Research Article

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Rising trends in cholangiocarcinoma: Is the ICD classification system misleading us?

Shahid A. Khan[1], Shireen Emadossadaty[1], Nimzing G. Ladep[1], Howard C. Thomas[1], Paul Elliott[2], Simon D. Taylor-Robinson[1], Mireille B. Toledano[2,*]

[1]*Liver Unit, Division of Diabetes Endocrinology and Metabolism, Department of Medicine, Imperial College London, London, United Kingdom;* [2]*MRC-HPA Centre for Environment and Health, Department of Epidemiology and Biostatistics, School of Public Health, Imperial College London, London, United Kingdom*

Background & Aims: Cholangiocarcinomas (CC) can be subdivided into intrahepatic (IHCC) or extrahepatic (EHCC). Hilar or 'Klatskin' tumours are anatomically extrahepatic. Most international studies, also from the UK, report increasing IHCC and decreasing EHCC incidence. The second edition of the International Classification of Diseases for Oncology (ICD-O-2) assigned 'Klatskin' tumours a unique histology code (8162/3), but this was cross-referenced to the topography code for intrahepatic (IHBD) rather than extrahepatic bile duct tumours (EHBD). Under the third ICD-O edition, 'Klatskin' tumours are cross-referenced to either IHBD or EHBD. New editions of the ICD-O classification are adopted at different time points by different countries. We investigated the impact of changing ICD-O classifications and the potential misclassification of hilar/'Klatskin' tumours on bile duct tumour and CC incidence rates in England and Wales and the US. We also examined whether coding practices by cancer registries in England and Wales could be influencing these rates.
Methods: We analysed age-standardised incidence rates (ASIR) in England and Wales for IHBD and EHBD tumours between 1990 and 2008, then transferred all 'Klatskin' tumours from IHBD to EHBD and reanalysed rates from 1995, when ICD-O-2 was introduced in the UK. We also compared trends in IHBD, EHBD, and 'Klatskin' tumours in England and Wales with those in the USSEER (Surveillance, Epidemiology and End Results) database. Coding practice at Cancer registry level in England and Wales was investigated via a questionnaire completed by all national cancer registries.
Results: In England and Wales, 1990–2008, ASIR of IHBD cancers rose (0.43–1.84/100,000 population in males; 0.27–1.51 in females) but fell for EHBD (0.78–0.51/100,000 population in males; 0.62–0.39 in females). After transferring all 'Klatskin' tumours from IHBD to EHBD, there remained a marked increase in ASIR of IHBD cancers and a decrease in ASIR for EHBD, as only 1% of CC were reportedly 'Klatskin'. The US SEER data showed that ASIR for IHBD gradually rose from 0.59/100,000 population in 1990 to 0.91 in 2001, then sharply fell before plateauing at 0.60 by 2007. ASIR for EHBD remained relatively stable at around 0.80/100,000 population until 2001, then began increasing, to 0.97 by 2007. Annually, between 1995 and 2008, the vast majority of 'Klatskin' tumours in England and Wales were coded as IHBD. This was also the case in the SEER data until 2001, when the situation was reversed and subsequently most 'Klatskin' tumours were coded as EHBD. US trends coincide with a switch from ICD-O2 to ICD-O-3 in 2001. In the UK, the switch to ICD-O-3 only occurred in 2008. On questioning, cancer registries in England and Wales stated they would not code a CC described as 'hilar' with the designated 'Klatskin' histology code. If the tumour site is unspecified, most registries classify CC as intrahepatic.
Conclusions: Changes in ICD-classification may be influencing observed changes in IHBD and EHBD incidence rates. Coding misclassification is likely to have been skewing CC registration to an intrahepatic site, thereby contributing to the previously reported rise in intrahepatic tumours.

Keywords: Cholangiocarcinoma; Intrahepatic; Extrahepatic; 'Klatskin'; Hilar; Misclassification; Cancer registries.
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* Corresponding author. Tel.: +44 20 7594 3298; fax: +44 20 7402 2150.
E-mail address: m.toledano@imperial.ac.uk (M.B. Toledano).
Abbreviations: CC, cholangiocarcinoma; IHCC, intra-hepatic cholangiocarcinoma; EHCC, extra-hepatic cholangiocarcinoma; ICD (-O), International Classification of Diseases (for Oncology); ASIR, age-standardised incidence rates; IHBD, intra-hepatic bile duct; EHBD,extra-hepatic bile duct; SEER, Surveillance, Epidemiology and End Results; WHO, World Health Organisation; SAHSU, Small Area Health Statistics Unit; ASpIR, age-specific incidence rates.

Introduction

Cholangiocarcinoma (CC) is the commonest and most lethal malignancy of the biliary tract. CC are divided into intrahepatic (IHCC), which arise in the liver parenchyma, and extrahepatic (EHCC), arising in the biliary tract outside the liver. Intrahepatic cholangiocarcinoma (IHCC) is the second most common primary hepatic malignancy worldwide, after hepatocellular carcinoma [1]. CC arising at the liver hilum (hilar CC) are anatomically defined as a subset of EHCC, since the bifurcation of the hepatic ducts lies outside the liver parenchyma. IHCC are conventionally documented to account for 5–10% of all CC cases; hilar CC for 60–70%; and EHCC for 15–20% [2–4]. The eponym 'Klatskin' tumour has been adopted for hilar CC, particularly in the USA,

after the American hepatologist who first described the unique features of these tumours in 1965 [4]. The terms 'hilar' and 'Klatskin' are interchangeable.

IHCC, hilar, and EHCC have distinct clinical and morphological features and often require different approaches to management [2–4]. Previous studies from England and Wales have shown that age-standardised mortality rates per 100,000 population for intrahepatic bile duct tumours (IHBD) increased markedly over a 30-year period since 1968, from 0.10 to 1.49 in men and 0.05 to 1.24 in women [5]. There was a 15-fold increase in age-specific mortality rates in those aged 45 years and above; and since 1993, tumours of the IHBD are the commonest recorded cause of primary liver tumour-related death in England and Wales [5]. Age-standardised incidence rates (ASIR) for IHBD cancers increased concomitantly, approximately 12-fold [6]. These studies showed an accompanying fall in mortality and incidence rates for extrahepatic bile duct tumours (EHBD) [5,6]. Recently, a number of international studies have reported increasing mortality and incidence rates for IHBD and decreasing rates for EHBD, over the last few decades [7–12]. In contrast, a recent study of Danish Cancer Registry data between 1978 and 2002 showed a fall in incidence rates of both IHBD (1.27–0.46 per 100,000 population) and EHBD (1.05–0.74). This occurred across all age groups and in both sexes [13]. A recent study of a well defined French population in Burgundy reported a fall in age-standardised incidence rates for intrahepatic biliary tract cancer between 1976–1980 and 2001–2005, from 0.3 to 0.2/100,000 population [14].

The reasons for these dynamic trends in different sub-groups of CC are unclear. Why IHBD is reportedly increasing in most countries but not in others is unknown. The trends may reflect genuine changes in the incidence of these tumours. However, given the complexity over how CC are classified and several revisions of the International Classification of Diseases (ICD) coding system for liver and biliary tract tumours over the past three decades, with each revision being adopted by different countries at different times, trends in CC rates could theoretically be influenced by coding misclassification. This is particularly likely if hilar/'Klatskin' tumours, which account for the majority of CC and are in fact extrahepatic, are misclassified as intrahepatic tumours. To date, only one published study has examined this issue [15]. This US investigation examined the impact of classification of 'Klatskin' CC on IHCC and EHCC incidence rates using data from the Surveillance, Epidemiology and End Results (SEER) cancer registry program of the US National Cancer Institute (NCI) [15]. Studying data from 1992 to 2000, before ICD-O-3 was introduced, the investigators found that 91% of the 'Klatskin' CC reported between 1992 and 2000 were incorrectly coded as IHCC, rather than EHCC, resulting in an overestimation of IHCC incidence by 13% and a similar underestimation of EHCC incidence. They also found a lower than expected proportion of 'Klatskin' tumours in the SEER dataset (8%). This remains unexplained. No similar studies have been done elsewhere and no previous study has directly questioned cancer registries as to how they code different sub-groups of bile duct tumours.

The aims of our study were to:

(1) analyse incidence trends in IHBD and EHBD tumours in relation to changes in ICD-O classification, and to investigate the impact of potential misclassification of hilar/'Klatskin' tumours on site-specific incidence rates for bile duct tumours in England and Wales and the US.

(2) investigate whether coding practices by cancer registries in England and Wales could affect reported rates of subgroups of CC.

Materials and methods

According to the World Health Organisation's (WHO) bi-axial International Classification of Diseases for Oncology (ICD-O), CC are classified as intra- or extrahepatic. The ICD-O was introduced in 1979 and assigns two codes dependent upon the tumour's anatomical topography and morphology (based on histology) [16]. Topography codes are defined in the neoplasm section of the ICD, and are applicable to all tumours, regardless of whether their growth behaviour is malignant, benign, *in situ* or uncertain. A number of different revisions of the ICD and ICD-O have been introduced over the past 40 years. In the 10th revision of the ICD, currently in use for cancer registration statistics in England and Wales, primary tumours of the liver are coded as C22.0, tumours of the intra-hepatic bile duct (IHBD) as C22.1, and tumours of the extra-hepatic bile duct (EHBD) as C24.0 [17]. These codes include several morphological/histological sub-codes for more specific delineation of tumours, as outlined in ICD-O, including: 8180/3 for combined hepatocellular carcinoma and CC, 8160/3 for CC, 8010/3 for carcinoma 'not otherwise specified (NOS)', 8140/3 for adenocarcinoma NOS, 8000/3 for 'malignant neoplasm' and 8162/3 for 'Klatskin' tumours. IHBD (coded to C22.1) are considered a primary liver malignancy (C22), whereas EHBD (C24.0) are recognised as a subset of biliary tract cancers (C24).

In the first edition of the ICD-O, hilar/'Klatskin' tumours were not assigned a specific morphology/histology code and could therefore be classified as either intrahepatic (C22.1) or extrahepatic (C24.0). In the second edition (ICD-O-2), 'Klatskin' tumours were given a unique histology code, 8162/3, but this was cross referenced to the topography code for intra- rather than extrahepatic bile duct tumours [15,18]. ICD-O-2 came into use in the US in 1992 and in England and Wales in 1995. In ICD-O-3, which came into use in the US in 2001 but later in the UK in 2008, the histology code 8162/3 was cross-referenced to either intra- or extrahepatic bile duct tumours. Thus, hilar/'Klatskin' tumours may have been misclassified in all versions of the ICD-O, and in particular may have been misclassified to intrahepatic tumours during the period when ICD-O2 was in use.

England and Wales cancer registration data

Registration data, including full details of histological classification, for all cancers coded as IHBD (C22.1) and EHBD (C24.0) in the whole of England and Wales, 1990–2008, were extracted from the National Cancer Registry held at the Small Area Health Statistics Unit (SAHSU) at Imperial College London. The SAHSU holds national routinely collected birth, death and cancer registrations at the individual level, maintained by the Office for National Statistics (ONS). Annual population estimates were obtained from the ONS.

US cancer registration data

US data between 1990 and 2007 on incidence of IHBD (C22.1), EHBD (C24.0) and 'Klatskin' tumours were obtained from the SEER program of the US NCI, an authoritative source of information on cancer incidence and survival in the United States [19]. SEER currently collects and publishes cancer data from population-based cancer registries covering almost 30 percent of the US population.

Data analysis

For each country, the total number of cases and the ASIR of IHBD, EHBD and 'Klatskin' tumours were analysed by year and sex. ASIR in England and Wales were standardised using the 2001 European standard population as the reference population. Age-specific incidence rates (ASpIR) were calculated using the following age groups: 20–44, 45–64, 65–74 and over-75 years. For England and Wales, we also analysed age-standardised incidence data for IHCC and EHCC specifically between 1990 and 2008. IHCC was defined by topography code C22.0 (primary liver tumours) and histology codes 8160 and 8161 or by topography code C22.1 (intrahepatic bile duct) and histology codes 8140, 8160, 8161, 8020, and 8010. EHCC was defined by topography code C24.0 and histology codes 8010, 8020, 8041, 8070, 8140, 8144, 8160, 8161, 8260, 8310, 8480, 8490, and 8560. All 'Klatskin' tumours (8162/3) were removed from the IHCC dataset and included in the EHCC dataset and ASIR trends reanalysed. We then compared incidence data from England and Wales with that from the US SEER program with respect to whether

'Klatskin' tumours were coded as IHBD or EHBD, between 1995 and 2007. During this entire time period, ICD-O-2 was in use in England and Wales, whereas in the US, ICD-O-3 came into use in 2001.

Coding practice of cancer registries

To investigate the coding practice of cancer registries for hilar/'Klatskin' CC, we sent a questionnaire to all nine cancer registries in England and Wales, covering a population of approximately 60 million people, between March and December 2008. The cancer registries were asked four questions:

(a) When is a tumour classified as a 'Klatskin' tumour?
(b) When is a tumour classified as a 'hilar' cholangiocarcinoma?
(c) Are there any differences between a tumour classified as 'Klatskin' and a tumour classified as 'hilar' according to the cancer registry; and if so, are hilar and 'Klatskin' tumours put into different codes?
(d) If a death certificate simply says 'cholangiocarcinoma' but does not specify intra- or extra-hepatic, what code is it given?

The registries contacted were:

(1) East Anglian Cancer Registry.
(2) Northern and Yorkshire Cancer Registry and Information Service.
(3) North West Cancer Intelligence Service.
(4) Oxford Cancer Intelligence Unit.
(5) South West Cancer Intelligence Service.
(6) Thames Cancer Registry.
(7) Trent Cancer Registry.
(8) Welsh Cancer Registry.
(9) West Midlands Cancer Intelligence Unit.

Results

Total number of cases

Between 1990 and 2008 in England and Wales, the total number of cases reported as IHBD (C22.1) rose from 226 to 1311 (Table 1A). Male cases increased from 116 to 639, and females from 110 to 672. In the same period, the number of cases reported as EHBD (C24.0) declined from 465 to 329. The decline in male cases was from 211 to 170, and in female cases from 254 to 159. In contrast, the US SEER data showed the rise in the total number of cases reported as IHBD (C22.1) rose much less during a similar time period (1990–2007): from 120 (56 males, 64 females) to 177 (89 males, 88 females). The total number of cases reported as EHBD also rose: from 168 (86 males, 82 females) to 278 (148 males, 130 females) (Table 1B). The largest single increase in the rise of EHBD cases occurred in 2001, when ICD-O-3 was introduced in the US.

Incidence rates

In England and Wales, ASIR of IHBD tumours (C22.1) increased between 1990 and 2008 (Fig. 1).The rise was from 0.43 to 1.84 per 100,000 population/year in males (Fig. 1A), and from 0.27 to 1.51 in females (Fig. 1B). In the same time period, ASIR of EHBD tumours (C24.0) declined from 0.78 to 0.51 in males (Fig. 1A), and

Table 1. Number of cases per year of IHBD (C22.1) and EHBD (C24.0) in England and Wales and the US (SEER). (A) England and Wales, 1990–2008. (B) US (SEER database), 1990–2007.

A

Year	IHBD			EHBD		
	F	M	Total	F	M	Total
1990	110	116	226	254	211	465
1991	127	99	226	226	215	441
1992	167	142	309	256	233	489
1993	176	151	327	235	200	435
1994	194	168	362	216	178	394
1995	297	291	588	210	168	378
1996	362	305	667	189	172	361
1997	413	361	774	157	139	296
1998	417	359	776	194	151	345
1999	385	367	752	189	144	333
2000	504	420	924	138	127	265
2001	473	437	910	138	110	248
2002	506	441	947	127	109	236
2003	474	464	938	126	110	236
2004	473	489	962	100	110	210
2005	592	559	1151	135	139	274
2006	676	608	1284	155	162	317
2007	691	557	1248	138	186	324
2008	672	639	1311	159	170	329
Total	7709	6973	14,682	3342	3034	6376

B

Year	IHBD			EHBD		
	F	M	Total	F	M	Total
1990	64	56	120	82	86	168
1991	61	68	129	80	80	160
1992	75	76	151	94	90	184
1993	95	108	203	72	65	137
1994	79	115	194	85	81	166
1995	95	94	189	77	84	161
1996	102	98	200	83	94	177
1997	110	117	227	87	95	182
1998	100	122	222	85	115	200
1999	105	125	230	93	81	174
2000	104	126	230	82	116	198
2001	64	77	141	106	136	242
2002	70	82	152	120	128	248
2003	70	76	146	119	147	266
2004	79	73	152	144	141	285
2005	77	86	163	124	149	273
2006	85	92	177	134	136	270
2007	88	89	177	130	148	278
Total	1523	1680	3203	1797	1972	3769

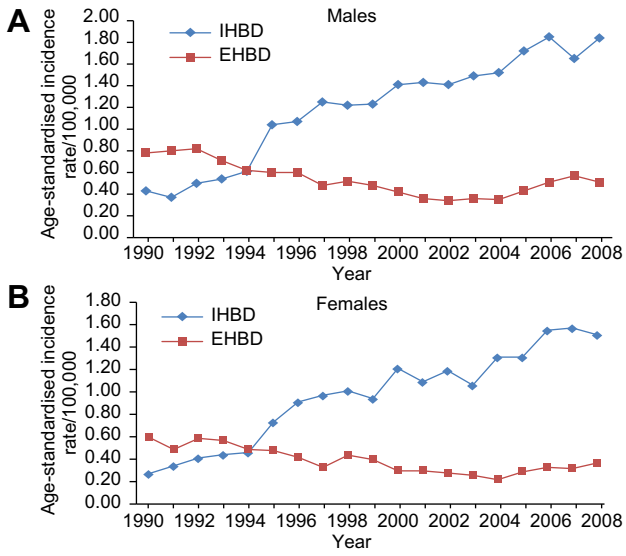

Fig. 1. Comparison of age-standardised incidence rates (ASIR) per 100,000 population/year for tumours coded to C22.1 (IHBD, intrahepatic bile duct) and C24.0 (EHBD extrahepatic bile duct) between 1990 and 2008 in England and Wales. (A) Males, (B) females.

from 0.62 to 0.39 in females (Fig. 1B). All cases with histology code 8162/3 (i.e. 'Klatskin' tumours specifically) were then removed from the IHBD (C22.1) dataset and included with the EHBD (C24.0) dataset prior to reanalysis of the incidence rates (Fig. 2). There was still a marked increase in the ASIR of IHBD cancers (C22.1), even when 8162/3-coded tumours were excluded, from 0.87 to 1.62 per 100,000 population, between 1995 (when ICD-O-2 was introduced) and 2008 (Fig. 2), males and females combined. Concurrently, even after all the 'Klatskin' tumours were included in the EHBD (C24.0) data, a marked decrease in ASIR remained from 0.55 in 1995 to 0.47 in 2008.

In the US SEER data, ASIR for IHBD tumours (C22.1) initially rose from 0.59 per 100,000 population in 1990 to 0.91 in 2000 after which there was a sharp fall in 2001 to 0.55 and a subsequent plateauing to 0.60 by 2007 (Fig. 3). Conversely, ASIR for EHBD tumours (C24.0) fell after the introduction of ICD-O2 in 1992, but thereafter rose, with the sharpest increase being seen following the introduction of ICD-O3 in 2001 (Fig. 3).

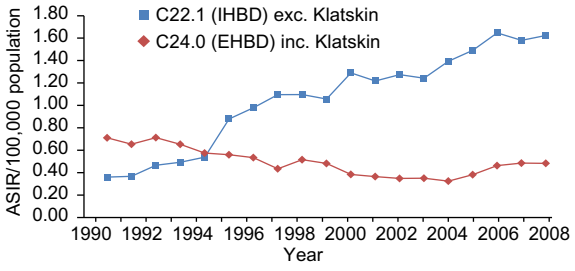

Fig. 2. Comparison of age-standardised incidence rates (ASIR) per 100,000 population/year, for tumours coded to C22.1 (excluding M8162/3) and C24.0 (including M8162/3), between 1990 and 2008 in England and Wales. Males and females combined.

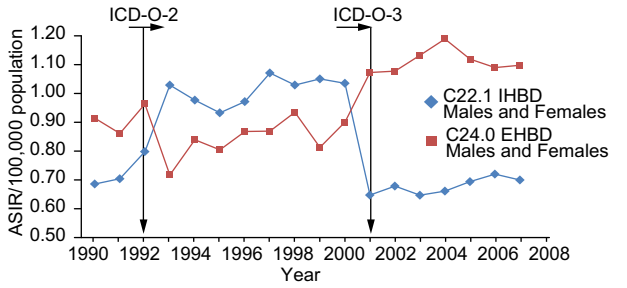

Fig. 3. Trends in age-standardised incidence rates (ASIR) per 100,000 population/year, for tumours coded to C22.1 (IHBD, intrahepatic bile duct) and C24.0 (EHBD, extrahepatic bile duct) between 1990 and 2007 in SEER database. The graph also indicates when ICD-O-2 and ICD-O-3 were introduced in the US.

Age-specific incidence rates (ASpIR)

In England and Wales, ASpIR analysis showed that the greatest increase in incidence for IHBD (C22.1), excluding 8162/3 ('Klatskin' tumours), occurred in the age group of 75+ years (Fig. 4A). This was the case in both sexes. The decline in incidence rates for EHBD (C24.0), including 8162/3 ('Klatskin' tumours), was most marked in those over 75 years (Fig. 4B). Again, this pattern was seen in both sexes.

Analysis of CC as defined by a combined topographical–histological grouping

Rates for IHCC and EHCC, i.e. cholangiocarcinoma specifically, as opposed to bile duct cancers (IHBD, EHBD), were then analysed and compared to the US analysis by Welzel and colleagues [15]. The ASIR of IHCC and EHCC in England and Wales are compared in Fig. 5. After all 'Klatskin' tumours were included in the EHCC data, there was still a marked increase in the incidence rates of

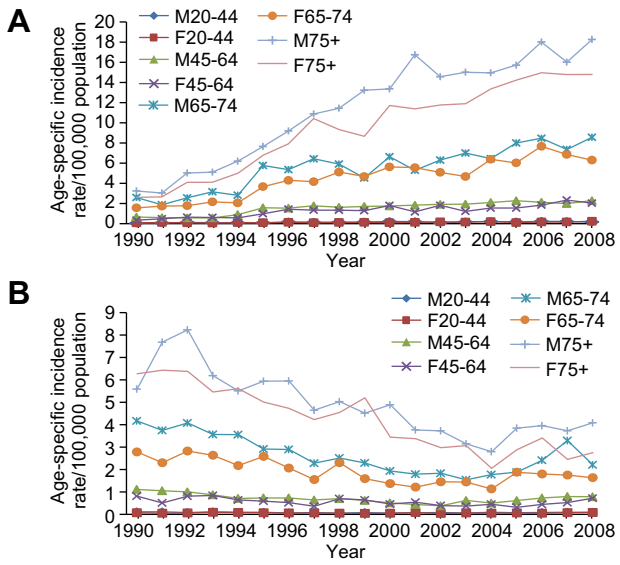

Fig. 4. Age-specific incidence rates by gender per 100,000 population/year, for bile duct cancers in England and Wales, 1990–2008. (A) C22.1/IHBD (excluding M8162/3). (B) C24.0/EHBD (including M8162/3).

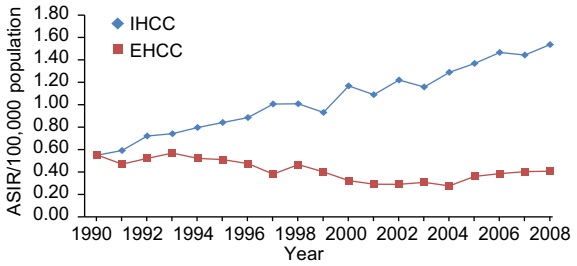

Fig. 5. Comparison of age-standardised incidence rates per 100,000 population/year, for intrahepatic cholangiocarcinoma (IHCC) and extrahepatic cholangiocarcinoma (EHCC) between 1990 and 2008 in England and Wales.

IHCC and a marked decrease in rates of EHCC (data not shown). Fig. 5 also shows that even before ICD-O-2 was introduced, IHCC incidence rates were increasing and EHCC rates were decreasing. Compared to the US data reported by Welzel and colleagues [15], between 1992 and 2000, the overall percentage of CC reported as 'Klatskin' tumours in England and Wales was even lower: less than 1% (Table 2).

Trends in percentage of 'Klatskin' tumours (histology code 8162/3) coded as IHBD or EHBD in England and Wales and US SEER data, 1995 onwards

In England and Wales, between 1995 (when ICD-O-2 was introduced) and 2004, only 87 tumours were reported as 'Klatskin'. Of these, 82 'Klatskin' tumours were reported as C22.1 (IHBD) and 5 'Klatskin' tumours were reported as EHBD (C24.0) (Table 3A). Every year between 1995 and 2004, the vast majority of 'Klatskin' tumours (86–100%) were reported as IHBD. ICD-O-2 was in use throughout this time period. In the US, between 1995 and 2001, the vast majority of 'Klatskin' tumours were coded as IHBD. However, from 2001, when ICD-O-3 came into use in the US, the majority of 'Klatskin' tumours were coded as EHBD (Table 3B).

Cancer registry questionnaire results

All nine cancer registries in England and Wales replied to the questionnaire.

Q1. When is a tumour classified as a 'Klatskin' tumour?

If the pathology report states a CC as a 'Klatskin', 8 out of 9 cancer registries (89%) responded that the CC would be coded under 8162/3 ('Klatskin' tumours) for morphology and C22.1 (IHBD) for site. One cancer registry stated that the term 'Klatskin' is not used, but would code the CC according to whether it is described as IHBD (C22.1) or EHBD (C24.0), as both sites are now accepted in ICD-O-3 under the term 'Klatskin'.

Table 3. Total number and relative percentages of 'Klatskin' tumours (histology code 8162/3) classified as C22.1 (IHBD) and C24.0 (EHBD) per year in England and Wales and the US (SEER). (A) England and Wales, 1995–2004 (ICD-O-2 was in use throughout this period). (B) US (SEER database), 1995–2007 (ICD-O-2 was in use until 2001, after which ICD-O-3 was adopted).

A

Year	C22.1 (IHBD) Total number (%)	C24.0 (EHBD)	Total
1995	3 (100%)	0 (0%)	3
1996	6 (100%)	0 (0%)	6
1997	6 (100%)	0 (0%)	6
1998	11 (92%)	1 (8%)	12
1999	9 (100%)	0 (0%)	9
2000	6 (86%)	1 (14%)	7
2001	9 (100%)	0 (0%)	9
2002	10 (91%)	1 (9%)	11
2003	10 (100%)	0 (0%)	10
2004	12 (86%)	2 (14%)	14
Total	82	5	87

B

Year	C22.1 (IHBD) Total number (%)	C24.0 (EHBD)	Total
1995	22 (88%)	3 (12%)	25
1996	25 (86%)	4 (14%)	29
1997	34 (97%)	1 (3%)	35
1998	31 (94%)	2 (6%)	33
1999	21 (78%)	6 (22%)	27
2000	29 (88%)	4 (12%)	33
2001	9 (45%)	11 (55%)	20
2002	16 (62%)	10 (38%)	26
2003	16 (43%)	21 (57%)	37
2004	6 (38%)	16 (62%)	22
2005	11 (48%)	12 (52%)	23
2006	9 (35%)	17 (65%)	26
2007	10 (42%)	14 (58%)	24
Total	239	121	360

Table 2. Comparison of data between the UK and the USA between 1992 and 2000.

	USA (Seer-9)	England and Wales
No. of cholangiocarcinoma	3350	8468
No. of intrahepatic CCA	1710 (51%)	5560 (66%)
No. of extrahepatic CCA	1640 (49%)	2908 (34%)
No. of Klatskin (hilar) tumors	269 (8%)	43 (0.5%)
Proportion of Klatskin reported as IHCC	246/269 (91%)	41/43 (95%)

Q2. When is a tumour classified as a 'hilar' cholangiocarcinoma? and

Q3. Are there any differences between a tumour classified as 'Klatskin' and a tumour classified as 'hilar' according to the cancer registry? If so, are hilar and 'Klatskin' tumours put into different codes?

Seven out of nine cancer registries (78%) do not recognise the term 'hilar' as this is not specifically mentioned in the ICD coding, even though the terms 'hilar' and 'Klatskin' are interchangeable as clinical terms. One registry would classify a CC called 'hilar' under site C22.9 (Liver NOS) and one registry would classify it under C24.8 (overlapping lesion of the biliary tract). The remaining seven cancer registries would classify a 'hilar' CC under 8160 (CC) for morphology and C22.1 (IHBD) for site. Only one registry specifically acknowledged recognising that 'Klatskin' and 'hilar' CC are exactly the same diagnosis.

Q4. If a death certificate simply says 'cholangiocarcinoma' but does not specify intra- or extra-hepatic, what code is it given?

In this situation, 7 out of 9 cancer registries (78%) would classify the tumour under M8160 (CC) for morphology and C22.1 (IHBD) for topographical site. Two out of nine (22%) would classify the tumour C24.9 (Biliary Tract Unspecified) for site.

Discussion

This study includes the first European investigation to analyse the impact of possible misclassification of hilar/'Klatskin' tumours on CC incidence rates using national cancer registration data for the whole of England and Wales together with an informative comparison of up-to-date data from a large cancer dataset in the US, and the first ever investigation of coding practice for CC by cancer registries, covering a large national population of almost 60 million people. 'Klatskin' and 'hilar' CC are the same entity and should be coded as extrahepatic tumours, yet our investigation's major finding is that of confusion and inconsistency regarding the ICD topographical classification of CC. Discrepancies between coding guidelines in the first and second versions of the ICD-O may have resulted in the classification of anatomically-unspecified CC/'Klatskin' tumours as malignant neoplasms of intrahepatic rather than extrahepatic bile ducts. Our investigation sheds light on an important unanswered question, namely: why have IHBD tumours been reportedly increasing in the UK, and most European and Western-industrialised countries over the past few decades. Our findings suggest that reported increasing rates for IHBD could be due to the incorrect classification of hilar/'Klatskin' CC as intrahepatic tumours rather than extrahepatic.

The rising incidence of CC coded as intrahepatic in England and Wales has been sustained into the 21st century, as has the falling incidence of CC coded as extrahepatic. However, this is not the case in the US, as indicated by the SEER data. In the US, IHBD incidence rates increased and EHBD rates decreased until 2001. Until this time, ICD-O-2 was in use and under this classification system, 'Klatskin' tumours were cross referenced to IHBD. After the introduction of ICD-O-3 in the US in 2001, when 'Klatskin' tumours could be cross referenced to either IHBD or EHBD, rates of IHBD began falling and EHBD rates increased. In the US, since the introduction of ICD-O-3 in 2001, most 'Klatskin' tumours are correctly coded to EHBD. Given that the UK adopted ICD-O-3 in 2008, it is likely that there will be a similar change in IHBD and EHBD trends in England and Wales after 2008. However, data from this time point onwards are currently unavailable.

After excluding 8162/3 ('Klatskin' tumours) from the IHBD (C22.1) group, there was still a marked increase in the ASIR from these cancers. This is because the misclassification of 'Klatskin' tumours resulted in overestimation of IHBD incidence rates by only 1%. Yet, according to published studies, as well as clinical experience in our centre, 'Klatskin'/hilar tumours account for the majority of all CC. Welzel and colleagues also acknowledged that the number of 'Klatskin' tumours in the US SEER database was low, at 8% [15]. We found that the proportion of 'Klatskin' tumours registered in England and Wales was even lower; 0.9% during the period 1995–2004, when ICD-O-2 was in use. Even if the estimations that 'Klatskin' tumours make up 60–70% of all CCs [2–4] are overstated, the proportion of 'Klatskin' tumours found in this study (0.9%) is undoubtedly a substantial under-representation of the true number. Our analysis of the coding practice of hilar/'Klatskin' CC by cancer registries has provided a likely explanation for this under-representation. Cancer registries in England and Wales do not code a tumour described as a 'hilar' CC with the designated 'Klatskin' code, 8162/3. Thus, 'hilar' and 'Klatskin' CC are coded differently, even though they are the same entity, and it is therefore not currently possible to determine the true prevalence of all hilar/'Klatskin' tumours. As a result of this, it is also not possible to determine the true prevalence of IHCC and EHCC in England and Wales.

In our experience, 'hilar' is preferred over 'Klatskin' as a clinical term in the UK. This could explain the low number of CC coded as 'Klatskin' in our data. Most hilar CC pathology reports in the UK are not likely to specify 'Klatskin', but rather state 'hilar' or simply 'cholangiocarcinoma', with no site specified. Cancer registries stated that if the site of the CC is unspecified, i.e. if the tumour is simply noted as 'cholangiocarcinoma', then it could be recorded as IHBD (C22.1), EHBD (C24.0), or C22.0 ('tumours of the liver'); and under a variety of histological codes, including M80003 ('malignant neoplasm'), or M81603 ('cholangiocarcinoma'). Most registries would reportedly classify such a CC as IHBD (C22.1). Therefore, it is likely that extrahepatic CC (including hilar CC), where the location of the CC has not been specified, are incorrectly being registered as intrahepatic tumours.

One of the most surprising findings in this study was the very low overall proportion of CC coded as 'Klatskin'. This appears to be due to several factors: that, under the 10th revision of the ICD, hilar/'Klatskin' CC may be coded under different topographical codes; that 'hilar' CC do not appear to be given the specific morphology code designated for 'Klatskin' tumours, although they are one and the same; and that, in England and Wales at least, there is variability in coding practice of CC between local cancer registries. Moreover, the current ICD classification system together with local coding practices, skew registration of CC to an intrahepatic site, thereby contributing to the reported rising national trend in this category of tumour. A large-scale case-control study may be required to corroborate these findings. As they stand, the ICD classification system and coding practices by cancer registries for CC appear to be unclear, inconsistent, and not reflective of clinical experience. As a result, we consider routine national cancer registration statistics to be limited in their provision of accurate incidence data for these tumours. Recognition of our findings by the international hepatobiliary community is essential, particularly for a fatal tumour whose incidence is reportedly increasing worldwide.

Coding is not the only issue here. There are several potential weak points in the registration process which need to be addressed. Pathologists should be encouraged to seek clarification on the site of a reported CC to prevent unspecified extrahepatic CC being classified as IHBD in concordance with current ICD rules. Clinicians need to be clearer too when documenting medical notes and death certificates. Given that documentation and writing of death certificates in the UK tends to be carried out by relatively junior members of the specialist team, clearer guidance on accurate documentation needs to come from senior specialists.

Close surveillance of incidence trends for hepatobiliary tumours is recommended, particularly in light of recently reported dynamic changes. Trends should be adjusted for the potential misclassification of 'Klatskin' tumours until the WHO establishes an accurate and consistent classification practice for CC. Rigorous classification of hilar/'Klatskin' CC would permit more accurate monitoring of incidence trends of intrahepatic and extrahepatic CC. We recommend raising awareness amongst cancer registries that the terms hilar CC and 'Klatskin' tumour are the same entity; otherwise the code 8162/3 for 'Klatskin' tumours is not particularly useful. Consensus in coding practice should be reached on this important matter by the UK Association of Cancer Registries as well as all relevant international bodies [19]. We propose that a revision of the ICD-O be considered, ensuring that all hilar/'Klatskin' tumours are coded topographically to extrahepatic tumours only, rather than as currently to intra- or extrahepatic. Moreover, the description of code 8162/3 should be changed from 'Klatskin' to hilar/'Klatskin'. Alternatively, bile duct cancers could be sub-classified as 'intrahepatic', 'perihilar' or 'distal' with the term 'Klatskin' being omitted altogether. Intrahepatic mass lesions impinging on common hepatic duct, the right and/or the left hepatic ducts should be termed perihilar; the terms intrahepatic versus extrahepatic are unhelpful in this situation [19,20]. There is increasing consensus that intra, perihilar and distal extrahepatic CC are distinct entities due to their differing epidemiology, pathobiology, clinical presentations and management [20,21].

We suggest similar studies on cancer registry practices are carried out in other countries which have reported changes in CC rates. A consistent global classification of CC is required to accurately compare trends around the world. Finally, it is important to note that however CC are classified, the incidence of these cancers appears to be increasing overall and the reasons for this need to be investigated.

Conflict of interest

The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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