



Ratib, Sonia and West, Joe and Crooks, Colin J. and Fleming, Kate M. (2014) Occurrence of liver cirrhosis in England, a cohort study, 1998-2009: a comparison with cancer. *American Journal of Gastroenterology*, 109 (2). pp. 190-198. ISSN 1572-0241

Access from the University of Nottingham repository:

http://eprints.nottingham.ac.uk/32564/1/Manuscript_Ratib_AJGastro.pdf

Copyright and reuse:

The Nottingham ePrints service makes this work by researchers of the University of Nottingham available open access under the following conditions.

- Copyright and all moral rights to the version of the paper presented here belong to the individual author(s) and/or other copyright owners.
- To the extent reasonable and practicable the material made available in Nottingham ePrints has been checked for eligibility before being made available.
- Copies of full items can be used for personal research or study, educational, or not-for-profit purposes without prior permission or charge provided that the authors, title and full bibliographic details are credited, a hyperlink and/or URL is given for the original metadata page and the content is not changed in any way.
- Quotations or similar reproductions must be sufficiently acknowledged.

Please see our full end user licence at:

http://eprints.nottingham.ac.uk/end_user_agreement.pdf

A note on versions:

The version presented here may differ from the published version or from the version of record. If you wish to cite this item you are advised to consult the publisher's version. Please see the repository url above for details on accessing the published version and note that access may require a subscription.

For more information, please contact eprints@nottingham.ac.uk

Occurrence of liver cirrhosis in England, a cohort study, 1998-2009: a comparison with cancer

Occurrence of liver cirrhosis in England, 1998-2009

Sonia Ratib, Joe West, Colin J. Crooks, Kate M. Fleming

Division of Epidemiology & Public Health, University of Nottingham, UK

Correspondence:

Sonia Ratib

Division of Epidemiology and Public Health

University of Nottingham

Nottingham NG5 1PB, UK

Tel: +44 0115 8231344

Fax: +44 0115 8231946

E-mail: sonia.ratib@nottingham.ac.uk

Word count: 3517 (excluding study highlights, abstract, references)

Study highlights

What is current knowledge

- Liver disease is the only major cause of mortality that is rising in England.
- There is no routine registration of the occurrence of newly diagnosed cases of cirrhosis in the UK.

What is new here

- The occurrence of cirrhosis increased by 51% during 1998 to 2009 in England.
- Incidence of cirrhosis increased for all aetiologies and for both men and women.
- Incidence rates of cirrhosis increased more than that of the top four cancers in the UK.
- We estimate approximately 17000 newly diagnosed people with cirrhosis in 2009 in the UK, more than that of the fifth most common cancer.
- Strategies to monitor and reduce the incidence of cirrhosis are urgently needed.

ABSTRACT

Background There is no routine registration of the occurrence of newly diagnosed cases of cirrhosis in the UK. This study seeks to determine precise estimates and trends of the incidence of cirrhosis in England, and directly compare these figures with those for the twenty most commonly diagnosed cancers in the UK.

Design: We used the Clinical Practice Research Datalink and linked English Hospital Episode Statistics to perform a population-based cohort study. Adult incident cases with a diagnosis of cirrhosis between January 1998 and December 2009 were identified. We described trends in incidence by sex and aetiology. We performed a direct standardisation to estimate the number of people being newly diagnosed with cirrhosis in 2009, and calculate the change in incidence between 1998 and 2009.

Results: 5118 incident cases of cirrhosis were identified, 57.9% were male. Over the 12-year period crude incidence increased by 50.6%. Incidence increased for both men and women and all aetiology types. We estimated approximately 17000 people were newly diagnosed with cirrhosis in 2009 in the UK, greater than that of the fifth most common cancer non-hodgkin's lymphoma. The percentage change in incidence of cirrhosis between 1998 and 2009 for both men (45.2%) and women (28.4%) was greater than that seen for the top four most commonly diagnosed cancers in the UK (breast, lung, bowel and prostate).

Conclusion: The occurrence of cirrhosis increased more than that of the top four cancers during 1998 to 2009 in England. Strategies to monitor and reduce the incidence of this disease are urgently needed.

Keywords: Cirrhosis; Cancer; Epidemiology

INTRODUCTION

In her most recent report the Chief Medical Officer of the UK has highlighted liver disease as the only major cause of mortality and morbidity that is rising in England [1]. However, in contrast to other chronic diseases with similar spectra of aetiology and survival such as cancer, where national registries have been collecting data for over 80 years [2], the UK currently has no registry to monitor the occurrence of newly diagnosed cases of cirrhosis. The assessment of the healthcare burden of liver disease remains reliant on mortality statistics [3,4]. The use of mortality data to monitor trends in incidence of liver disease, and in particular cirrhosis, is inadequate as these figures do not reflect the present day burden of a disease, as not all patients with cirrhosis will die as a direct result of their liver disease, particularly those with compensated disease.

Previous population-based studies looking at cirrhosis, have used either primary or secondary care records in isolation to estimate the occurrence of cirrhosis in the UK [5,6,7]. Our previous work is an example of a study where primary care data alone were used as hospital registry data, at the time of the study, were unavailable. Limiting data to just one source inevitably results in a selected population of either principally ambulatory people or patients with decompensated disease and consequently under- or over-estimates the occurrence of disease. Now, for the first time, through the relatively recent linkage of primary and secondary care data in England, we have established a comprehensive population-based cohort that is representative of the whole population of people with cirrhosis from which incidence rates can be estimated more precisely than before.

Cirrhosis, like cancer, is preventable, can be detected early and has a high mortality rate. If trends in disease can be adequately monitored, as in the case of cancer, patients can be diagnosed earlier and provided with appropriate treatments and/or interventions to improve modifiable lifestyle factors. By comparing the occurrence of cirrhosis systematically with that of the top twenty diagnosed cancers in the UK our study puts a context to the burden of cirrhosis.

The aim of this study is to establish a comprehensive and well-validated study population of patients with cirrhosis to determine precise estimates of the incidence in England, the rate of change in incidence and to directly compare these figures with those for the twenty most commonly diagnosed cancers in the UK.

METHODS

Study design

We used population-based routinely collected electronic healthcare data from primary and secondary care registries in England to identify incident cases of cirrhosis.

Primary care data

The Clinical Practice Research Datalink (CPRD) is a longitudinal electronic database consisting of anonymised primary care records of over 10 million patients in the UK, collected since 1987. The data are coded using the Read code system [8]. Participating practices are assigned an up to standard (UTS) date on completion of regular audits confirming data quality and completeness; patient-level data are also assessed [9]. The CPRD has previously been shown to be representative of the population of the UK [10].

Secondary care data

The Hospital Episodes Statistics (HES) database comprises statutory records of all admissions (excluding outpatients) conducted in NHS hospitals and independent treatment centres in England, since 1989. For each period of time under the care of a consultant, a patient is assigned a primary diagnosis and up to 19 secondary diagnoses, coded using the ICD10 (International Classification of Diseases, tenth revision), and/or up to 24 recorded procedures coded using the OPCS4 (Office of Population, Censuses and Surveys' classification of surgical operations and procedures, fourth revision). We accessed data for patients registered at CPRD practices in England that have given consent to be linked to the HES database.

Death registry data

The Office for National Statistics (ONS) provides death registry data for CPRD practices that are linked to the HES.

Study population

We had access to data from all 244 CPRD practices in England linked to HES between April 1997 and August 2010 and to the ONS between April 1998 and December 2010. We defined cirrhosis in primary care if a person had a record containing a Read code for cirrhosis, oesophageal varices and/or portal hypertension in the CPRD. The Read code lists were adapted and updated from our previous externally validated definition [5]. We developed code lists for cirrhosis diagnosis in secondary care from ICD10 (K70.3, K71.7, K72.1, K74.4, K74.5, K74.6, K76.6, I85.0, I85.9, I86.4, I98.2) and OPCS4 (J06.1, J06.2, T46.1, T46.2, G10.4, G10.8, G10.9, G14.4, G17.4, G43.7).

Incident observation period

The incident observation period commenced on the latest of (i) 1st January 1998, (ii) one year after the patient's current registration date or (iii) the practice's UTS date. The one year cut-off was used to avoid including potential prevalent cases, adapted from Lewis et al.'s methodology [11]. The period terminated on the earliest of (i) date of death, (ii) date the patient left the practice, (iii) the practice's last data collection date or (iv) 31st December 2009.

Validation of case definition

For people with a cirrhosis diagnosis recorded in primary care we established how many had a subsequent hospital admission related to liver disease (e.g. alcoholic liver disease or chronic hepatitis).

For patients identified with cirrhosis from secondary care records only, we searched in both their primary and secondary care records and ONS death registry data for codes related to liver disease. We also examined primary care free text data for any of the following terms: 'cirrhosis', 'ascites', 'varices', 'liver', 'portal hypertension', 'hepatic', 'jaundice', or 'paracentesis'.

Diagnosis date

For each patient we assigned the date of diagnosis as the first date associated with a Read or ICD10/OPCS4 code for cirrhosis within the observation period. Patients younger than 18 years at diagnosis were excluded.

Aetiology

We searched the patient's medical records for evidence of viral hepatitis, autoimmune and metabolic diseases. We defined patients as having an underlying alcoholic aetiology if there was any mention in their primary or secondary care records of alcoholism, alcohol abuse, addiction or dependence, 'problem drinking' or referral to alcohol cessation services, or if their weekly alcohol consumption in their primary care records exceeded the Chief Medical Officer's recommended amount (14 units for women, 21 units for men) [12]. Our Read code list for this was adapted from previous work [5] and our ICD10 code list was adapted from the codes used by Statistics on Alcohol, England [13]. Aetiology was ascribed in a hierarchical fashion of viral hepatitis, autoimmune or metabolic disease and alcoholic cirrhosis. All remaining patients with no recorded aetiology were defined as cryptogenic cirrhosis.

Statistical analysis

We excluded patients whose date of diagnosis was concurrent with death. We used t-tests and difference in proportions for continuous and categorical variables respectively. We calculated crude incidence by dividing the number of cases by the total number of person-years from the HES-linked CPRD population at risk during the incident observation period. For each valid year we calculated the proportion of person-years at risk excluding the first year post-registration. We looked at incidence by age, sex, aetiology and year of diagnosis. We fitted a Poisson model to determine adjusted incidence rate ratios (IRR). We calculated two separate point estimates of prevalence using all cases who were contributing data to

HES-linked CPRD at 1 July 1999 and 1 July 2009. The total HES-linked CPRD population aged 18 years or older at each time point was used as the denominator. Stata version 12/MP4 was used for all statistical analyses.

Comparison with cancer

To make a comparison with the incidence of cancer we obtained the number of new cases diagnosed in 2009 for the top twenty most diagnosed cancers from Cancer Research UK [14]. To determine the percentage change in incidence over time, for each cancer, Cancer Research UK applied their age-specific incidence figures to the age-standardised European population and determined age-standardised rates per 100,000 person-years for men and women. From this they calculated the percentage change between the period 1998-2000 to 2007-2009. We applied the same methodology to our cirrhosis incidence figures to estimate the number of new cases diagnosed in 2009 in the UK and the percentage change in incidence for European age-standardised rates for men and women over the same period. We added our cirrhosis figures to graphs provided by Cancer Research UK.

RESULTS

Study cohort

Combining 2282 patients identified in secondary care with 2965 patients who had a diagnosis in primary care, and excluding 129 (2.5%) patients whose date of diagnosis was concurrent with death, we established an incident study cohort of 5118 people diagnosed with cirrhosis during the observation period.

Patient characteristics

In the cohort of 5118 patients, with a mean age of 59.3 (sd=14.3) years, there were slightly more men (57.9%) than women, and just over half of the population had alcoholic cirrhosis (53.9%). Median follow-up was 1.97 [inter-quartile range: 0.42, 4.39] years. The following patients had a non-alcohol aetiology: 574 (11.2%) chronic viral hepatitis, 362 (7.1%) autoimmune disease, 143 (2.8%) metabolic disease and 1283 (25.1%) cryptogenic cirrhosis. Numbers in the autoimmune and metabolic disease categories were small so have been combined for all subsequent analyses.

Incidence

Over the 12-year period crude incidence was 30.7 cases per 100,000 person years, increasing from 25.8 in 1998 to 37.5 per 100,000 person years in 2009 (Table 1). This increase fitted a continuous model with an average yearly incidence rate ratio of 1.04 (95% CI [1.03 to 1.05]) adjusted for age and sex, corresponding to a 50.6% increase over the time studied. Incidence was about 50% higher in men than women, 36.2 cases per 100,000 person-years and 25.4 cases per 100,000 person-years, respectively, IRR 1.50 (95% CI [1.42 to 1.58]) adjusted for age and year of diagnosis) (Figure 1). Adjusted incidence rate ratios are shown in Table 1.

Aetiology

A higher proportion of men than women had alcoholic cirrhosis, 61.9% vs.42.8% respectively ($P<0.001$) and the distribution of aetiology varied by age ($P<0.001$). For men, a larger proportion of the younger patients had alcoholic cirrhosis. For women twice as many had cryptogenic cirrhosis, compared to men, in the younger age-groups and approximately four times as many had cryptogenic compared to alcoholic cirrhosis in those older than 75 years (Table 2).

Between 1998 and 2009, adjusting for age, statistically significant increases in the incidence of both alcoholic and non-alcoholic cirrhosis were seen in men, 32.8% (95% CI [4.0% to 69.5%]) and 72.1% (95% CI [24.8% to 137%]) respectively. In women, a 25.9% (95% CI [-12.1% to 80.5%]) increase was seen in those with alcoholic cirrhosis and a statistically significant 43.6% increase (95% CI [5.2% to 95.9%]) in those with non-alcohol related cirrhosis. Figures 2 and 3 show the trends over time for each type of aetiology, for men and women respectively. There was a consistently higher proportion of men with alcoholic-cirrhosis than with non-alcohol related aetiology. The converse was true for women. In cases with cryptogenic cirrhosis, in particular, there was a 1.7 fold (IRR 1.69 95% CI [1.10, 2.60]) increase in incidence in men and a 2.5 fold (IRR 2.52 95% CI [1.57 to 4.05]) increase in incidence in women, adjusted for age.

Prevalence

Using all cases contributing to the HES-linked CPRD at two separate time points we saw an increase in the prevalence of cirrhosis between 1 July 1999 and 1 July 2009 from 24.7 to 179 per 100,000 population aged 18 years or above representing over a seven-fold increase in the prevalence of this disease over this ten year period.

Comparison with cancer

We estimated that 10478 and 6808 cirrhosis cases were newly diagnosed in men and women respectively in the UK in 2009. Figure 4 shows that our estimated number of cirrhosis cases was greater than that of the fifth most common cancer, non-hodgkin's lymphoma, for both men and women. There was a 45.2% increase in European age-standardised incidence rates of cirrhosis incidence in males comparing the period 1998-2000 to 2007-2009. For women the percentage increase was 28.4%. Supplementary Figures 1 and 2 show how these percentage changes compare to the twenty most commonly diagnosed cancers in the UK for the same period. The increase in incident cirrhosis was greater than all cancers apart from malignant melanoma, thyroid, kidney and liver (the latter three for women only).

Validation of case definition

Of the 2975 people identified as incident cirrhosis cases in primary care records during the study period 2230 (75%) had a hospital admission related to liver disease. Ten patients had a cirrhosis code in secondary care in 1997 so were excluded.

Of the 2282 patients who had a cirrhosis diagnosis in secondary care only during the study period, and no cirrhosis diagnostic Read code in primary care, 2062 (90.3%) had either death or additional evidence related to liver disease in their records, or a confirmation of a cirrhosis diagnosis in their free text.

DISCUSSION

We found a 50.6% increase in incidence of cirrhosis in England between 1998 and 2009. Over this period cirrhosis occurred more commonly and at younger ages in men than women. A significant increase in both alcoholic and non-alcoholic related cirrhosis was seen for men across the period under study. In women there was a significant increase for non-alcoholic cirrhosis only, specifically in cryptogenic cirrhosis. We estimate that, over the age of 18, approximately 17000 people were newly diagnosed with cirrhosis in 2009 in the UK. In comparison with the top twenty most diagnosed cancers in the UK, the estimated burden (new diagnoses) of cirrhosis was greater than all bar the big four cancers of breast, lung, bowel and prostate. In addition, the percentage change in European age-standardised incidence rates of cirrhosis from 1998 to 2009 was higher than that seen in all of these top four cancers and lower only than the percentage change in malignant melanoma, (and thyroid, liver and kidney in women only).

Strengths and limitations

This is the first population-based study using linked primary and secondary healthcare data to establish a comprehensive cohort to measure the occurrence of cirrhosis in England. Given that using one data source alone does not capture all incident cases of cirrhosis, we are confident that our estimates of incidence are more accurate than has been determined previously, including those provided in our own previous work [5]. To be able to widely generalise our findings we need to be confident that the population we have studied is truly representative of all patients with cirrhosis. Given that the data we have used is broadly similar in terms of demographics to that of England we believe we have a representative population [10].

Our definition of cirrhosis in secondary care, compared to that used by other studies, which included codes for chronic hepatitis and alcoholic liver disease [4,15], ensures that we are only including patients who have good evidence of cirrhosis. While we have assigned a diagnosis date as the incident date of disease in our study (so as to be able to calculate rates of occurrence from a defined denominator) we appreciate that given the long sojourn time for cirrhosis to develop this will not be the onset of disease. However this is analogous to the situation for most cancers meaning that our comparisons of incidence are on the same footing.

There are often questions raised about the validity of coding seen in both primary and secondary care data [16,17,18] but in most studies that have validated recording of chronic disease accuracy has been high [19,20]. A limitation of the HES data is that they cannot be directly validated against medical records due to the anonymisation process used. But a recent government audit found 91% median accuracy in clinical coding of diagnoses and procedures [21]. The linked data in our study have improved our case definitions by providing supporting evidence of liver disease among the various healthcare records.

Finally, we identified a record of alcohol use consistent with it being the underlying aetiology of disease in just over 50% of the patients. This is almost identical to that found by Saunders et al. (52%) between 1959 and 1976 and that of Fleming et al. (50.3%) based on primary care records only [5,7]. It is therefore highly likely that we have underestimated alcohol consumption, possibly reflecting poor recording of alcohol intake.

Other studies

A summary of the findings of selected, large, population-based previous studies are presented in Table 3. While not exhaustive this table allows us to provide a context for our results in comparison to studies that are broadly similar in scope and nature to ours. Our study is best compared to the two largest previous studies estimating incidence of liver cirrhosis in the UK [5,7]. The study by Saunders et al. identified one tenth the size of our study population in the West Midlands using hospital and death registry data and reported an increase in incidence from 5.6 to 15.3 per 100,000 person-years during the period 1959-1976. Our group's previous study that used solely primary care data found a 48% increase in incidence from 1992 to 2002, from 12 to 17 per 100,000 person years. Our overall estimate of incidence of 30 per 100,000 person years is higher than both these studies which is unsurprising given that Saunders et al.'s study was carried out more than fifty years ago and the study by Fleming et al. most probably underestimated the burden of disease due to not having access to linked secondary care data. However, the rate of change we describe is almost identical to that of the latter study.

In comparison to some studies conducted in Denmark, one used both in- and out-patients during 1996-2006 and therefore had a comprehensive cohort similar to ours [25]. Their overall incidence findings were similar to ours however the authors did not look at trends over time nor make a comparison between the different types of aetiology. In contrast to our findings, the other Danish study found no discernable trend in incidence of alcoholic cirrhosis during the study period, 1995-2006 [23]. Even though there has been an increase in alcohol consumption in the UK over the last twenty years [26], our study also shows that there has been a concurrent rise in the number of people with non-alcohol cirrhosis. In particular we have reported a substantial increase in those with cryptogenic cirrhosis. Many cases of cryptogenic cirrhosis are likely to be end stage non-alcoholic steatohepatitis encompassed within the spectrum of non-alcohol fatty liver disease (NAFLD) [27]. Obesity is linked to NAFLD [28], and the increase in the incidence of cryptogenic cirrhosis we report may reflect the increase in obesity seen in the UK over the last few decades [29].

Comparison with cancer

In England more than one in three people will develop cancer at some stage in their lives [30]. In the year 2000 the British government established a NHS plan for cancer: a comprehensive strategy for bringing together prevention, screening, diagnosis, treatment and care [30]. National registries have been set up in England over the last 80 years to monitor trends of incidence [2]. In contrast, no services for monitoring and detecting cirrhosis have been provided despite the fact that in 2001 the CMO reported a dramatic increase in the occurrence of liver disease in the UK [31]. Our use of population-based, routinely available, linked electronic health records has allowed us to show that the incidence of cirrhosis has increased more than that of the top four cancers during the period 1998 to 2009 in England. According to Cancer Research UK's predictions overall cancer death rates are expected to fall by 17% by 2030 in the UK [32]. Stark contrast to that predicted for alcohol related liver deaths and implied both by our incidence figures and by the rising mortality rates recently reported [3,33]. We have demonstrated how electronic routine healthcare databases could fill the gap that currently exists given that the UK has no registry to monitor the occurrence of cirrhosis which is escalating at an alarming rate. In addition to filling this gap, using electronic routine databases will help answer other research questions such as the regional variation of the disease and implications on cost and optimisation of healthcare resource allocation.

Conclusion

Cirrhosis represents a serious and growing burden of morbidity and mortality across England, for all aetiologies and for both men and women. Our study is the first to establish a comprehensive, representative sample of people with cirrhosis using population-based data analogous to cancer registries in England therefore allowing a direct comparison to be made with the incidence of cancer. The aetiology of cirrhosis encompasses many preventable exposures such as chronic viral hepatitis, alcohol consumption and the causes of obesity therefore it is crucial to be able to count the number of newly occurring diagnoses of this disease over time in a reproducible manner. This will allow one to assess the impact of both individual and population level intervention on the occurrence of this disease. Given the continued rise in cirrhosis which we have described, greater than that seen for almost all of the most commonly diagnosed cancers in the UK it is imperative that strategies are put in place to monitor the trends in this disease more closely.

REFERENCES

1. CMO report 2012 [Internet]. Available at <https://www.gov.uk/government/publications/cmo-annual-report-2011-volume-one> (last accessed 7th May 2013).
2. Eastern cancer registration and information centre [Internet]. Available at <http://www.ecric.nhs.uk> (last accessed 7th May 2013).
3. Bhala N, Aithal G, Ferguson J. How to tackle rising rates of liver disease in the UK. *BMJ* 2013; 346:f807.
4. Leon DA, McCambridge J. Liver cirrhosis mortality rates in Britain from 1950 to 2002: an analysis of routine data. *Lancet* 2006; 367(9504):52-6.
5. Fleming KM, Aithal GP, Solaymani-Dodaran M *et al*. Incidence and prevalence of cirrhosis in the United Kingdom, 1992-2001: A general population-based study. *J Hepatol* 2008; 49:732-738.
6. Roberts SE, Goldacre MJ, Yeates D. Trends in mortality after hospital admission for liver cirrhosis in an English population from 1968 to 1999. *Gut* 2005; 54(11):1615-21.
7. Saunders JB, Walters JR, Davies AP *et al*. A 20-year prospective study of cirrhosis. *Br Med J (Clin Res Ed)* 1981; 282(6260):263-6.
8. NHS Connecting for health [Internet]. Available at <http://www.connectingforhealth.nhs.uk/systemsandservices/data/uktc/readcodes> (last accessed 7th May 2013).
9. Medicines and Healthcare products Regulatory Agency. Data quality assessment in CPRD. London: Crown Copyright, 2007.
10. Walley T, Mantgani A. The UK General Practice Research Database. *Lancet* 1997; 350:1097-9.

11. Lewis JD, Biker WB, Weinstein RB *et al.* The relationship between time since registration and measured incidence rates in the General Practice Research Database. *Pharmacoepidemiol Drug Saf* 2005; 14:443-451.
12. Chief Medical Officer [Internet]
http://www.dh.gov.uk/en/Publichealth/Alcoholmisuse/DH_125368.
13. Information Centre [Internet]. Available at <http://www.hscic.gov.uk/pubs/alcohol12> (last accessed 7th May 2013).
14. Cancer Research UK [Internet]. Available at <http://info.cancerresearchuk.org/cancerstats/> (last accessed 7th May 2013, figures constantly updated).
15. Liu B, Balkwill A, Reeves G *et al.* Body mass index and risk of liver cirrhosis in middle aged UK women: prospective study. *BMJ* 2010; 340:c912.
16. Herrett, E, Thomas SL, Schoonen WM *et al.* Validation and validity of diagnoses in the General Practice Research Database: a systematic review. *Br J Clin Pharmacol* 2010. **69**(1): p. 4-14.
17. Williams JG, Mann RY. Hospital episode statistics: time for clinicians to get involved? *Clinical Medicine. Journal of the Royal College of Physicians* 2002; 2:34-37.
18. Westaby S, Archer N, Manning N *et al.* Comparison of hospital episode statistics and central cardiac audit database in public reporting of congenital heart surgery mortality. *BMJ* 2007; 335(7623):759.
19. Khan NF, Harrison SE, Rose PW. Validity of diagnostic coding within the General Practice Research Database:a systematic review. *British Journal of General Practice* 2010; 60:e128-e136(9).
20. Kramer JR, Davila JA, Miller ED *et al.* The validity of viral hepatitis and chronic liver disease diagnoses in Veterans Affairs administrative databases. *Aliment Pharmacol & Ther* 2007; 274-282.
21. Audit Commission. Improving data quality in the NHS Annual report on the PbR assurance programme. Audit Commission Publishing Team; 2010.

22. Ludviksdottir D, Skulason H, Jakobsson F *et al.* Epidemiology of liver cirrhosis morbidity and mortality in Iceland. *Eur J Gastroenterol Hepatol* 1997; 9(1):61-6.
23. Jepsen P, Vilstrup H, Andersen PK *et al.* Comorbidity and survival of Danish cirrhosis patients: a nationwide population-based cohort study. *Hepatology* 2008;48:214-20.
24. Gunnarsdottir SA, Olsson R, Olafsson S *et al.* Liver cirrhosis in Iceland and Sweden: incidence, aetiology and outcomes. *Scand J Gastroenterol* 2009; 44(8):984-93.
25. Fiolla AD, Schaffalitzky de Muckadell OB, Lassen AT. Incidence, etiology and mortality of cirrhosis: a population-based cohort study. *Scand J Gastroenterol* 2012; 47:702-709.
26. Smith L, Foxcroft D. *Drinking in the UK: an exploration of trends.* Joseph Rowntree Foundation; 2009.
27. Farrell GC, Larter CZ. Nonalcoholic fatty liver disease: from steatosis to cirrhosis. *Hepatology* 2006; 43(2 Suppl 1):S99-S112.
28. Angulo P, Lindor K. Non-alcohol fatty liver disease. *Journal of Gastroenterology and Hepatology* 2002; 17: 186-190.
29. Department of Health [Internet]. Available at <https://www.gov.uk/government/policies/reducing-obesity-and-improving-diet> [Last accessed 7th May 2013].
30. Cancer NHS plan [Internet]. Available at http://webarchive.nationalarchives.gov.uk/+/www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4009609 [Last accessed 7th May 2013].
31. Chief Medical Officer [Internet]. Available at <http://www.dhsspsni.gov.uk/index/phealth/cmoannualreport.htm> [Last accessed 7th May 2013].
32. Wise J. UK cancer death rates are predicted to fall 17% by 2030. *BMJ* 2012; 345:e6473.
33. Sheron N, Gilmore I, Parsons C *et al.* Projections of alcohol-related deaths in England and Wales-tragic toll or potential prize? *The Lancet* 2012; 379:687-8.

Guarantor of the article: S.R accepts full responsibility for the conduct of the study and had access to the data and control of the decision to publish.

Specific author contributions: J.W. had the original idea for the study and all authors contributed to its interpretation. S.R. was responsible for data management, performed the data analysis and initially drafted the paper. J.W., K.M.F., and C.J.C. revised the paper critically and all authors approved the final version. Approval was given by the Independent Scientific and Ethical Committee of the CPRD for this study (09_065RA_3).

Financial support: University of Nottingham/National University Hospitals NHS Trust/National Institute for Health Research Senior Clinical Research Fellowship). The funders of this study had no role in the design, analysis or interpretation of the data. S.R. is funded by the Fellowship awarded to J.W. Approval was given by the Independent Scientific and Ethical Committee of the CPRD for this study (09_065RA_3).

Potential competing interests: None.

Figure Legends

Figure 1: Incidence of cirrhosis (per 100,000 person-years) by year and sex, England, 1998-2009

Figure 2: Incidence of cirrhosis (per 100,000 person-years) by aetiology, males 1998-2009 (colour)

Figure 3: Incidence of cirrhosis (per 100,000 person-years) by aetiology, females 1998-2009 (colour)

Figure 4: The number of cases for the 20 most common cancers in the UK and cirrhosis of the liver, in 2009. Adapted from Cancer Research UK [14].

Supplementary Figure Legends

Supplementary Figure 1: Percentage change in European age-standardised rates per 100,000 person-years for cirrhosis of the liver and the most common cancers in the UK, females, 1998-2000 to 2007-2009. Adapted from Cancer Research UK [14].

Supplementary Figure 2: Percentage change in European age-standardised rates per 100,000 person-years for cirrhosis of the liver and the most common cancers in the UK, males, 1998-2000 to 2007-2009. Adapted from Cancer Research UK [14].

Table 1: Incidence of cirrhosis, 1998-2009

Total	Cases	P-yrs	Crude Incidence rates [95% CI] per 100,000 pyrs	Adjusted incidence rate ratios [95% CI]¥
	5118	16,672753	30.70 (29.87 to 31.55)	
Sex				
Female	2153	8,490,621	25.36 (24.31 to 26.45)	1
Male	2965	8,182,132	36.24 (34.96 to 37.57)	1.50 (1.42 to 1.58)
Age (years)				
18-34	189	4124431	4.58 (3.97 to 5.28)	1
35-44	561	3271016	17.15 (15.79 to 18.63)	3.75 (3.18 to 4.42)
45-54	1149	2974413	38.63 (36.46 to 40.93)	8.45 (7.24 to 9.85)
55-64	1302	2613275	49.82 (47.19 to 52.60)	10.85 (9.32 to 12.64)
65-74	1020	1889873	53.97 (50.76 to 57.39)	11.93 (10.22 to 13.94)
75-84	714	1299395	54.95 (51.06 to 59.13)	12.49 (10.64 to 14.66)
85+	183	500350	36.57 (31.64 to 42.28)	8.67 (7.07 to 10.62)
Aetiology*				
Alcohol	2756	16,672753	16.53 (15.92 to 17.16)	
Viral hepatitis	574	16,672753	3.44 (3.17 to 3.74)	
Autoimmune/Metabolic diseases	505	16,672753	3.03 (2.78 to 3.30)	
Cryptogenic	1283	16,672753	7.70 (7.29 to 8.13)	
Year of diagnosis				
1998	239	925730	25.82(22.74 to 29.31)	1
1999	262	1071075	24.46 (21.67 to 27.61)	0.95 (0.80 to 1.13)
2000	340	1252827	27.14 (24.40 to 30.18)	1.05 (0.89 to 1.24)
2001	350	1351657	25.89 (23.32 to 28.75)	1.00 (0.85 to 1.17)
2002	398	1401538	28.40 (25.74 to 31.33)	1.09 (0.93 to 1.28)
2003	409	1430505	28.59 (25.95 to 31.50)	1.09 (0.93 to 1.28)
2004	453	1458347	31.06 (28.33 to 34.06)	1.18 (1.01 to 1.38)
2005	453	1481626	30.57 (27.88 to 33.52)	1.16 (0.99 to 1.36)
2006	486	1521211	31.95 (29.23 to 34.96)	1.22 (1.04 to 1.42)
2007	526	1561949	33.68 (30.92 to 36.68)	1.28 (1.10 to 1.49)
2008	594	1594729	37.25 (34.37 to 40.37)	1.42 (1.22 to 1.65)
2009	608	1621559	37.49 (34.63 to 40.60)	1.42 (1.23 to 1.65)

Pyrs=person-years; CI=confidence intervals; *Adjusted IRRs cannot be calculated as denominator data cannot be categorised by aetiology and compared with one another; ¥ Adjusted for age, sex or year of diagnosis.

Table 2: The distribution of aetiology by age-group and by sex: row %s (95%CI)

Aetiology	n	Cryptogenic	Alcoholic	Viral hepatitis	Autoimmune/Metabolic diseases
MEN					
Age (years)					
18-34	105	21 (13.1 to 28.8)	54.3 (44.7 to 63.9)	17.1 (9.9 to 24.4)	7.6 (2.5 to 12.7)
35-44	341	8.5 (5.5 to 11.5)	65.1 (60 to 70.2)	21.7 (17.3 to 26.1)	4.7 (2.4 to 6.9)
45-54	702	8.7 (6.6 to 10.8)	70.4 (67 to 73.8)	16.4 (13.6 to 19.1)	4.6 (3.0 to 6.1)
55-64	790	13.9 (11.5 to 16.3)	70.0 (66.8 to 73.2)	9.4 (7.3 to 11.4)	6.7 (5.0 to 8.5)
65-74	580	28.6 (24.9 to 32.3)	58.3 (54.3 to 62.3)	5.7 (3.8 to 7.6)	7.4 (5.3 to 9.5)
75-84	369	46.9 (41.8 to 52)	40.7 (35.6 to 45.7)	4.6 (2.5 to 6.7)	7.9 (5.1 to 10.6)
85+	78	66.7 (56.1 to 77.2)	25.6 (15.9 to 35.4)	5.1 (0.2 to 10.1)	2.6 (-1.0 to 60.9)
Overall	2965	20.7 (19.2 to 22.1)	61.9(60.1 to 63.3)	11.3(10.2 to 12.4)	6.2 (5.3 to 7)
WOMEN					
Age (years)					
18-34	84	42.9 (32.2 to 53.5)	35.7 (25.4 to 46)	15.5 (7.7 to 23.3)	6.0 (0.9 to 11)
35-44	220	20.0 (14.7 to 25.3)	56.4 (49.8 to 62.9)	15.9 (11.1 to 20.8)	7.7 (4.2 to 11.3)
45-54	447	13.7 (10.5 to 16.8)	63.5 (59.1 to 68)	13.2 (10.1 to 16.3)	9.6 (6.9 to 12.4)
55-64	512	21.3 (17.7 to 24.8)	53.5 (49.2 to 57.8)	9.6 (7 to 12.1)	15.6 (12.5 to 18.8)
65-74	440	35.7 (31.2 to 40.2)	31.8 (27.5 to 36.2)	10.7 (7.8 to 13.6)	21.8 (18 to 25.7)
75-84	345	55.4 (50.1 to 60.6)	17.1 (13.1 to 21.1)	8.4 (5.5 to 11.3)	19.1 (15 to 23.3)
85+	105	68.6 (59.6 to 77.5)	10.5 (4.6 to 16.4)	6.7 (1.9 to 11.5)	14.3 (7.6 to 21)
Overall	2153	31.1(29.2 to33.1)	42.8(40.7 to 44.9)	11.1(9.8 to 12.4)	15(13.4 to 16.5)

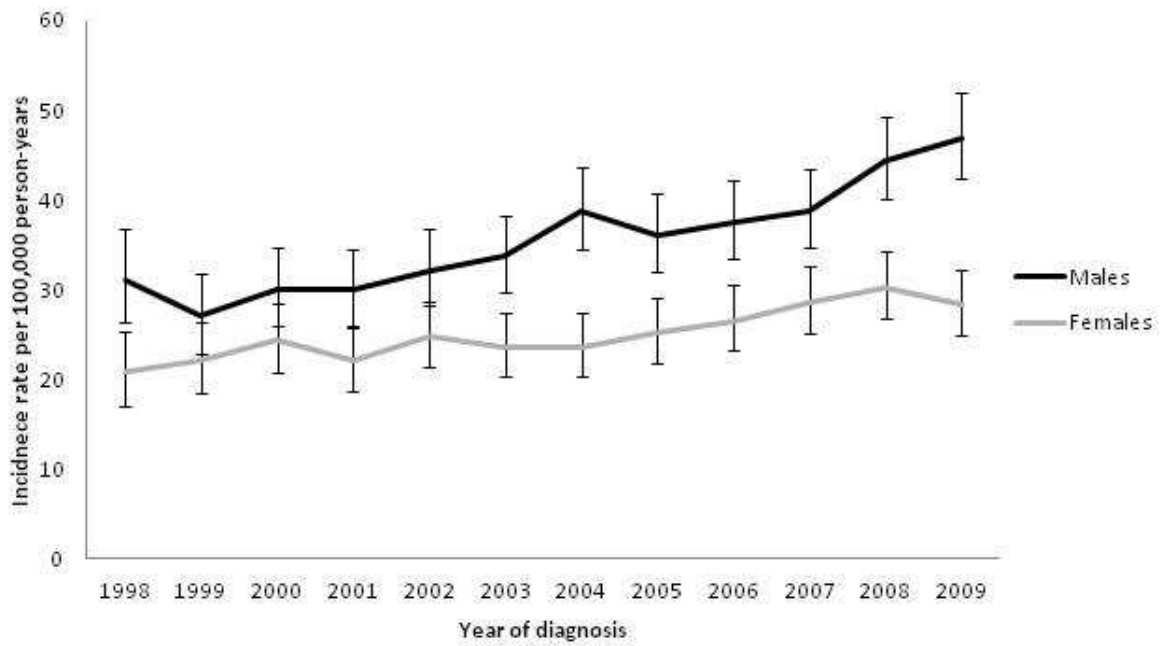
CI=confidence intervals

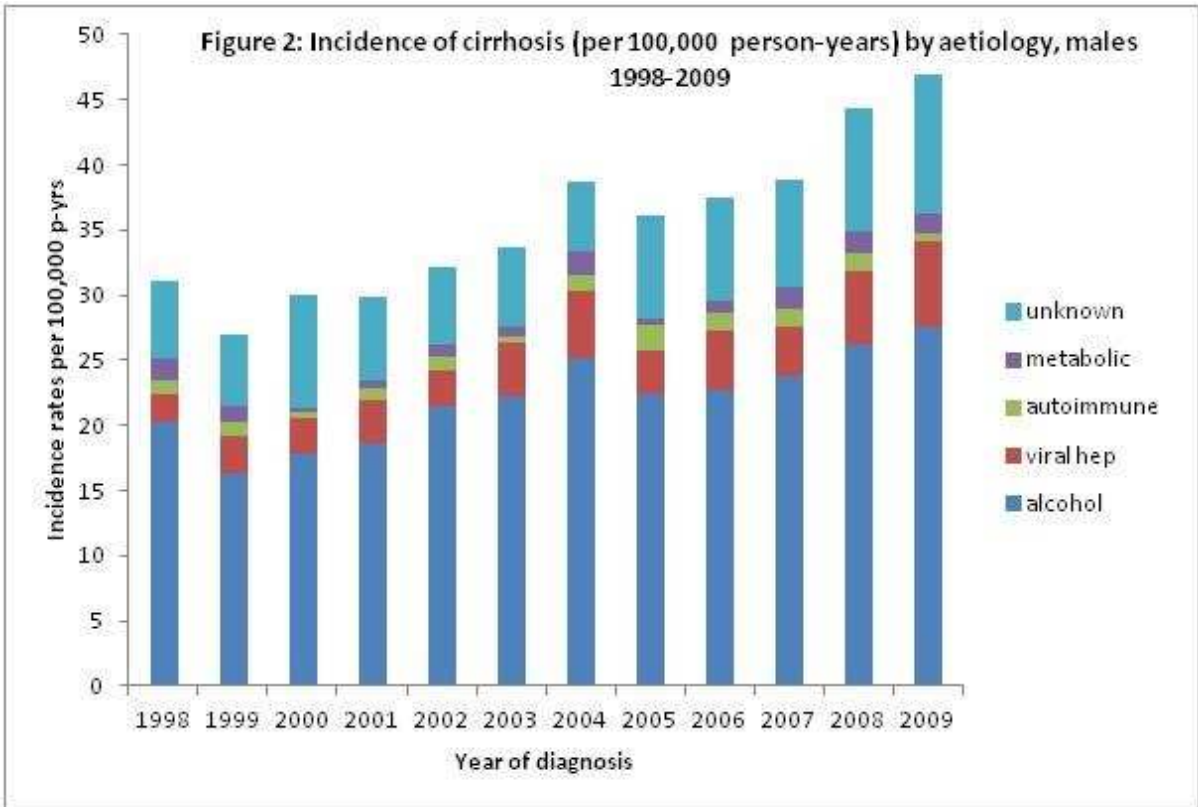
Table 3: Summary of selected studies of the incidence of cirrhosis of the liver

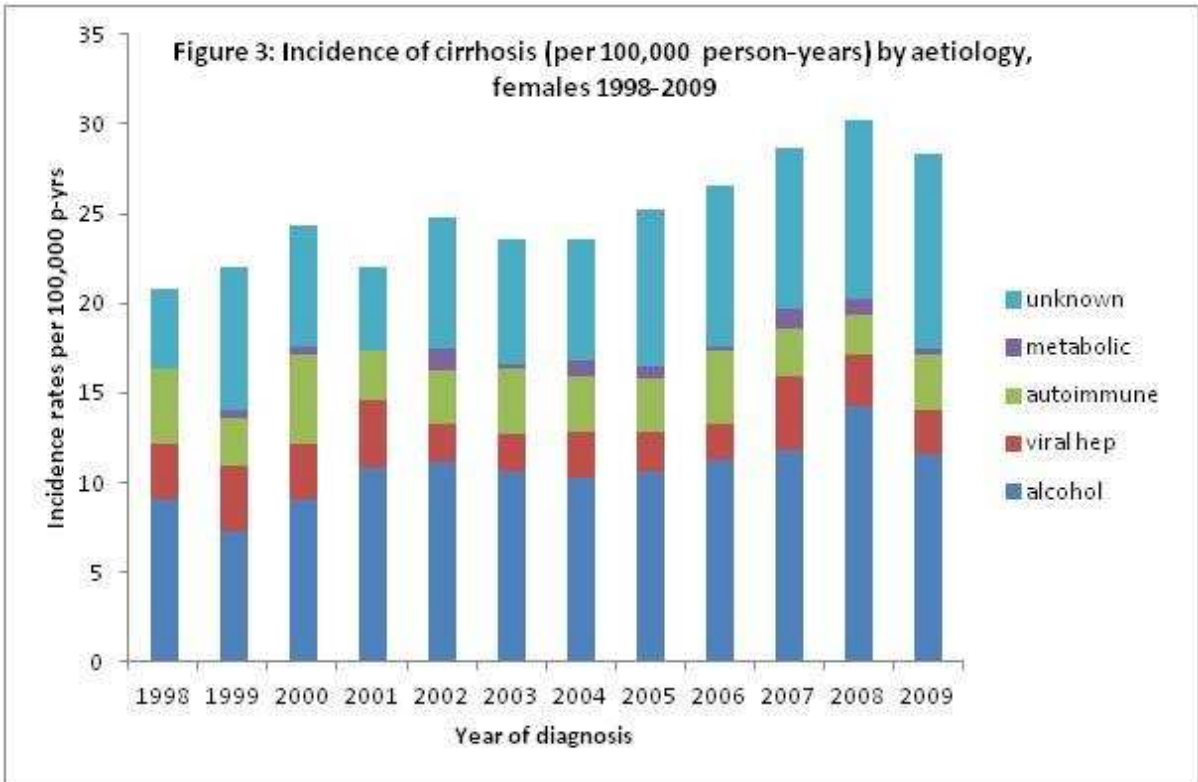
Author/Year	Study location	Time period	Data source & population	Cohort size	Definition of cirrhosis diagnosis	Demographics	Incidence
Saunders et al. 1981 ⁷	W. Midlands UK	1959 - 1976	Hospital registry Pathology registry Age 15 years +	512	Medical notes: evidence from liver biopsy, post-mortem or clinical biochemical results. Pathology : autopsy files, death certificates	Does not present % of men. Mean age for men alcohol cirrhosis was 53 years, for women 55.2 years. Alcohol cirrhosis was 50.6%.	5.6 per 100,000 in 1959 15.3 per 100,000 in 1974
Ludviksdottir et al. 1996 ²²	Iceland	1971-1990 Age 20 years +	Death registry Hospital registry Biopsy/autopsy records	142	Histological evidence (liver biopsy)	Men 45% Alcohol cirrhosis 44%	22.1 per 1,000,000 pyrs for AC 25.9 per 1,000,000 pyrs for NAC
Roberts et al. 2005 ⁶	Oxford UK	1968 - 1999	Hospital registry Age 15 years +	8192	ICD9: Alcohol Cirrhosis (571.0, 571.1, 571.2, 571.3); Non-Alcohol Cirrhosis (571.4, 571.5,571.8,571.9) ICD10: K70, K73, K74, K76.0	Men 55% Mean age 57.5	Not reported
Leon et al. 2006 ⁴	Britain	1950-2002	WHO mortality database		ICD7: 581 ICD8/9: 571 ICD10: K70, K73, K74	No age provided or % men	Not reported
Jepsen et al. 2008 ²³	Denmark	1995-2006	National Hospital registry Death registry	14,976	ICD8: 571.09, 571.92, 571.99 ICD10: K70.3, K74.6	Men 66.4% Alcohol cirrhosis 68.7%	Not reported
Gunnarsdottir et al. 2009 ²⁴	Iceland & Sweden (Got'berg)	1994-2003	Hospital & outpatient registry. No age criteria specified.	1016	Diagnosis database used to identify patients first. Clinical criteria used to confirm cirrhosis and define mortality.	Sweden n=918, alcohol 62%, men 69.3% Iceland n=98, alcohol 32%, men 52%	Gothenburg: 15.3 per 100,000 pyrs p.a Iceland: 3.3 per 100,000 pyrs p.a
Lui et al 2010 ¹⁵	UK	Recruitment from 1996 to 2001. F/up to 2003 in England, 2005 in Scotland	Hospital registry	1811	ICD10: K70, K73, K74	Mean age at recruitment 56	1.2 per 1000 women over five years
Fleming et al. 2011 ⁵	UK	1992 - 2001	Primary care records Age 25 + years	3360	Read codes for cirrhosis, portal hypertension and oesophageal varices	Men 58% Median age 56.3 (men) 61.3 (women) Alcohol cirrhosis 38.3%	14.5 per 100,000 pyrs
Fialla et al. ²⁵ 2012	Funen, Denmark	1996 - 2006	Hospital & outpatient registry	1369	Initially 35 ICD10 codes including: K70, K73, K74, K830, B18, K717, K718, K738, K739, K758, K759, K761, K721, K729, K767, E831, E88, I850, I859, I864, R189, C220, Z944 and then clinical criteria: liver biopsy or post-mortem autopsy, portal hypertension, prolonged bleeding time, irregular liver surface, evidence of complications.	Men 67% Alcohol cirrhosis 79%	33 per 100,000 pyrs

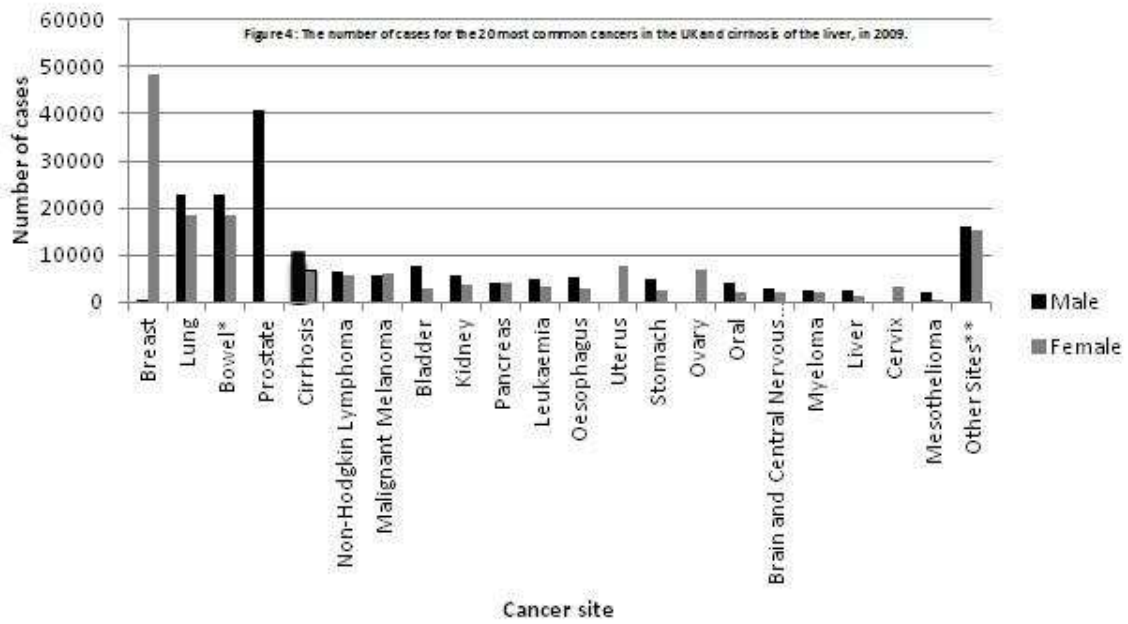
AC=alcoholic cirrhosis; NAC=non-alcoholic cirrhosis; pyrs=person-years; F/up=follow-up. ICD=International Classification of Diseases

Figure 1: Incidence of cirrhosis (per 100,000 person-years) by year and sex, England, 1998-2009.









* bowel including anus. **4% of all female cancer cases and 3% of all male cancer cases are registered without specification of the primary site. Adapted from Cancer Research UK [14].