1.37 in 1998 for females and males, respectively, bringing the total number of deaths in that year to 864.

Unspecified tumours of the liver

ASMR for liver tumours in this ICD category showed a small decrease overall, although there was a marked fall in ASMR from 1978 to 1993 in both sexes (fig 1A, B).

TUMOURS OF THE GALL BLADDER AND EXTRAHEPATIC BILIARY TREE

There was a steady decrease in ASMR between 1968 and 1996 (fig 1A, B). Between 1968 and 1978, the total number of deaths for men and women was relatively stable at approximately 700 per year for women and approximately 400 per year for men. Subsequently, the total number of deaths fell from 1043 in 1979 to 585 in 1996 (table 1).

Tumours of the gall bladder

Between 1968 and 1996, both ASMR and total number of deaths attributed to malignant neoplasm of the gall bladder decreased steadily. ASMR fell from 1.21 and 0.84 in 1968 to 0.55 and 0.30 in 1996 for females and males, respectively.

Tumours of the extrahepatic bile ducts

ASMR for malignant tumours of the extrahepatic bile duct fluctuated between 1968 and

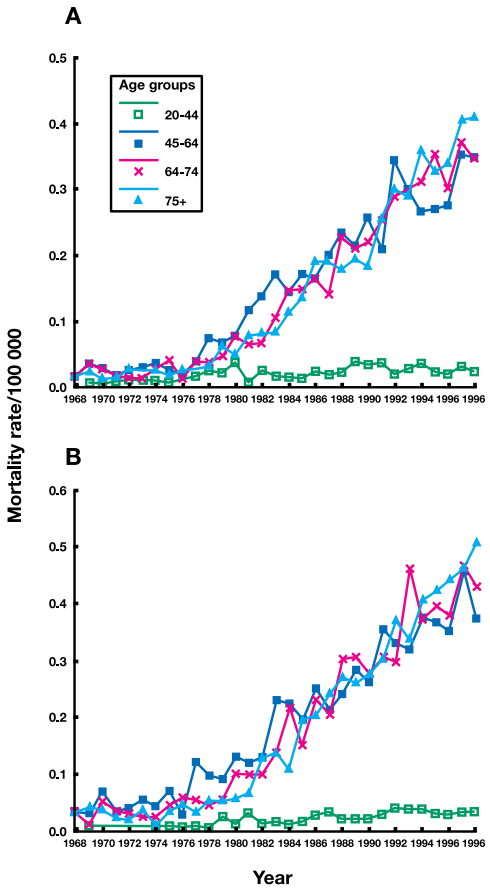

Figure 2 Age specific mortality rates per 100 000 population of England and Wales in (A) females and (B) males for intrahepatic cholangiocarcinoma (ICD-9 155.1).

1979, after which they began to fall from 0.71 for females and 0.80 for males in 1980 to 0.23 in 1996 for both sexes.

Combined intrahepatic and extrahepatic cholangiocarcinoma (ICD-9 code 155.1 and 156.1)

The combined ASMR from all tumours of the biliary tract increased over the time period 1968–1996. The absolute number of deaths also increased from 466 (240 females, 226 males) in 1968 to 912 (493 females, 419 males) in 1996 (table 1).

PANCREATIC TUMOURS

ASMR showed a slight decline for both sexes but this was less marked for females (fig 1A, B). However, the absolute number of deaths rose between 1968 (total 4898; 2279 females; 2619 males) and 1996 (total 5873; 3044 females; 2829 males).

Discussion

In England and Wales there has been a steady rise in mortality coded to intrahepatic cholangiocarcinoma. Although ASMR for extrahepatic cholangiocarcinoma have decreased, the increase in intrahepatic tumours outweighs this with a rise in ASMR and in absolute number of deaths for both these two ICD-9 categories combined. Cholangiocarcinoma, arising from the intrahepatic biliary tree, is much less common than HCC on a worldwide basis, but since 1993 this tumour is the commonest recorded cause of malignant liver tumour related death in England and Wales. In South East Asia and China, development of cholangiocarcinoma is mainly associated with liver flukes.[9] In the West the aetiology is largely unknown although the obsolete radiological contrast agent thorotrast has been implicated in causing cholangiocarcinoma.[10] Smoking and alcohol have also been implicated but the evidence is weak.[11 12] Primary sclerosing cholangitis is the commonest predisposing factor in the UK but it is associated with only a minority of cases.[9]

The steadily increasing ASMR for intrahepatic cholangiocarcinoma may represent an artefactual trend, introduced into the mortality figures by improvement in diagnosis (case ascertainment) resulting from better imaging techniques, by changes in coding practices, or from misclassification of ICD coding (diagnostic transfer). It is also possible that this trend represents a real increase in mortality from this tumour.

Better ascertainment from improved diagnostic imaging, use of image guided biopsies, and from the national availability of techniques such as endoscopic retrograde cholangiopancreatography (ERCP) could account for these observations. ERCP was first available in the UK in the late 1970s after the rise in ASMR started, and became available in most UK hospitals in the mid 1980s.[13 14] The increased mortality rates have continued after the initial endoscopic learning curve and the general availability of the technique should have led to an expected plateau in these values. It is therefore unlikely that our observations on intrahepatic cholangiocarcinoma are solely caused by an improvement in diagnosis from ERCP. Furthermore, it is the distally located extrahepatic bile duct tumours, total numbers of deaths from which have actually decreased, that are more easily visualised with ERCP, rather than the intrahepatic tumours which often involve much smaller bile ducts. The definitive diagnosis of intrahepatic bile duct tumours is histological, and in a large proportion of cases this is made from tissue obtained at surgery or at post mortem.[15] However, this is dependent on the experience of the local pathologist and therefore there may be interobserver differences in interpretation. This factor in itself would not account for the year-on-year rise in intrahepatic cholangiocarcinoma that we have reported.

There have been a few changes to the collection and coding of mortality data from 1968 to 1998 which could potentially render our findings artefactual. However, no discernible "steps" in mortality trends for intrahepatic cholangiocarcinoma have been introduced by changes in coding practices. This is in stark contrast with the mortality trends for primary liver tumours (mainly HCC) and for unspecified liver tumours, which provide clear illustrations of the impact of coding changes. In 1979 when ICD-9 was first introduced, subtle changes in the number and type of diseases which fed into both these categories of tumours led to an increase in primary liver tumours and a simultaneous decline in unspecified liver tumours. In 1993, both the rule 3 coding change and the death certificate changes introduced further artefact, with the latter having the dominant effect on these tumour types. Prior to 1993, it was routine practice for OPCS to obtain follow up information from the certifying doctor about the cause of death, approximately six weeks after the initial death certification. In many instances, information that became available with post mortem confirmed or changed the cause of death and this was rectified with this process. With the absence of follow up medical enquiries on death certificates from 1993, there was an increase in the number of deaths assigned to categories of less specific causes.[7] The sudden change in mortality statistics between 1979 and 1993 for primary and unspecified liver tumours are thus artefactual and any examination of time trends for these tumours is limited to cautious comparisons of data from before 1979 and after 1993.

Diagnostic transfer from tumours of the gall bladder and extrahepatic biliary tree to intrahepatic cholangiocarcinomas is an alternative explanation for our findings but the increase in ASMR and absolute number of deaths from intrahepatic tumours outweighed the decrease in the other malignancies. Simple diagnostic transfer is therefore unlikely. Diagnostic transfer may also occur between intrahepatic cholangiocarcinoma and undifferentiated metastatic adenocarcinoma in the liver but it is probable that histologically ill defined tumours

tend to be reported in the unspecified category than reported specifically as intrahepatic cholangiocarcinoma.[16] Diagnostic transfer from pancreas to intrahepatic cholangiocarcinoma could account for the small decrease in ASMR for pancreatic tumours and the marked increase in ASMR for intrahepatic bile duct tumours but this is unlikely because it is unusual to confuse the two diagnoses from an anatomical standpoint.

Another explanation for the steady rise in ASMR for intrahepatic cholangiocarcinoma between 1968 and 1998 is a true increase in incidence of this tumour. The reason intrahepatic cholangiocarcinomas have increased in place of tumours of the rest of the biliary tract may be because of the larger surface area of the intrahepatic biliary tree[17] compared with that of the gall bladder and extrahepatic biliary tree, allowing greater exposure to potential carcinogens, which may have been more prevalent over the past 30 years. Furthermore, intrahepatic bile ducts contain the majority of actively dividing cholangiocytes, which would make malignancies of this part of the biliary tree more likely.[18] If improved imaging and the availability of ERCP has led to better case ascertainment, intrahepatic tumours may be detected at an earlier stage, before invasion of the extrahepatic biliary tree has occurred. However, the absolute rise in both ASMR and total number of deaths from the combined ICD-9 categories for intra- and extrahepatic bile duct tumours is also further evidence that the observed trend may, in part, be real rather than apparent.

The oral contraceptive pill has also been implicated in the development of cholangiocarcinoma[19 20] although case control studies have failed to substantiate an increased risk.[21] The time period when oral contraceptives became widely available in England and Wales and the age groups involved with increased mortality from intrahepatic cholangiocarcinoma do not entirely match.[22] Furthermore, this trend in mortality statistics is also seen in men, making the "pill" an unlikely candidate as the sole cause of this phenomenon, although there are many chemicals which could potentially have entered the food chain which have oestrogenic properties.

We have shown a dramatic increase in ASMR and ASpMR for intrahepatic cholangiocarcinoma from 1968 to 1998 in England and Wales. Epidemiological studies are required to determine whether there is any geographical clustering of cases around the UK and whether any clusters can be related to occupational exposure. Further studies are needed to compare the observed trend in mortality statistics with that for other countries. Given that current treatment outcomes for cholangiocarcinoma are poor, such studies may lead to a better understanding of the aetiology of these tumours and institution of appropriate preventative measures.

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