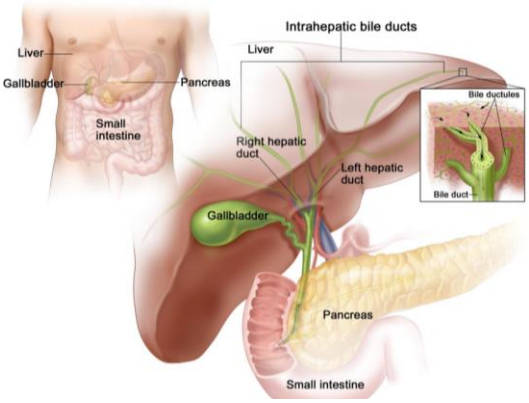
National Cancer Registry Ireland **Cancer Trends**

Primary Liver Cancer

Cancers of hepatobiliary system: some key facts

The hepatobiliary system consists of the liver, gallbladder and bile ducts (Figure 1). The liver produces bile, used in digestion and in the excretion of waste products from the body. Bile is passed from the liver, through the bile ducts and stored in the gallbladder.

Figure 1. Diagram of the hepatobiliary system[1]



1 Between 2012 and 2014, just over 450 primary cancers of the hepatobiliary system were diagnosed in Ireland per year. Almost 60% were located in the liver (including intrahepatic bile ducts), with 73 women and 191 men diagnosed per year (Table 1). Although liver cancer incidence was three times higher in men than in women, cancer of the gallbladder, while rarer than liver cancer, was more commonly diagnosed in women, with 46 female patients diagnosed per year compared to 18 male patients.

Table 1. Incidence of primary cancer of the hepatobiliary system, annual average 2012–2014

	Females	Males	Total
TOTAL HEPATOBILIARY (ICD10: C22-C24)			
Number of cases	179	272	451
% all invasive cancers	1.8%	2.5%	2.2%
Rate~	6.5	11.6	8.9
Risk (to age 75)	4.4%	8.6%	6.5%
Median age at diagnosis	75	70	71
LIVER (ICD10: C22)			
Number of cases	*73*	*191*	*264*
% all invasive cancers	*0.8%*	*1.7%*	*1.3%*
Rate~	*2.7*	*8.2*	*5.3*
Risk (to age 75)	*1.9%*	*6.4%*	*4.2%*
Median age at diagnosis	*72*	*68*	*69*
GALLBLADDER (ICD10: C23)			
Number of cases	*46*	*18*	*64*
% all invasive cancers	*0.5%*	*0.2%*	*0.3%*
Rate~	*1.7*	*0.8*	*1.2*
Risk (to age 75)	*1.1%*	*0.4%*	*0.7%*
Median age at diagnosis	*75*	*77*	*76*
OTHER BILIARY (ICD10: C24)			
Number of cases	*60*	*63*	*123*
% all invasive cancers	*0.6%*	*0.6%*	*0.6%*
Rate~	*2.1*	*2.7*	*2.4*
Risk (to age 75)	*1.4%*	*2.0%*	*1.7%*
Median age at diagnosis	*76*	*72*	*73*

~ rate per 100,000 per year (European (1976 model) age standardised)

There was an annual average of 141 cancers diagnosed in the bile ducts; both intrahepatic (within the liver) and extrahepatic (included in the category 'other biliary'). These represented over one third of all hepatobiliary tumours in women (37%) and a quarter of all those in men (26%).

The remainder of this report focuses on primary liver cancer including the intrahepatic ducts only (ICD10: C22).

Liver cancer tumour types

During 2012-2014, a little over half (58%) of all primary liver cancers were histologically confirmed, 37% were diagnosed radiologically only via x-ray, MRI/CT scan etc. and 5% did not have a method of diagnosis specified. Reflecting the high proportion of patients without a microscopic diagnosis, over one-third of all liver cancers were of unspecific histological subtype (Table 2). The majority of cancers that were histologically confirmed were either hepatocellular carcinomas (HCC) or cholangiocarcinomas (CC), the latter occurring in the bile ducts specifically. Interestingly while the bulk of histologically diagnosed tumours in male patients (66%) were HCC, the majority in females (62%) were CC. While the male-female rate ratio for all liver cancers was 3.0, for HCC it was 6.5 and for CC, 1.3.

Other (and much rarer) subtypes included sarcomas, neuroendocrine tumours and hepatoblastoma, the latter occurring in children (aged under 15) only.

Table 2 Case numbers (n), incidence rates (r) and % of all liver cancers by subtype, annual average 2012–2014

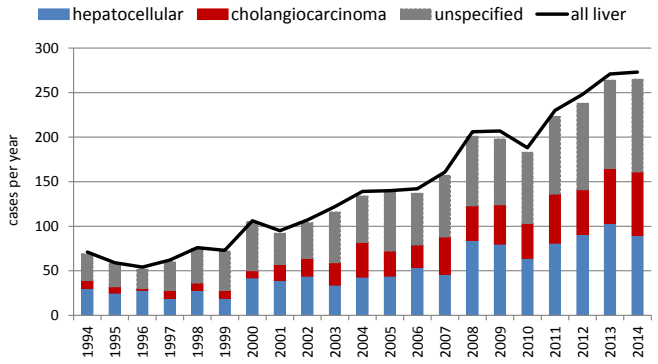
	Females	Males	Total
Total liver cancer	n=73 r=2.7	n=191 r=8.2	n=264 r=5.3
Hepatocellular carcinoma	n=13 r=0.5 (18%)	n=81 r=3.5 (43%)	n=95 r=1.9 (36%)
Cholangiocarcinoma	n=28 r=1.1 (38%)	n=33 r=1.4 (17%)	n=61 r=1.3 (23%)
Other subtypes	n=4 (6%)	n=8 (4%)	n=12 (5%)
Unspecified	n=28 (38%)	n=68 (36%)	n=96 (36%)

Time trends in incidence

Numbers of primary liver cancers have increased by over 300% in the 21 year period from 1994 to 2014, from an average of approximately 60 cases per year in the mid-1990s to over 270 patients diagnosed in both 2013 and 2014 (Figure 2). Incidence rates have increased significantly for both sexes since 1994, with an annual percentage increase of 5% (95%CI: 3.4-6.5%) in women and 6.5% (95%CI: 5.6-7.4%) in men (Figure 3).

Median age at diagnosis and male-female ratio have remained unchanged over time.

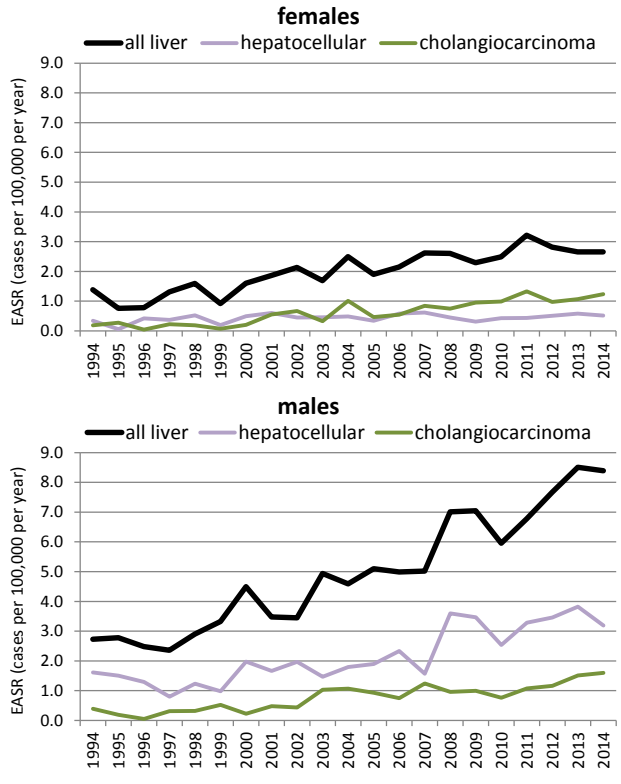
Figure 2. Number of cases of liver cancer diagnosed per year 1994-2014



Although making up a smaller proportion of all liver cancers compared to HCC, CC of the intrahepatic bile ducts showed a particularly large increase in incidence since 1994, with annual percentage increases of 13.6% recorded in females and 11.7% in males. This compared with a much lower APC of 3.7% and 6.2% respectively for HCC.

Increasing incidence of CC has been previously reported in Ireland[2] and internationally[3]. As most patients with intrahepatic CC have no clearly identified risk factors for the disease, the rising incidence of this cancer has not been linked to any demographic trend and changes in cancer reporting and coding practices have been suggested as a likely cause[3]. HCC on the other hand is well documented to be linked to alcohol consumption (as well as hepatitis B & C virus infections, metabolic syndrome, haemochromatosis and aflatoxin B exposure)[1] . The increase in alcohol consumption observed in Ireland in recent decades[4] is likely to have had a strong influence on the increase observed in HCC incidence, particularly in men.

Figure 3. Trends in the incidence of liver cancer subtypes in females and males between 1994 and 2014



Geographical variation in incidence

Liver cancer incidence was highest in the most socio-economically deprived parts of Ireland for both sexes, significantly so for males (Figure 4). However the relationship between incidence and deprivation was not clear-cut and rates were variable between the other deprivation strata, although female rates suggest a somewhat gradual increase with deprivation. There was also a very clear and significant urban-rural divide in the case of male incidence rates with urban areas having 64% higher incidence than in rural areas. There was little difference in female incidence rates between urban and rural areas.

Incidence rates varied considerably between counties (Figure 5) and while male incidence in Dublin was statistically significantly higher than the national average (in line with the higher urban incidence observed) no other county was found to have rates significantly different from overall national incidence.

Figure 4. Incidence of liver cancer: variation with deprivation index (DI)[5] and urban/rural area of residence, 2004–2013[6] *(rural areas defined by population density <1 person per hectare)*

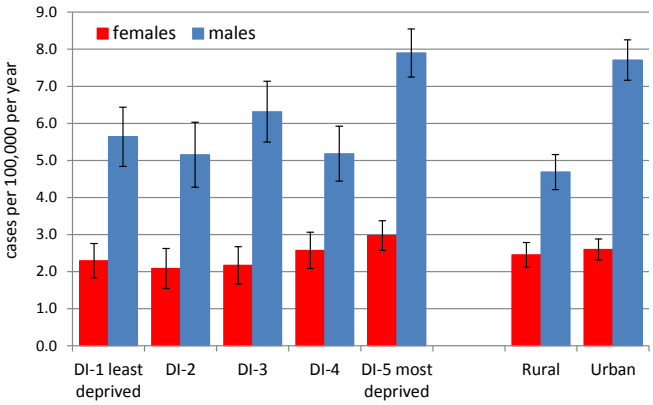
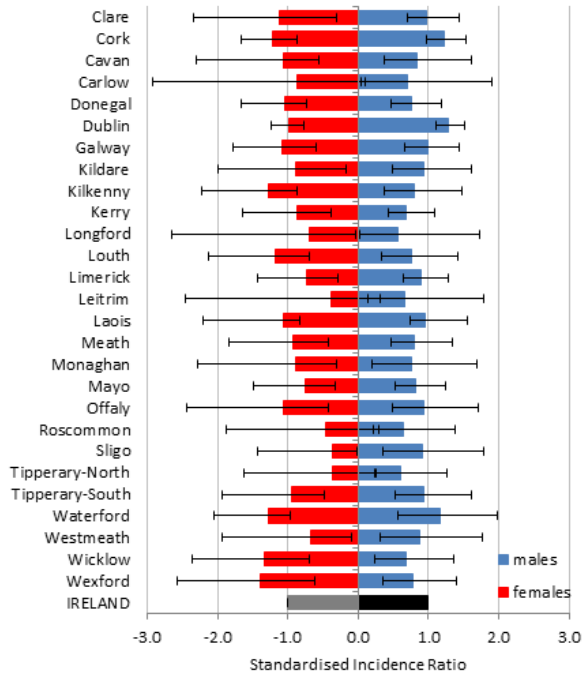


Figure 5. Incidence of liver cancer: variation by county, 2004–2013



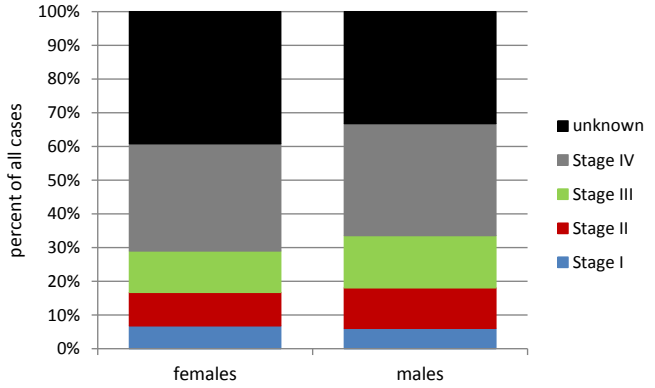
** Female SIRs shown on negative axis for illustration purposes only, values ranged from 0.36 to 1.40 (male values ranged from 0.57 to 1.29)*

Stage

Prognostic modelling of liver cancer, particularly HCC, is difficult because cirrhosis is involved in up to 80% of cases[1]. TNM staging, commonly used for most cancers is limited in value as liver function is not taken into account. Despite this limitation, TNM staging highlights the fact that a large proportion of liver cancer patients were already at an advanced stage (IV) when diagnosed (involving >1 lobe, invading surrounding tissues or with distant metastasis: TNM 5th-edition) (Figure 6). During 2009-2013, stage IV cases represented just over half of all staged cancers and it is likely that many unstaged patients (39% of females and 33% of males) were already late stage at diagnosis.

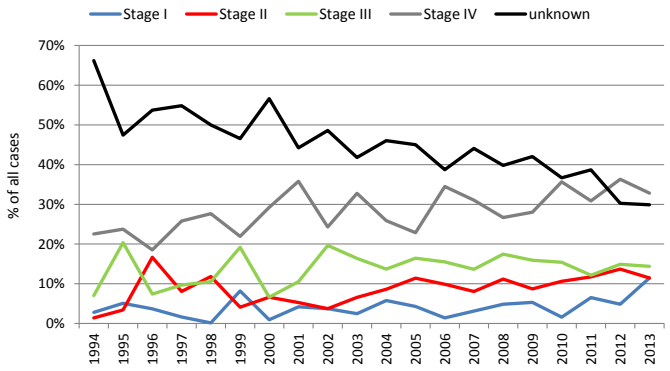
The proportions of early stage tumours were fairly similar between the sexes and males had slightly great proportions of stage III tumours compared to females.

Figure 6 Distribution of liver cancer by tumour stage (TNM 5th edition), 2009-2013[7]



Although there was little change in the proportion of patients diagnosed histologically over time (remaining fairly constant at approximately 50%), the percentages of patients with unstaged cancers have declined (Figure 7). This is likely due to greater proportions of patients having investigations to further assess the stage of their cancer. The decline in unknown stage has been accompanied by a gradual increase in the proportion of stage IV cases but relatively little change in the earlier staged cancers.

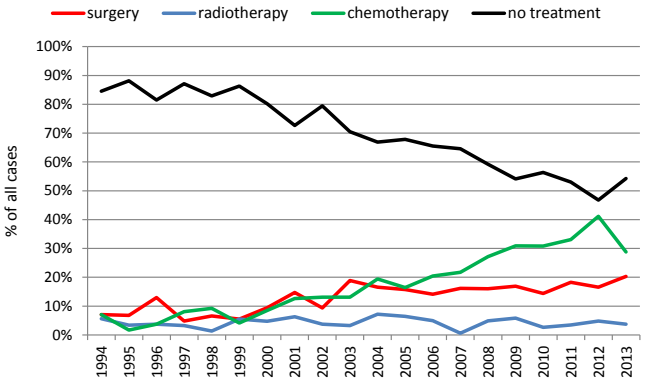
Figure 7. Variation in cancer stage over time, 1994-2013[7]



Treatment[7]

Liver cancer is often inoperable due to tumours either being too large, having grown into major blood vessels or patients having multiple small tumours that are spread throughout the liver, making surgery too risky or impractical. In addition chemotherapy has historically been fairly ineffective at treating liver cancer. For this reason, the proportion of patients having no tumour-directed treatment is one of the highest for all cancers. In the mid to late 1990s over 80% of patients had no tumour-directed treatment for their cancer (although some patients did have other procedures for symptom relief etc.) (Figure 8). Since then, there has been an increase in the proportion of patients having treatment targeted at the tumour directly, particularly chemotherapy, although approximately 50% of patients still remain untreated.

Figure 8. Treatment of liver cancers over time, 1994-2013[7]



Looking at the most recent 5 year period for which we have complete treatment data, approximately 18% of patients had tumour-directed surgery, 33% chemotherapy and 4% radiotherapy (Table 3). Both sexes were equally likely to have had radiotherapy and chemotherapy but rates of tumour-directed surgery were slightly higher for males.

Table 3. Treatments received by liver cancer patients, diagnosed 2009-2013[7]

	Females	Males	Total
Total cases diagnosed	352	792	1144
% surgery	14.8	18.7	17.4
% radiotherapy	3.4	4.4	4.1
% chemotherapy	32.4	33.3	33.0
% no treatment	58.2	50.3	52.7
% other procedure only	*25.6*	*17.8*	*14.4*
% stent inserted	*16.5*	*10.1*	*7.2*
of patients having tumour-directed surgery			
% local excision	5.8	8.8	8.0
% partial hepatectomy	61.5	45.9	49.5
% transplant	17.3	39.9	34.0
% radio frequency ablation	15.4	6.8	9.0
% other surgery only	1.9	2.0	2.0

as some patients can have >1 treatment, percentages do not add to 100%

The greater use of surgery in males and male/female differences in type of surgery reflect the greater relative proportion of intrahepatic tumours (cholangiocarcinomas, CC) in females and hepatocellular carcinomas (HCC) in males - 28% of HCC had tumour-directed surgery compared to 19% of CC (Table 4). Males were more likely to have a liver transplant (total hepatectomy) (40% of all male surgeries compared to 17% for females, 46% HCC compared to 4% CC), while females were more likely to have a partial hepatectomy/lobectomy (85% CC compared to 41% HCC) or radiofrequency ablation compared to males. For those patients that did not have tumour-directed therapy, females were more likely to have a stent inserted (17% females, 10% males, 21% CC, <1% HCC), allowing bile to drain through ducts blocked with tumour tissue, thereby relieving jaundice and other symptoms. Three out of four patients with unspecified histology had no tumour-directed therapy, with 21% receiving chemotherapy only.

As frequently observed with other cancers, treatment also varied by patient age with younger patients more likely to have surgery (40% of patients aged <50 compared to just 8% aged 70 or over). Older patients were also more likely to have no tumour directed treatment (72% of patients aged 70 or older compared to 27% in <50 year olds).

Table 4. Variation in treatment by histological subtype, all cases diagnosed 2009-2013[7]

	HCC	CC	Unspec-ified
Total cases diagnosed	419	242	437
% surgery	28.2	19.0	3.4
% radiotherapy	5.3	6.2	2.1
% chemotherapy	35.6	43.8	22.9
% no treatment	37.7	45.0	73.9
% other procedure only	*5.5*	*35.1*	*19.7*
% stent inserted	*0.5*	*20.7*	*13.3*
of patients having tumour directed surgery			
% local excision	8.5	6.5	0.0
% partial hepatectomy	40.7	84.8	0.0
% transplant	45.8	4.3	40.0
% radio frequency ablation	6.8	2.2	60.0
% other surgery only	0.8	6.5	0.0

as some patients can have >1 treatment, percentages do not add to 100%

Details of the chemotherapies administered to patients are available for patients diagnosed 2011-2013. During this time, 34% of all liver cancer patients had chemotherapy, the most common drugs registered being doxorubicin, sorafenib and gemcetabine (Table 5). Drugs were closely linked to the subtype of cancer, with doxorubicin and sorafenib almost exclusively administered to patients with HCC and gemcetabine, fluoruoracil and cisplatin for CC specifically.

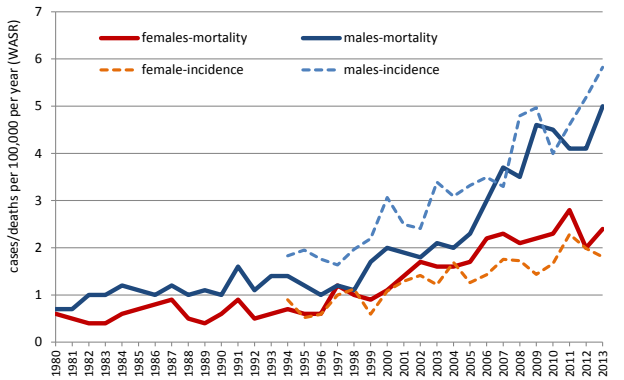
Table 5. Most commonly administered chemotherapy drugs for patients diagnosed, 2011-2013[7]

	Females	Males	HCC	CC	Total
Total cases	230	519	275	160	749
% patients had chemotherapy	36%	33%	33%	44%	34%
Main chemotherapies administered					
Doxorubicin	*28%*	*31%*	*37%*	*1%*	*30%*
Gemcetabine	*48%*	*18%*	*1%*	*90%*	*28%*
Sorafenib	*17%*	*36%*	*50%*	*1%*	*30%*
Fluorouracil	*8%*	*6%*	*1%*	*20%*	*7%*
Cisplatin	*31%*	*14%*	*2%*	*54%*	*20%*
Capecitabine	*4%*	*3%*	*1%*	*9%*	*3%*

Mortality

Although mortality from liver cancer was low and relatively stable from 1980 to the late 1990s averaging 17 female and 23 male deaths per year, mortality rates have increased substantially since and in 2013, a total of 122 females and 184 males died from liver cancer[8] (Figure 9). Since 1994, male mortality rates increased by an annual average of 8.9% (95%CI 7.5-10.2%) while female mortality rates increased by 10.7% (95%CI 7.4-14.1%) up to 2006 and have continued to increase at a slower pace (2.3% per year) since. Reflecting the very poor prognosis for liver cancer, mortality/ incidence ratios are high and averaged 1.3 for females and 0.9 for males between 2010 and 2014. Numbers of female deaths have exceeded the number of newly diagnosed cases almost every year since 1994, which is difficult to explain. One possible explanation might be if a higher number of female deaths from secondary liver cancer were incorrectly attributed to primary liver cancer deaths. 10% of all registered metastatic liver cancers originated from either female breast cancer or female-specific cancers, and errors in classifying cause of death as the secondary rather than the primary cancer might particularly impact on female death figures. It is also possible that not all primary liver cancers are registered as such – many late stage tumours may be registered as "primary site unspecified" (ICD10:C80) although this would not explain the unusual mortality/incidence ratio for females particularly.

Figure 9. Mortality from liver cancer in Ireland, 1980-2013[8]

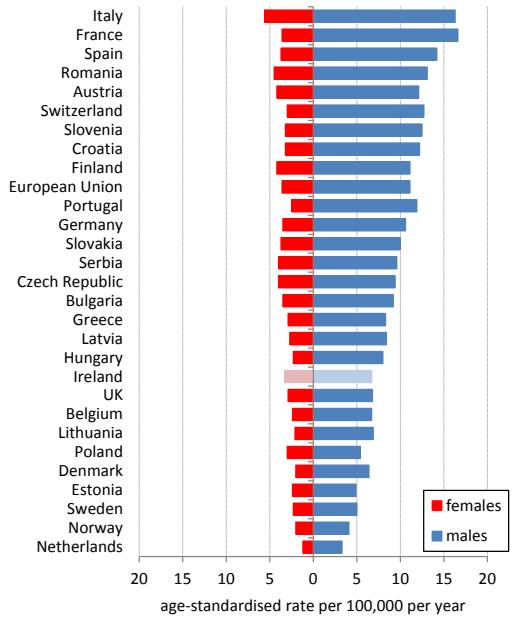


Note rates above are standardised according to the world standard population

International variation in incidence and mortality[9]

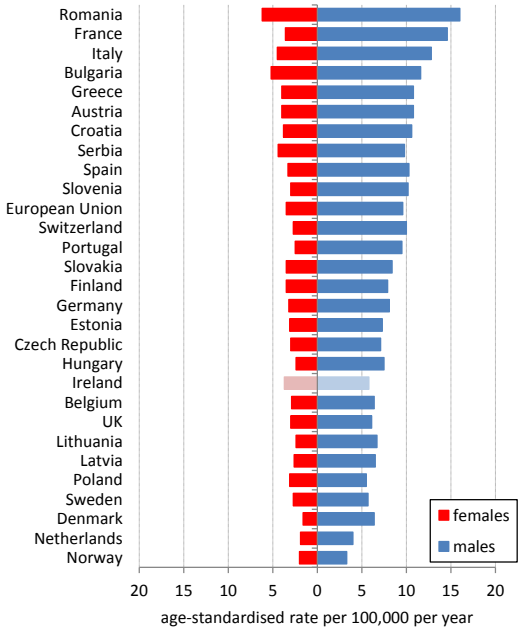
As observed in Ireland, liver cancer incidence was considerably higher in men than in women throughout Europe and male rates were also more variable (Figure 10). Rates were highest in Italy and France, and lowest in northern European countries: including the Netherlands, Norway and Sweden. Incidence in Ireland ranked amongst the lowest third of EU countries with males rates here on average 40% lower than the EU average. Female rates in Ireland were closer to the EU average, approximately 8% lower.

Figure 10. Estimated incidence of primary liver cancer in European countries 2012[9]



Liver cancer mortality showed a similar pattern to that observed for incidence, with highest rates for males in Romania, France and Italy (Figure 11). Lowest mortality rates were observed in Scandinavian countries and the Netherlands. Mortality rates for Irish females were marginally higher than the EU average (6%) but as for incidence, male mortality rates in Ireland were 40% lower than the EU overall.

Figure 11. Estimated mortality from primary liver cancer in European countries 2012[9]



5

Survival and prevalence

Survival from liver cancer is poor and the latest estimate of five-year net survival in Ireland was just 17% (Table 6). However survival has improved significantly since the mid-1990s when fewer than 5% of patients survived 5 years post diagnosis. Most improvement was observed in the early 2000s although survival has continued to progress. Five-year net survival was strongly correlated with patient age and in 2009-2013 ranged from just 8% for 75+ year olds to 37% for patients aged under 45.

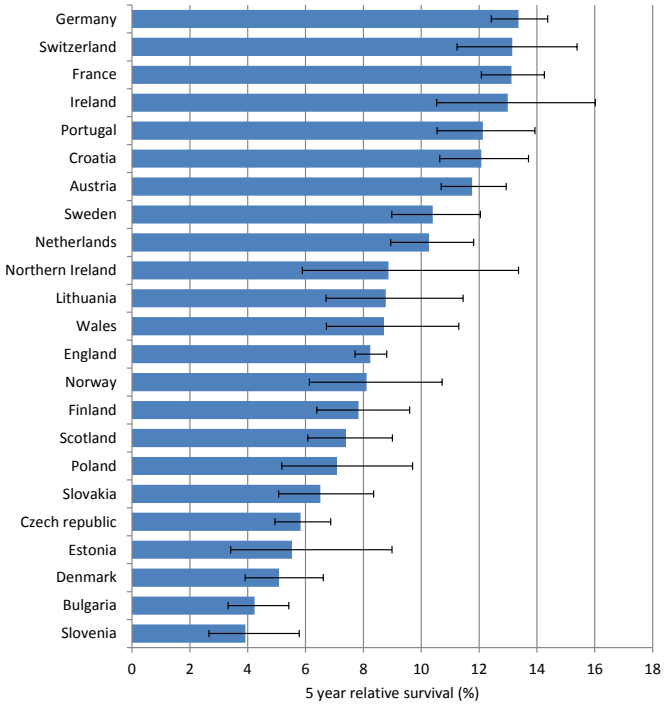
Table 6. Five-year net survival (NS) for liver cancers in adults diagnosed in various 5 year periods, 1994-2014

	NS (%)	95% CI (range)
1994-1998	4.5	2.5 – 6.5
1999-2003	11.0	8.2 – 13.8
2004-2008	12.0	9.6 – 14.4
2009-2013	17.0	14.0 – 20.1

Due to its relatively poor survival, the prevalence of liver cancer (i.e. the number of survivors) is small compared to many other cancers. Of all 3,028 patients diagnosed in Ireland since 1994, a total of just 498 (368 males and 130 females) or 16% were known to be still alive at the end of 2014.

Comparing liver cancer survival across Europe for patients diagnosed between 2000 and 2007, Ireland ranked 4th highest after Germany, Switzerland and France (Figure 12). Despite wide 95% confidence intervals around the survival estimate, survival rates in Ireland were found to be significantly higher than in many countries. Poorest survival was calculated for Slovenia, Bulgaria, Denmark and Estonia.

Figure 12. Comparison of 5 year relative survival for liver cancer patients diagnosed between 2000 and 2007 across Europe[10]



References and notes

1. Figure taken from the US National Cancer Institute PDQ on liver and bile duct cancer https://www.cancer.gov/types/liver/hp/bile-duct-treatment-pdq.
2. National Cancer Registry. 2010. Cancer of the liver and biliary tract. Cancer Trends No. 10
3. Saha SK et al, 2016. Forty year trends I cholangiocarcinoma incidence in the US: intrahepatic disease on the rise. The Oncologist 21: 1-6
4. "Alcohol consumption in Ireland almost trebled over four decades between 1960 (4.9 litres) and 2001 (14.3 litres)" - Alcohol Action Ireland http://alcoholireland.ie/facts/how-much-do-we-drink/
5. Small Area Health Research Unit (SAHRU), Department of Public Health & Primary Care, Trinity College Dublin. (2013) *SAHRU National Deprivation Index* [Online]. Available from: http://www.thehealthwell.info/node/464302
6. Geocoding complete for cases diagnosed up to 2013 only
7. Stage and treatment data is complete up to 2013. Only treatments administered within 1 year of diagnosis are included. Details of chemotherapy drugs provided for 2011-2013 only.
8. Data (1980-2013) extracted from the WHO database (http://www-dep.iarc.fr/WHOdb/WHOdb.htm). Note rates are standardised to the world standard population.
9. Source: European Cancer Observatory (ECO), EUCAN database. Rates standardised to the European (1976) standard population. http://eco.iarc.fr/EUCAN/Cancer.aspx?Cancer=34
10. Survival of cancer patients in Europe - the EUROCARE-5 study, figures extracted from online database https://w3.iss.it/site/EU5Results

