ORIGINAL ARTICLE

Incidence and mortality of primary liver cancer in England and Wales: Changing patterns and ethnic variations

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Abstract

AIM: To explore recent trends, modes of diagnosis, ethnic distribution and the mortality to incidence ratio of primary liver cancer by subtypes in England and Wales.

METHODS: We obtained incidence (1979-2008) and mortality (1968-2008) data for primary liver cancer for England and Wales and calculated age-standardised incidence and mortality rates. Trends in age-standardised mortality (ASMR) and incidence (ASIR) rates and basis of diagnosis of primary liver cancer and subcategories: hepatocellular carcinoma, intrahepatic bile duct and unspecified liver tumours, were analysed over the study period. Changes in guidelines for the diagnosis of primary liver cancer (PLC) may impact changing trends in the rates that may be obtained. We thus explored changes in the mode of diagnosis as reported to cancer registries. Furthermore, we examined the distribution of these tumours by ethnicity. Most of the statistical manipulations of these data was carried out in Microsoft excel® (Seattle, Washington, United Sttaes). Additional epidemiological statistics were done in Epi Info software (Atlanta, GA, United Sttaes). To define patterns of change over time, we evaluated trends in ASMR and ASIR of PLC and intrahepatic bile duct carcinoma (IHBD) using a least squares regression line fitted to the natural logarithm of the mortality and incidence rates. We estimated the patterns of survival over subsequent 5 and 10 years using complement of mortality to incidence ratio (1-MIR).

RESULTS: Age-standardised mortality rate of primary liver cancer increased in both sexes: from 2.56 and 1.29/100000 in 1968 to 5.10 and 2.63/100000 in 2008 for men and women respectively. The use of histology for diagnostic confirmation of primary liver cancer increased from 35.7% of registered cases in 1993 to plateau at about 50% during 2005 to 2008. Reliance on cytology as a basis of diagnosis has maintained a downward trend throughout the study period. Although approximately 30% of the PLC registrations had information on ethnicity, there was a relatively higher registration of the major tumour subtypes in patients whose ethnic backgrounds were from high incident regions of the world. Survival from PLC is estimated to get poorer in 10 years (2018) relative to 2008, particularly as a result of IHBD.

CONCLUSION: Incidence and mortality of PLC, and particularly IHBD, have continued to rise in England

and Wales. Changes in the modes of diagnosis may be contributing.

Key words: Primary liver cancer; Hepatocellular carcinoma; Intrahepatic bile duct; England and Wales; Ethnicity

Core tip: It has been widely reported that primary liver cancer (PLC) has a poor prognosis and is increasing in many industrialised countries. We highlight an ongoing increase in the incidence of PLC in England and Wales, rendering artefactual explanations for the increase ever less convincing and, for the first time, describe ethnic variability in the incidence. More widespread use of histology in the confirmation of PLC is being embarked upon in England and Wales. These findings suggest that more aggressive screening efforts would be beneficial in England and Wales so as to improve survival. Targeted prevention programmes, including vaccination of at-risk population may be worthwhile.

INTRODUCTION

The incidence of primary liver cancer (PLC), otherwise coded as malignant neoplasm of the liver and intrahepatic bile duct in the International Classification of Diseases (ICD) version 10, in many industrialised countries is increasing[1]. Major PLC subcategories include: hepatocellular carcinoma (HCC), intrahepatic bile duct carcinoma (IHBD) and also tumours where the precise histological diagnosis is not specified by the reporting physicians (Liver NOS). Previous epidemiological studies of PLC in England and Wales have documented increases in mortality and incidence rates, but no data have been reported over the past decade[2,3]. Taylor-Robinson and co-workers observed that the mortality rate of IHBD in England and Wales almost doubled between 1979 and 1999, while rates of HCC remained stable[3]. A study of the incidence of liver cell cancer by West and colleagues during 1971-2001, reported a rising trend of HCC among men in England and Wales[4]. Despite this increase, England and Wales is a country with relatively low incidence of PLC compared to regions of sub-Saharan Africa and Asia. The rate of PLC is therefore likely to be higher in migrant populations (especially from regions known to be endemic to risk factors associated with PLC) than in the indigenous white population.

We aimed to study the incidence and mortality of PLC and major subcategories, HCC, IHBD and Liver NOS, not only to update previously documented trends, but also to explore information on the basis of diagnosis and, for the first time, the population-based ethnic distribution of these cancers in England and Wales, up until 2008. With rising rates of deaths from chronic liver disease during 1970 to 2006, and also reported increases in alcohol consumption[5], PLC is likely to be continuing to increase in England and Wales. Whereas earlier data during 1988-1992 reported a higher incidence of cirrhosis and liver cancer among ethnic minorities, it was limited by the fact that it included a small sample of middle aged people (20-69 years) and thus lacked generalisability to the wider population[2,6].

MATERIALS AND METHODS

Incidence (1979-2008) and mortality (1968-2008) data for PLC (C22 as coded by the 10th version of International Classification of Diseases) and PLC subcategories (C22.0 HCC, C22.1 IHBD, C22.9 liver tumours NOS) were extracted from the National Cancer Registry of England and Wales held at the Small Area Health Statistics Unit (SAHSU) of Imperial College London and maintained by the Office for National Statistics (ONS). Mid-year population estimates by 5-year bands for England and Wales for the period from 1968 to 2008 were obtained from SAHSU and ONS databases. Data were analysed using Epi Info™ statistical software (version 3.5.1, 2008, Atlanta GA, United States). Age standardised incidence rates (ASIR) and mortality rates (ASMR) per 100000 were calculated. The European standard population was used as the reference for direct age standardisation. To define patterns of change over time, we evaluated trends in ASMR and ASIR of PLC and IHBD using a least squares regression line fitted to the natural logarithm of the mortality and incidence rates.

Diagnoses of specific PLC sub-types are usually based on several modalities of investigation. The connotation, "Basis of Diagnosis", as practiced by coding officers during registration of incident cases of cancer, describes the most advanced method used in making a diagnostic decision for each case. The basis of diagnosis of PLC has been recorded by all Cancer Registries in England and Wales since 1993 using the following codes: 1 (imaging/radiology); 2 (other special tests such as clinical opinions and tumour markers); 3 (cytology); and 4 (histology). In clinical practice, histology of the liver is hierarchically ranked the gold standard of diagnosis, followed by imaging, cytology and serum tumour markers ("others"), in that order. The proportion of cases diagnosed using these modalities was determined for PLC overall, and specifically for HCC, IHBD and Liver NOS.

Information on ethnicity, recorded at the time of registration (incidence data), was obtained for PLC and subcategories annually. To reflect regional ethnic affiliation, rather than countries of origin, we categorised
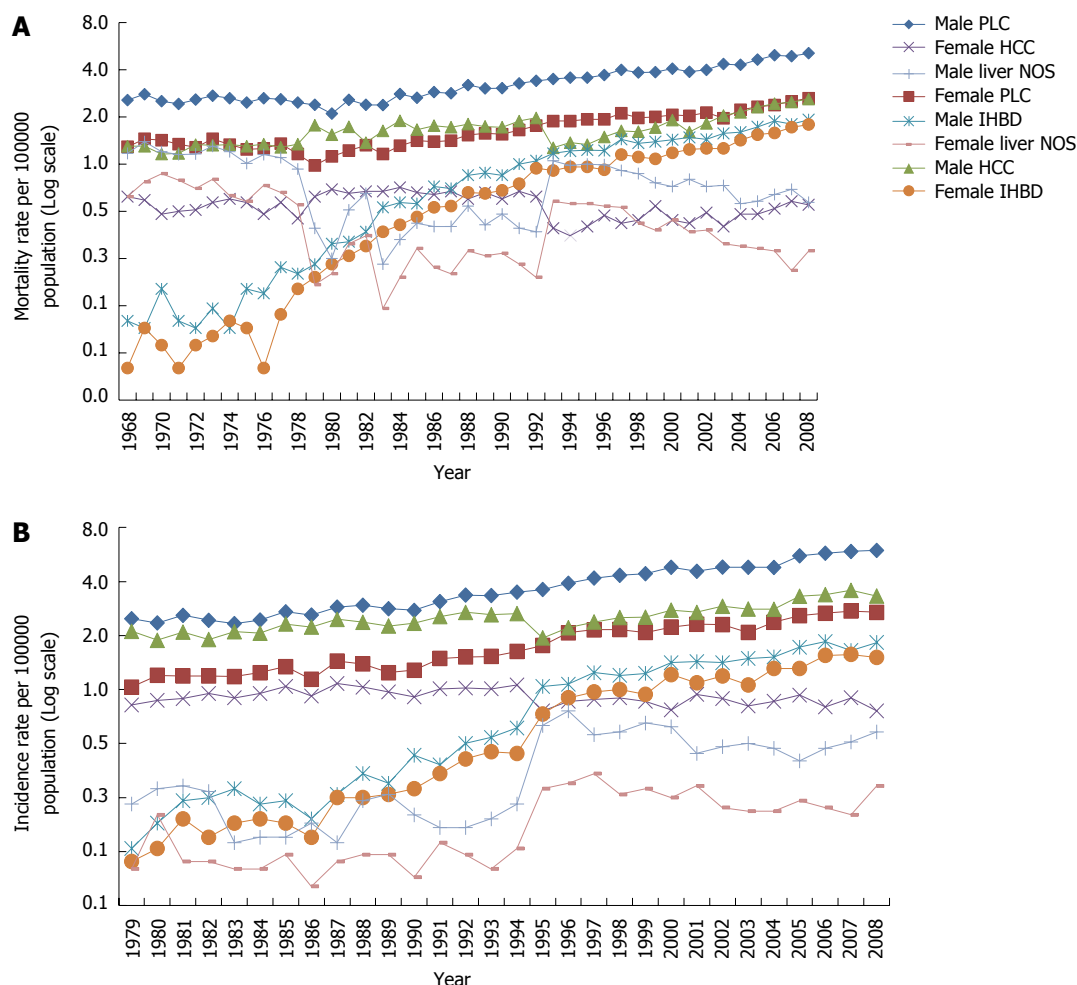
Figure 1 Age-standardised (A) mortality and (B) incidence rates of primary liver cancer, hepatocellular carcinoma, intrahepatic bile duct carcinoma and unspecified liver tumours (liver tumours, not otherwise specified) by gender and year. PLC: Primary liver cancer; HCC: Hepatocellular carcinoma; IHBD: Intrahepatic bile duct carcinoma; NOS: Not otherwise specified.

Indians, Pakistanis and Bangladeshis together as "South Asians". Other ethnic categories were as follows: white, Afro-Caribbeans, black Africans, Chinese, and other. We then calculated the proportion of PLC and subcategories registered in the incidence data, among each ethnic group annually. Given that many cancer registrations were recorded without ethnicity, we then compared these proportions with the proportion of the national population by ethnic groups annually. Projected mid-2008 population estimates by ethnic group released by the Office for National Statistics were utilised to calculate annual ethnic proportions[7].

Mortality to incidence ratios (MIR) have been utilised to not only interrogate the completeness of data in cancer registries[8] but additionally as a proxy to estimate 5 years survival of cancer patients[9]. We thus calculated these ratios for PLC overall and for HCC and IHBD by sex. The crude morality and incidence rates of PLC and the major subcategories were determined for the last 10 years of data (that is from 1999 to 2008), linearly projected to 2018 and the MIR calculated. We estimated the patterns of survival for these cancers over the next 5-10 years using complement of mortality to incidence ratio

$(1-MIR)$[9].

RESULTS

ASMR

Rising trends in mortality rate of PLC in England and Wales during 1968-1996 has been previously reported[3]. Overall, the absolute mortality and ASMR of PLC continued to increase during 1996-2008 in both males and females. In men, this rose from 1052 cases (ASMR: 3.70 per 100000) in 1996 to 1731 cases (ASMR: 5.10 per 100000) in 2008 and in women; from 770 cases (1.93 per 100000) to 1178 cases (ASMR: 2.63 per 100000) in the same period (Figure 1). The trend was more consistent in men than women. For HCC, men experienced a rise in the mortality rate (from 1.49 to 2.60 per 100000 in 1996 to 2008 respectively) whereas women had a relatively stable rate. There was a steady increase in the mortality rates of IHBD in both men and women that have persisted with a similar annual percent change of 9% and 10% in men and women respectively during 1968-2008. The numbers of those registered without a specific histological category (Liver NOS) fluctuated during 1968-1990,
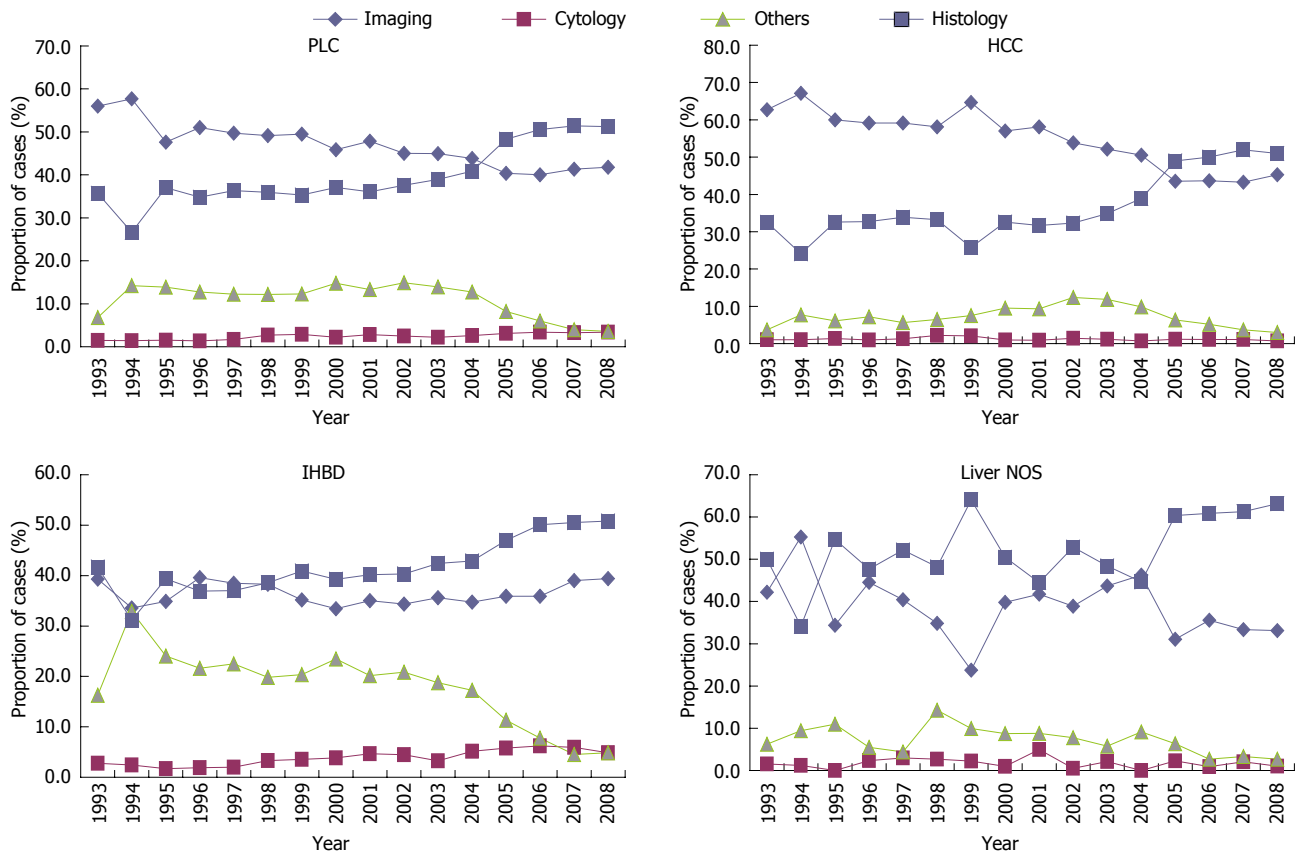
Figure 2 Proportion (%) of registrations (incidence) of primary liver cancer, hepatocellular carcinoma, intrahepatic bile duct carcinoma and liver tumours, not otherwise specified by the basis of diagnosis, England and Wales, 1993-2008. PLC: Primary liver cancer; HCC: Hepatocellular carcinoma; IHBD: Intrahepatic bile duct carcinoma; NOS: Not otherwise specified.

from which time it started to fall. This was 287 and 219 in 1996 and has fallen to 200 and 130 in 2008 for men and women respectively.

ASIR

Over the last decade, our data reveal an upward trend in the incidence of PLC among men in England and Wales, contrasted to a relatively static rate among women. There was a marginal rise in the trend of HCC among men compared to a non-significant decrease in the rate in women (774-1083 and 371-306 cases in men and women respectively) (Figure 1). IHBD markedly increased in both genders (annual percent change: 10% in both men and women) during 2001 to 2008 (437-639 and 473-672 in men and women respectively). The ASIR of unspecified liver tumours in both sexes has stabilised during 1995 to 2008.

Basis of diagnosis

There were increases in the proportion of patients registered to have required histology to establish specific diagnosis of liver tumours, in the incidence data, during the last 4 years of the study (2005-2008). Imaging was the most utilised technique for diagnosing HCC from 1993 up until 2005, when it was overtaken by histology (Figure 2). For IHBD, imaging and histology were relied upon with approximately equal proportion during 1993-1997. However, from 1998, histological confirmation of IHBD

was most commonly undertaken. The proportion of liver cancer registrations having unsophisticated means of diagnosis remained low during 1993-2008. Cytology is increasingly less relied upon in the diagnosis of liver tumours. However, for IHBD, cytology has slightly been increasing and "others" (including: those diagnosed by unsophisticated means, tumour markers and clinical opinion) have dropped dramatically from 31% in 1994 to 5% of cases in 2008.

Distribution of primary liver cancer by ethnicity

We found that the completeness of ethnic information in the incidence data, recorded during the study period, ranged from 19% to 51% of cases that were registered to have had PLC (Table 1). For HCC and IHBD, there was an initial increase (50.3% and 57.7% respectively) in the proportion of those registered with ethnicity from 1993 to 1998, after which it remained static for two years. Following that, there was a sharp drop in 2001 to 19% for both HCC and IHBD, rising steadily to 42% and 41% respectively in 2007. There were no clear patterns in the registration of ethnicity for those with unspecified liver tumours.

Figure 3 compares the proportion of ethnic groups in the population of England and Wales in 2008 (most recent year of study) with the corresponding distribution of ethnicity amongst cancer registrations for HCC, IHBD and Liver NOS. White people comprised 89% of

Table 1 Distribution of primary liver cancer in England and Wales by ethnic groups from 1993-2008 *n* (%)

Year	Primary liver cancer						
	All groups	Whites	Afro-Caribbeans	Black Africans	South Asians	Chinese	Others
1993	563 (38.3)	554 (98.4)	2 (0.4)	0 (0.0)	7 (1.2)	0 (0.0)	0 (0.0)
1994	570 (36.4)	561 (98.4)	1 (0.2)	1 (0.2)	4 (0.7)	0 (0.0)	3 (0.5)
1995	605 (35.9)	587 (97.0)	2 (0.3)	2 (0.3)	7 (1.2)	4 (0.7)	3 (0.5)
1996	888 (46.5)	863 (97.2)	3 (0.3)	3 (0.3)	7 (0.8)	4 (0.5)	8 (0.9)
1997	990 (48.7)	964 (97.4)	1 (0.1)	4 (0.4)	11 (1.1)	7 (0.7)	3 (0.3)
1998	1075 (51.4)	1034 (96.2)	5 (0.5)	8 (0.7)	15 (1.4)	5 (0.5)	8 (0.7)
1999	1003 (47.7)	953 (95.0)	11 (1.1)	3 (0.3)	15 (1.5)	8 (0.8)	13 (1.3)
2000	977 (41.9)	913 (93.4)	24 (2.5)	8 (0.8)	17 (1.7)	5 (0.5)	10 (1.0)
2001	443 (19.1)	365 (82.4)	35 (7.9)	8 (1.8)	11 (2.5)	7 (1.6)	17 (3.8)
2002	529 (21.3)	461 (87.1)	23 (3.9)	8 (1.5)	18 (3.4)	9 (1.7)	10 (1.9)
2003	508 (20.7)	436 (85.8)	20 (4.3)	11 (2.2)	25 (4.9)	3 (0.6)	13 (2.6)
2004	741 (28.4)	647 (87.3)	30 (4.0)	18 (2.4)	20 (2.7)	6 (0.8)	20 (2.7)
2005	908 (31.8)	784 (86.3)	57 (6.3)	17 (1.9)	26 (2.9)	8 (0.9)	16 (1.8)
2006	1156 (39.0)	962 (83.2)	96 (8.3)	13 (1.1)	49 (4.2)	10 (0.9)	26 (2.2)
2007	1276 (41.3)	1058 (82.9)	110 (8.6)	14 (1.1)	41 (3.2)	20 (1.6)	33 (2.6)
2008	1273 (40.3)	1135 (89.2)	43 (3.4)	12 (0.9)	34 (2.7)	11 (0.9)	38 (3.0)

the population and the corresponding proportions of cases of IHBD and HCC were 92% and 85% respectively. In contrast, Afro-Caribbeans constituted about 1% of the population of England and Wales in 2008, yet 3%, 5% and 1% of HCC, IHBD and Liver NOS, respectively were registered to people whose ethnic background was Afro-Caribbean in that year. Similarly, the proportions of PLC registration in the incidence data in black Africans and Chinese were slightly higher than the proportion of these ethnic groups in the population as a whole (1% *vs* 2% respectively) (Figure 3).

Mortality to incidence ratio
Women are projected to experience lower survival than men in general (Figure 4). For HCC, both men and women will experience rising MIR during the next 10 years unless changes that will ensure earlier detection and treatment is achieved, although this will plateau for men from 2014. These data suggest that a higher proportion of women than men will experience lower survival from IHBD.

DISCUSSION
This study has presented for the first time both mortality and incidence rates together for primary liver cancer and shown that they have continued to rise in England and Wales throughout the last decade. The greatest rise was in IHBD in both men and women (44% increase: from 910 cases in 2001 to 1311 cases in 2008). Reassuringly, histological confirmation of PLC subcategories has become more widespread in diagnostic practice and less accurate modes of diagnosis, such as imaging techniques, have been declining as the sole mode of diagnostic confirmation. Generally, the registration of IHBD and HCC was proportionately highest among people whose ethnicity was registered as Afro-Caribbean.

Using data gathered towards the end of the last century, Taylor-Robinson *et al*[3], as well as West *et al*[4] in separate studies, had observed increases in mortality and incidence of liver cancer, respectively[3,4]. Global studies of PLC was reported by Khan *et al*[10] to show widespread increase in mortality from IHBD in all western countries that were studied. Whereas a variable mortality trend from HCC was found in studies across countries, the present study noted that both IHBD and HCC were rising in incidence and mortality in England and Wales. In contrast to other countries, however, the rate of increase in the mortality from PLC in England and Wales was greatest for IHBD, compared to HCC[10].

The progressive increase in the incidence and mortality rates of PLC in England and Wales either reflects a true increase, or an epidemiological artefact. For instance, our group recently published the contribution of misclassification of hilar cholangiocarcinoma to increasing the incidence of IHBD[11]. Another study in the United States has also shown that although coding error resulted in 15% overestimation of IHBD, there was a significant proportion of increase that was not explained by misclassification[12]. A true increase may thus underlie the trend in the mortality and incidence being reported in the present study. Furthermore, the fact that both incidence and mortality increased supports a non-artefactual effect and suggests there has not been any improvement in survival from PLC, despite changes in the diagnosis and treatment of PLC during the last decade.

While it has been a common cause of liver tumour-related death in England and Wales, IHBD is a less common subtype of PLC than HCC worldwide. Aetiological associations of IHBD are ill-understood, and are still being studied. Chronic infestation by liver fluke is associated with the aetiology of IHBD in South-East and East Asia[13,14]. Primary sclerosing cholangitis (PSC) is the commonest known predisposing factor for IHBD in the Western world, often associated with up to a tenth of cases of cholangiocarcinoma[15,16]. However, the incidence of PSC has not been shown to be increasing and thus cannot explain the current rise in the incidence
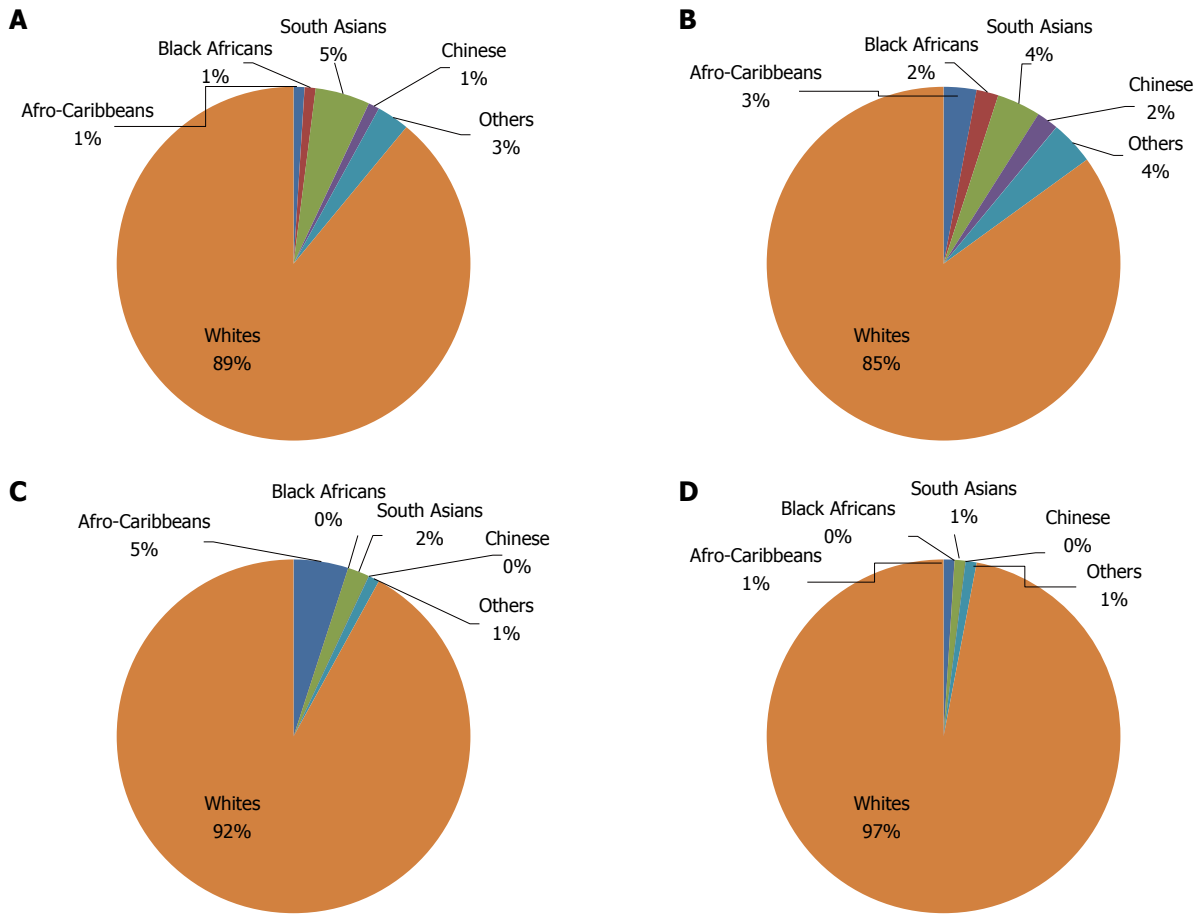
Figure 3 Comparison of ethnic groups in England and Wales (2008), as recorded in the (A) population of England and Wales, and the registration of (B) hepatocellular carcinoma, (C) intrahepatic bile duct carcinoma, and (D) liver tumours, not otherwise specified.

of IHBD[17]. Environmental toxins and genetic dispositions[18] have also been noted to be responsible for sporadic cases of IHBD and may underlie some of the observed differences in this present study.

Changes in the basis of diagnosis may have resulted in increased case ascertainment and thus contributed to the rising trends in the incidence and mortality rates observed. Our data show that the proportion of cases reported to cancer registries that had histology underpinning the diagnosis of PLC has been increasing, suggesting that suspicious "nodules" identified during routine screening or investigations incompletely characterised by dynamic imaging are being subjected to liver biopsy in many centres across England and Wales and hence diagnosed. Recent technological advances in the management of PLC[19-21], including the setting up of tertiary centres, modern hepatobiliary imaging, image-guided biopsies and widespread availability of magnetic resonance cholangiopancreatography (MRCP) may have contributed to the recent trends. The role of case ascertainment is further buttressed by the rising trend in the histological confirmation of PLC shown in this study, suggesting a more aggressive surveillance for PLC.

It would be expected that an outcome of improved diagnostic yield should lead to detection of early stage PLC and improvement in survival. There is yet a study to be undertaken that describes the impact of changes in screening guidelines and management of PLC in England and Wales. As mortality to incidence ratio has been recently validated to be a proxy indicator for cancer survival studies[22], our data confirms that PLC will continue to be associated with high case fatality, mostly contributed to by the low survival from IHBD. Also, a US study[23], has shown that although an increase in the incidence of IHBD was noted during recent years (1975 to 1999), there was neither a significant increase in the proportion of those found with localised disease, nor in the survival of those diagnosed. Survival from PLC is projected to be lower in women in England and Wales by 2018. Lead-time bias could be responsible for the observed mutual increase in the incidence and mortality rates of PLC in the face of improvements in diagnosis. It is thus possible that our finding represents a true increase in mortality due to an inherent poor prognosis associated with PLC.

The exploration of ethnic information confirms that sub-Saharan Africans and South Asians living in England and Wales have higher PLC incidence than indigenous white people[6,24]. Our population-based analysis confirms that the registration of HCC among Afro-Caribbeans, sub-Saharan black Africans and Chinese is higher than among indigenous white people in England and Wales. This finding is similar to a population-based US study in
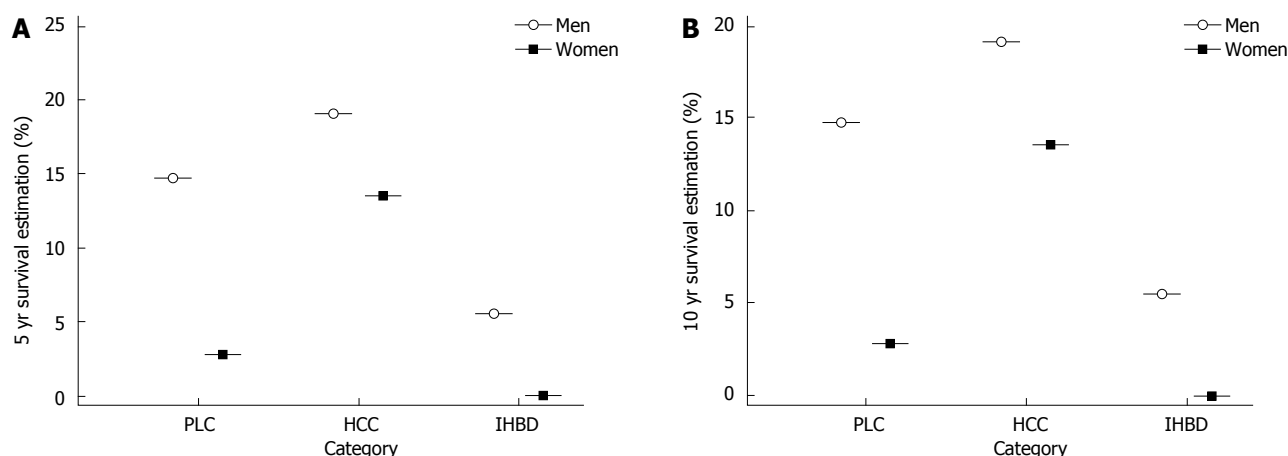
Figure 4 Estimated relative survival (A) 5 yr and (B) 10 yr projections; obtained from complement of mortality to incidence ratios × 100 that was extrapolated from 2008 to 2018. PLC: Primary liver cancer; HCC: Hepatocellular carcinoma; IHBD: Intrahepatic bile duct carcinoma.

2008 that reported a higher incidence of HCC among immigrant populations, compared to Caucasians[25]. Higher prevalence of HBSAg carriage status among immigrant populations may in part have predisposed ethnic minorities to HCC. The rates of HCC in people from Asian and African backgrounds were however, not as alarming as expected, perhaps reflecting the positive impact of hepatitis B virus (HBV) vaccination in the control of PLC. A landmark study in Taiwan confirmed that HBV immunisation in children introduced in 1984 significantly halved the annual incidence of HCC from 0.70/100000 in 1981-1986 to 0.36/100000 in 1990-1994[26].

We found registrations of IHBD at cancer registries proportionately highest among Afro-Caribbeans. Reasons for the higher proportional registration of IHBD in particular among Afro-Caribbean populations are not clear and require further investigation. It suggests a high prevalence of aetiological factors and/or more willingness to register ethnic information by Afro-Caribbean people. Ulcerative colitis is associated with PSC, which in turn is responsible for about 10% of IHBD[27]. Reports of PSC and indeed ulcerative colitis among ethnic minorities are scanty. A 15-year study, published 3 decades ago intriguingly observed a significant rarity of ulcerative colitis among Afro-Caribbeans[28]. Recent case control and cohort studies have implicated hepatitis C virus (HCV), HBV, cigarette smoking, obesity, gallstones and alcohol consumption, among others to be contributory to IHBD, although some of these associations are weak[29,30]. A descriptive study during the latter part of 2000 found a higher prevalence of obesity, cigarette smoking, alcohol drinking and cirrhosis of the liver from HCV in Afro-Caribbeans, compared to sub-Saharan black Africans[31]. To the best of our knowledge, there is no firm evidence of increasing HCC risk in women in relation to oral contraceptive (OCP) or other hormone use[32]. Hence, hormone use is unlikely to explain the increase in rates of HCC in women that we observed. On the contrary, a cross sectional study of over 3000 HCC patients confirmed OCP as an independent factor that conferred sig-

nificant survival benefit to female patients[33].

HCV-related HCC has been identified as one of many reasons for the rise in HCC incidence in some developed countries, including England and Wales[34]. The incidence of HCV in England and Wales rose significantly between 1960 and 1980[35], owing to the practice of intravenous drug use and the prevalence of HCV in the blood donor system prior to donor screening procedures in 1992. HCC would have only recently started to emerge in patients that were infected during this period as progression to end-stage liver disease (cirrhosis and HCC) can take 25-30 years[36]. Alcoholic liver disease has also been reported to have more than doubled between 1990 and 2003 in England and Wales[37]. With economic and social factors that have promoted consumption of alcohol, the influence of alcohol on the current rising incidence of HCC is likely to be exponential and has contributed to the current observation. A population-based study of the impact of alcohol consumption, obesity and other factors has recently lent support to the contribution of these lifestyle factors to rising incidence of PLC. A recently published case-control study of the European Prospective Investigation into Nutrition and Cancer cohort reported higher odds of HCC in people who smoked cigarettes, drank alcohol and/or were obese, compared to controls[38]. *Per capita* alcohol consumption in the United Kingdom has increased by 150% in the past 50 years[5], a factor that could well have added to the rising incidence of HCC.

Diabetes mellitus (DM), a recognised risk factor for HCC, is higher among migrant populations than among indigenous whites of England and Wales[39]. Since the mid-1990s, Gray *et al*[40] found that DM coexisting with HCV infection was significantly higher among Afro-Caribbeans than other ethnicities. That study also reported that persistent moderate elevations in serum transaminases of studied patients was higher among Afro-Caribbeans than in other studied ethnic minorities, a factor associated with poor outcome. This may therefore contribute to the higher and rising rate of HCC in Afro-Caribbeans, com-

pared to the rest of studied ethnic minorities. Indeed a study of obesity among ethnic minorities found that the highest rate of obesity was among Afro-Caribbeans (30%) relative to 19% in the reference white population.

We note that the registration of ethnicity was lacking in more than 60% of those that were registered with PLC in England and Wales cancer registries. Although we utilised data during a most recent year with 40% registration of ethnic information, it is possible that a disproportionate registration of ethnic information would have skewed our findings. With progressive increases in ethnic registration during liver cancer registration, follow up analyses should provide a better distribution of PLC by ethnic groups in England and Wales.

The major strength of the present study is the fact that it utilised the whole population cancer registry data of England and Wales. We have been able, for the first time, to demonstrate trends in both mortality and incidence together of PLC, the basis of diagnosis and ethnic distribution for the whole population of England and Wales. The information on the basis of diagnosis was objective evidence of the modality of investigation for PLC during the period when data on mode of diagnosis was collected routinely across the country. The ethnic trends in liver cancer registrations presented here provide important insight on high risk groups and possible focus for prevention strategies. However, due to the limited number of individual registrations recorded with ethnicity, the trends are estimations subject to error, based on the ethnic proportions in the population as a whole. We advocate further studies to corroborate and expand on our findings. To determine the impact of guidelines and improved management of PLC, information on adherence to surveillance schedules, tumour stage at diagnosis, ethnicity, and survival of patients will need to be gathered. Search for better performing screening and diagnostic tools should be a priority as current tools have low sensitivities and specificities. Newer techniques, including the use of urinary metabonomics hold some promise but wait on validation experiments. Our group has recently reported the impressive diagnostic performance of panels of urinary metabolites in discriminating HCC in some African populations[41,42] Follow-up studies of these changing trends in the mortality and incidence of PLC need to be closely monitored.

In conclusion, Mortality from PLC has continued to increase in both sexes in England and Wales. The incidence of IHBD increased in both genders, while that of HCC increased only among males. Increasing use of histological confirmation of PLC and subcategories lends support to better characterisation of liver tumours. While the proportional registration of all major categories of PLC was greatest in Afro-Caribbeans, there were modestly higher proportions of sub-Saharan black Africans and Chinese with HCC, compared to indigenous white populations. Better characterisation of PLC is being achieved in England and Wales, providing opportunities for targeted preventive programmes.

COMMENTS

Background

Primary liver cancer (PLC) is the 5th most commonly diagnosed cancer and 3rd cause of cancer-related death globally. Although less common than in the developing countries, an exponential increase in the mortality from PLC in England and Wales was reported towards the end of the last century. Lifestyle and temporal changes warrant close monitoring of the trends in not only the mortality, but additionally; incidence, modes of diagnosis and ethnic distribution of this fatal cancer.

Research frontiers

It remains less widely investigated whether changes in diagnosis, International Classification of Diseases (ICD) classification and immigration are impacting on the increasing rates of PLC in England and Wales. There is insufficient data on the most important factors responsible for rising rates of PLC in England and Wales. The rates of deaths from chronic liver disease in the United Kingdom has been reported to be going upwards in contradiction to declining death rates of more common diseases such as asthma and cardiovascular events. Recognising the impact of these changes through surveillance of most current trends in PLC would inform clinical care and management guidelines and efforts for prevention.

Innovations and breakthroughs

The authors have reported for the first time, information on changes in the mode of diagnosis and ethnic variation of PLC incidence by subcategories in England and Wales. Data were obtained from the national cancer registries, which include all incident cases and deaths from these cancers and are thus representative of the population. Although a significant proportion of the registered cases were found not to have information on basis of diagnosis and ethnic background, it highlights significant information that would be relevant for follow up studies.

Applications

These results highlight the need to ensure accurate registration of information on PLC diagnoses as well as provision of aggressive prevention strategies to at-risk groups, such as people of Afro-Carribean ethnicity. "Basis of diagnosis" is vague and needs to be given a standardised definition, otherwise if cancer registries differ in this definition, it could provide inaccurate data and hence faulty conclusions. The contribution of diets, obesity, smoking and alcohol consumption in the current trends would form a suitable subject of worthwhile study. Efforts at developing more sensitive and specific PLC screening tools in order to reverse the projected trend of worsening poor survival is engendered by these data.

Terminology

ICD is the internationally agreed alpha-numeric system by which diseases and deaths are classified into categories by national registration bodies. Basis of diagnosis describes the most advanced method used in making a diagnostic decision for PLC and subcategories.

Peer review

Ladep *et al* present an interesting analysis on liver cancer incidence and mortality in England and Wales. They divided the information into different types of tumours, gender and ethnicity. The manuscript reports very interesting findings that incidence and mortality of PLC, and particularly intrahepatic bile duct carcinoma, have continued to rise in England and Wales and the change observed may be caused by changes in the modes of diagnosis.

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