Chapter 4

Brain

Paul Silcocks, John Steward, Helen Wood

Summary

- In the UK and Ireland, in the 1990s, brain cancer accounted for about 1 in 60 newly diagnosed cancers and 1 in 50 cancer deaths. Brain cancer accounted for about a fifth of childhood cancers.
- Incidence rates were highest in Wales and Ireland (males) and, within England, in the south (excluding London) and the more urban areas of the north, and lowest in London, and parts of the midlands and north of England.
- The geographical pattern of mortality rates did not match closely with that for incidence. In particular, rates were lower than might have been expected from the incidence in many parts of the north of England and higher in parts of Scotland.
- There is a weak (negative) relationship between incidence and mortality and socio-economic deprivation, with lower than average rates in parts of London and some of the former heavily industrialised areas in the midlands and north of England, and higher rates in predominantly rural areas and/or in the south.
- There is no obvious link between the geographical variation in the incidence of brain cancer and any possible risk factors.

Introduction

This chapter concerns primary malignant neoplasms of the brain. In making comparisons with results in other publications, their inclusion criteria for these tumours should be scrutinised carefully. In particular, benign tumours may be included in some studies, especially those covering childhood. Cancers in other organs often metastasise to the brain – these secondary tumours have been excluded here.

Incidence and mortality

In the 1990s, on average 2,400 males and 1,900 females were diagnosed with brain cancer each year in the UK and Ireland. These cases represented 1.8 per cent of male and 1.4 per cent of female cancers, a male-to-female ratio of 1.3:1. The age-standardised incidence rates in males and females were 7.9 and 5.3 per 100,000, respectively (a ratio of 1.5:1 – slightly higher than the ratio of cases).

Although predominantly a disease affecting adults, brain cancer accounts for about a fifth of childhood cancers. In England and Wales, after a small peak in childhood, the age-specific incidence rates in both men and women rose with age, then declined after 75 years or so, the peak being greater in men.[1]

During the same period 1,900 males and 1,400 females died on average each year from brain cancers in the UK and Ireland, a male-to-female ratio of 1.4:1, slightly higher than the ratio for incident cases. These deaths represented 2 per cent of all cancer deaths, the proportion being slightly higher in males (2.2 per cent) than in females (1.8 per cent). The age-standardised mortality rates were 6.1 and 3.9 per 100,000, respectively (a ratio of 1.6:1).

Incidence and mortality trends

Age-specific incidence and mortality rates in both sexes have shown upward trends since the 1970s and the 1950s respectively, although analysis by birth cohort shows that for England and Wales at least, mortality has declined in cohorts born since the 1920s.[1,2] A similar pattern is evident in the USA, with declining mortality in adults.[3] There is evidence of increasing incidence of brain cancer in childhood in all countries.[4-6] There has also been an increase in incidence in the elderly.

The interpretation of trends in brain cancer incidence and mortality over time is complicated by the introduction of diagnostic techniques such as CT and MRI scans, which have made diagnosis more accurate in the elderly but also reduced the proportion of histologically-verified tumours, risk of misclassified secondary tumours, and the need for autopsy. This might also influence geographical variations within the UK and Ireland. These issues of interpretation are considered in detail by Swerdlow et al.[2]

Survival

Survival from brain cancer is quite low and has improved little in recent decades. One-year relative survival for patients diagnosed in England and Wales during 1996-99 was about 32 per cent in both sexes, while at five years it was about 13 per cent in men and 15 per cent in women.[7] Comparable figures were seen for patients diagnosed in the 1990s in Northern Ireland[8] and Scotland.[9] Across Europe for patients diagnosed in 1990-94, average relative survival rates were 38 per cent at

one year and 18 per cent at five years, with the exception of some Nordic countries such as Finland, where rates were markedly higher.[10]

Brain cancer encompasses different histological subtypes with different responses to treatment. The WHO classification is based on morphology,[11] reflected in ICDO2 rather than ICD10. For the malignant gliomas, the commonest subtype in adults, survival depends critically on grade, as well as other factors such as feasibility of complete surgical excision. There is a dichotomy such that five-year survival can be as high as 65 per cent for grades I-II and usually below 10 per cent for grades III-IV.[12] Relative survival decreases with age, as with most other tumour sites.[13] There is little difference in survival between males and females, with females having a marginally higher rate at five years. There has been only a modest increase in five-year survival over recent decades, of about 2 percentage points every five years.

Tumours of the central nervous system are the second most common form of cancer in children aged 0-14 years, constituting group 3 in the International Classification of Childhood Cancer.[14] It should be noted that this group includes some benign tumours such as pituitary adenomas and craniopharyngiomas. However, unlike most other sites, because of their special location, tumours in the brain may prove fatal even if judged to be histologically benign. It is often difficult to differentiate between malignant and benign histology so both are normally registered and included in specialist childhood cancer publications.

Geographical patterns in incidence

Within the countries of the UK and Ireland, the highest rates for incidence were found in Wales where the age-standardised rate for males was 14 per cent higher than the average, and that for females was 17 per cent higher (Figure 4.1). Rates were also higher than average for males in Ireland and South West England, and for both sexes in the South East. Incidence rates were lower than average in London and the West Midlands, and in Eastern England for males only.

At the health authority level there were few areas where incidence rates differed markedly from the average (Figure 4.3. Table B4.1). On the maps (Map 4.1) there were a large number of white areas, where rates were less than 10 per cent different from the average, although the health authority areas that were coloured purple or blue tended to be in small clusters. There were areas of relatively low incidence for both sexes in London, the West Midlands, North West England and the west of Scotland. For males there were clusters of relatively high incidence in Wales, South East and North West England, and the south of Scotland; for females there were clusters in South East, South West and North West England, Wales and Ireland. There was close similarity between males and females in the pattern of areas with relatively low incidence, whereas there was less similarity in the pattern of areas with relatively high incidence.

Geographical patterns in mortality

The geographical pattern of mortality rates did not match closely with that for incidence (Figure 4.2). Mortality rates were highest in Ireland for both males and females, but as the mortality-to-incidence ratios (Table B4.1) were particularly high for this country; this may have been due to the exclusion of death certificate only (DCO) cases. Mortality rates were slightly higher than average in the South East of England, as were incidence rates, and below average in the North West, and in London (females only). The rates were not significantly different from the UK and Ireland average in any of the other countries, or regions of England.

At the health authority level, as with incidence, the mortality rates differed from the overall average in only a handful of areas (Figure 4.4, Table B4.1). As for incidence, health authorities with low mortality were clustered around London and the North West, but the pattern of areas with high mortality was less clear than that for incidence. The map for mortality (Map 4.2) also confirmed the relatively small amount of variability at the health authority level. A striking difference between the incidence and mortality maps was the cluster of areas with particularly high mortality, for both males and females, in Ireland. In males, mortality was 23 per cent higher than average in Ireland, whereas incidence was only 11 per cent higher. As noted earlier, this may relate to the exclusion of cases registered solely from a death certificate.

Risk factors and aetiology

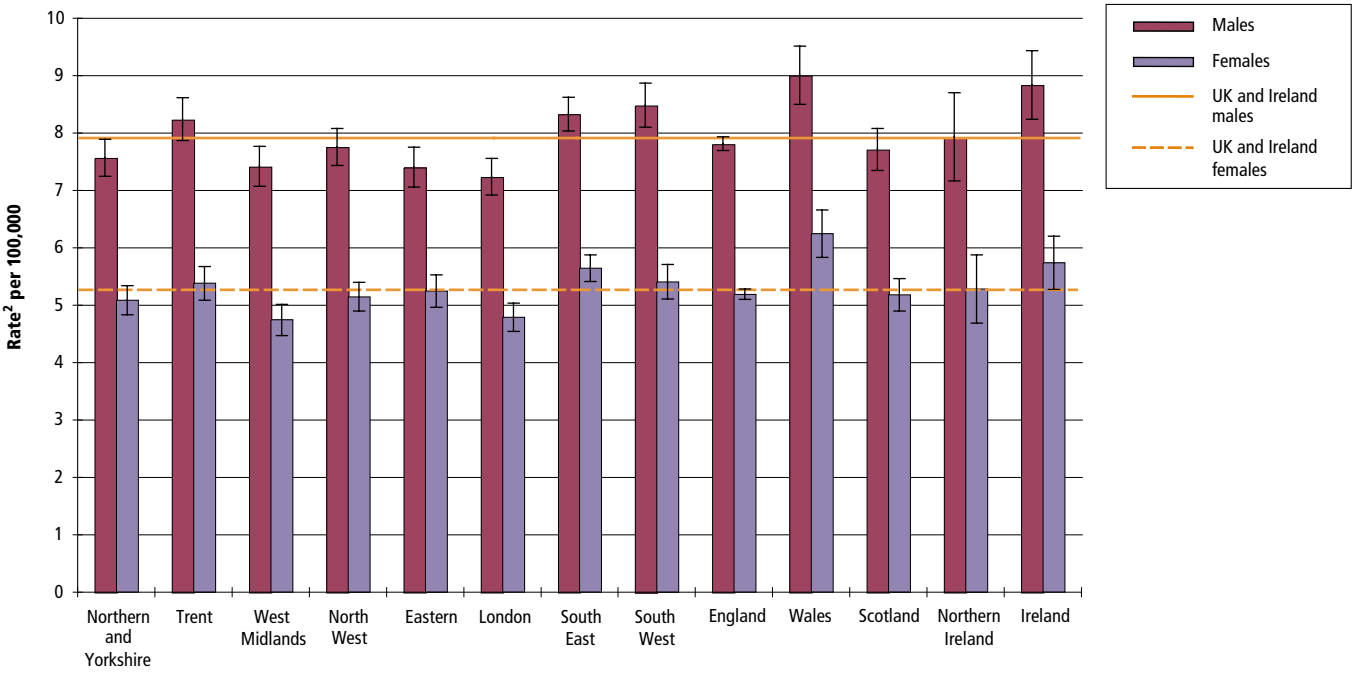
The reported increase in the incidence of brain cancer in all age groups, linked with advances in molecular biology and immunology, has prompted an intensive search for environmental causal factors in recent decades.[15,16] However, there have been few positive findings to date. One problem is that brain cancer comprises a heterogeneous group of diseases, most likely with different aetiologies. There seems to be some evidence emerging for a link between brain cancers and certain infections, possibly mediated through an effect on the immune system.

The only two established causes for primary brain cancer are high-dose ionising radiation and heritable syndromes such as Li-Fraumeni syndrome.

(continued on page 60)

Figure 4.1

Brain: incidence by sex, country, and region of England UK and Ireland 1991-99[1]

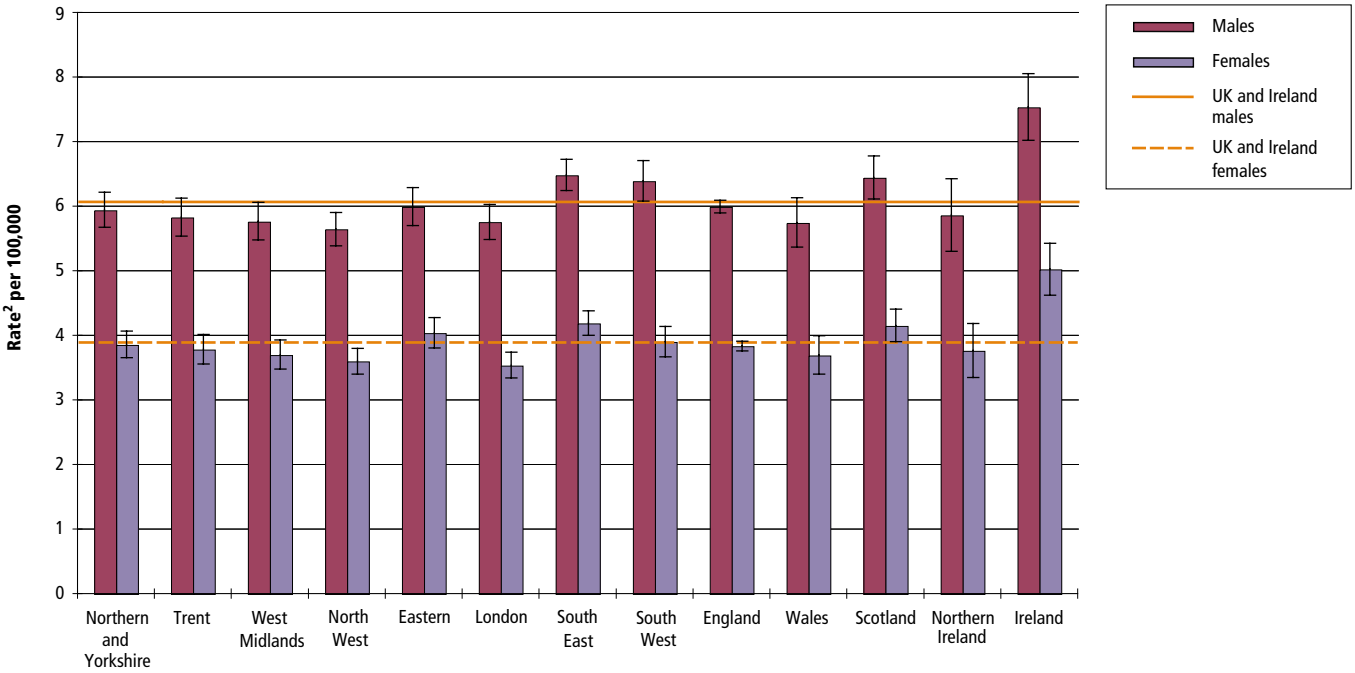


1 Northern Ireland 1993-99, Ireland 1994-99

2 Age standardised using the European standard population, with 95% confidence interval

Figure 4.2

Brain: mortality by sex, country, and region of England UK and Ireland 1991-2000[1]

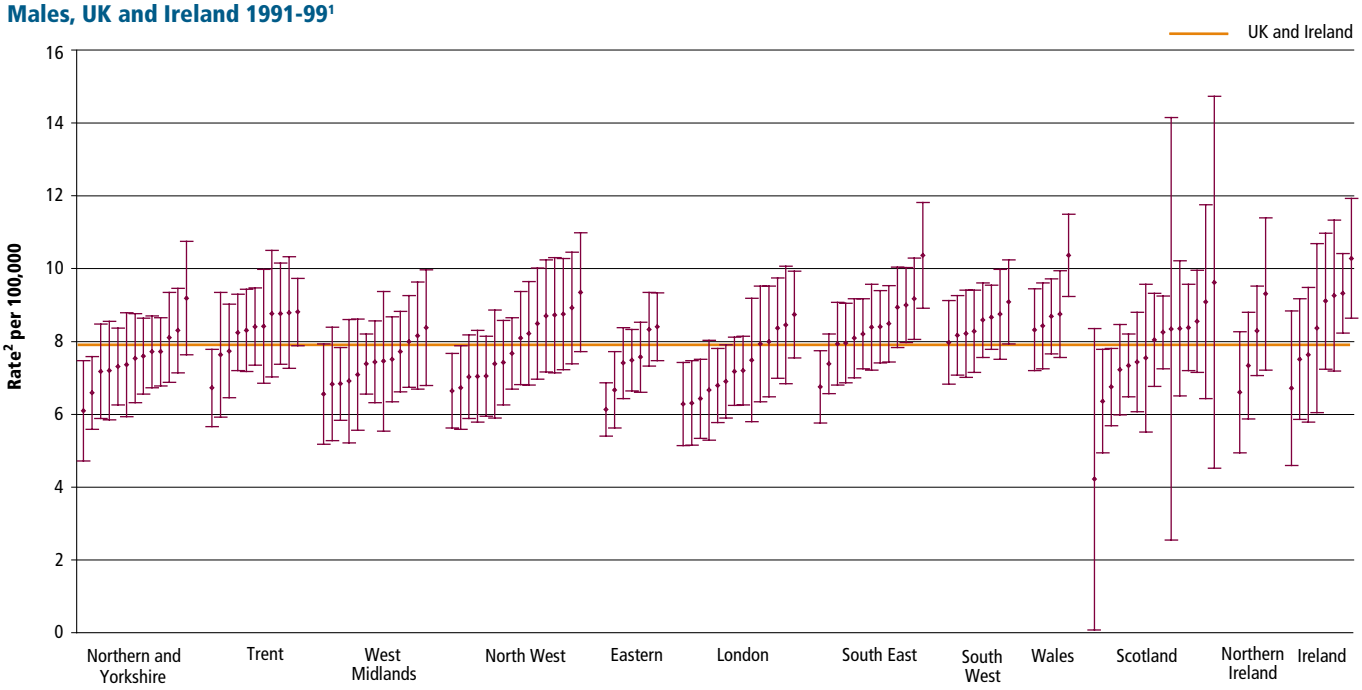


1 Northern Ireland 1991-99, Ireland 1994-2000

2 Age standardised using the European standard population, with 95% confidence interval

Figure 4.3a

Brain: incidence by health authority within country and region of England
Males, UK and Ireland 1991-99[1]

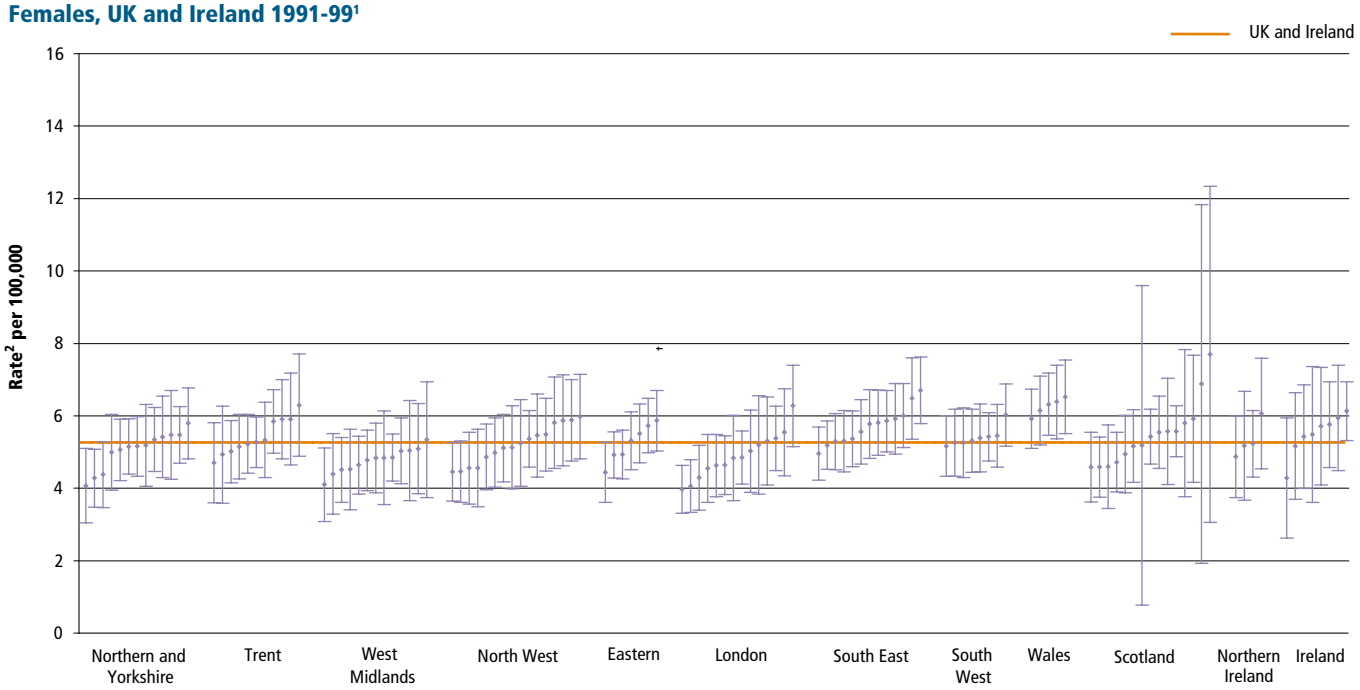


1 Northern Ireland 1993-99, Ireland 1994-99

2 Age standardised using the European standard population, with 95% confidence interval

Figure 4.3b

Brain: incidence by health authority within country, and region of England
Females, UK and Ireland 1991-99[1]

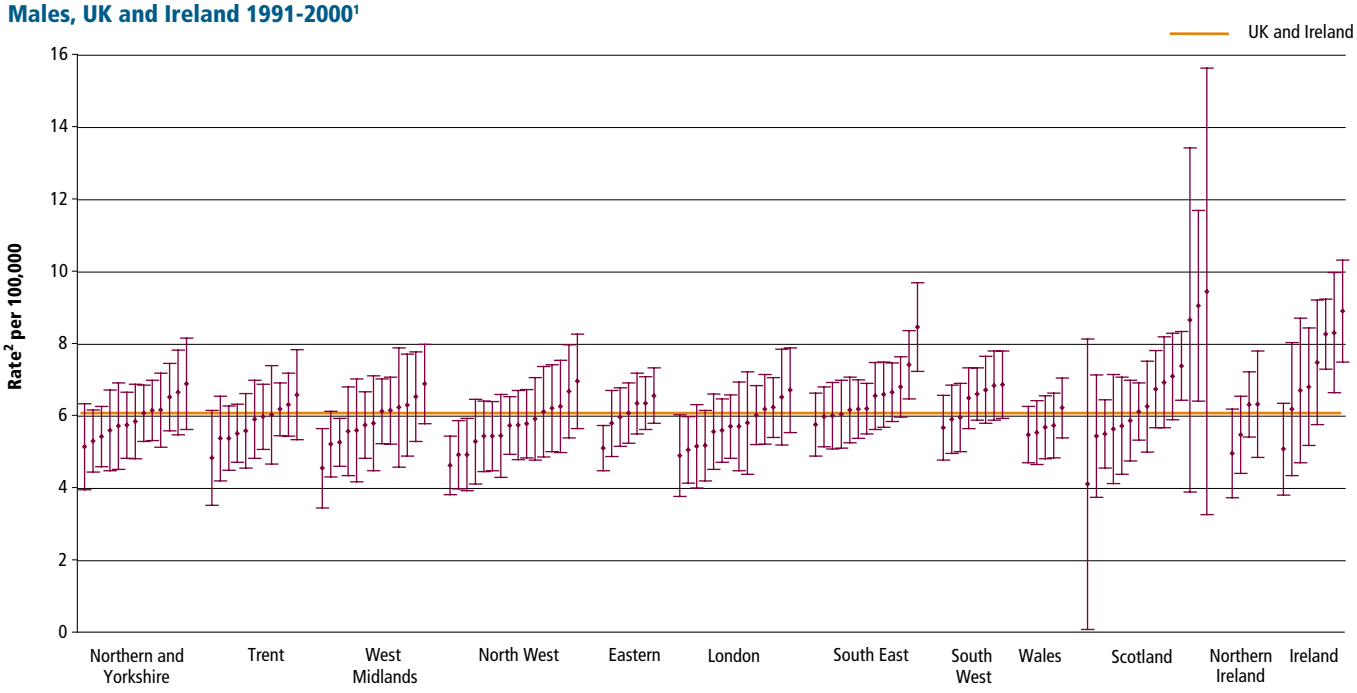


1 Northern Ireland 1993-99, Ireland 1994-99

2 Age standardised using the European standard population, with 95% confidence interval

Figure 4.4a

Brain: mortality by health authority within country and region of England
Males, UK and Ireland 1991-2000[1]

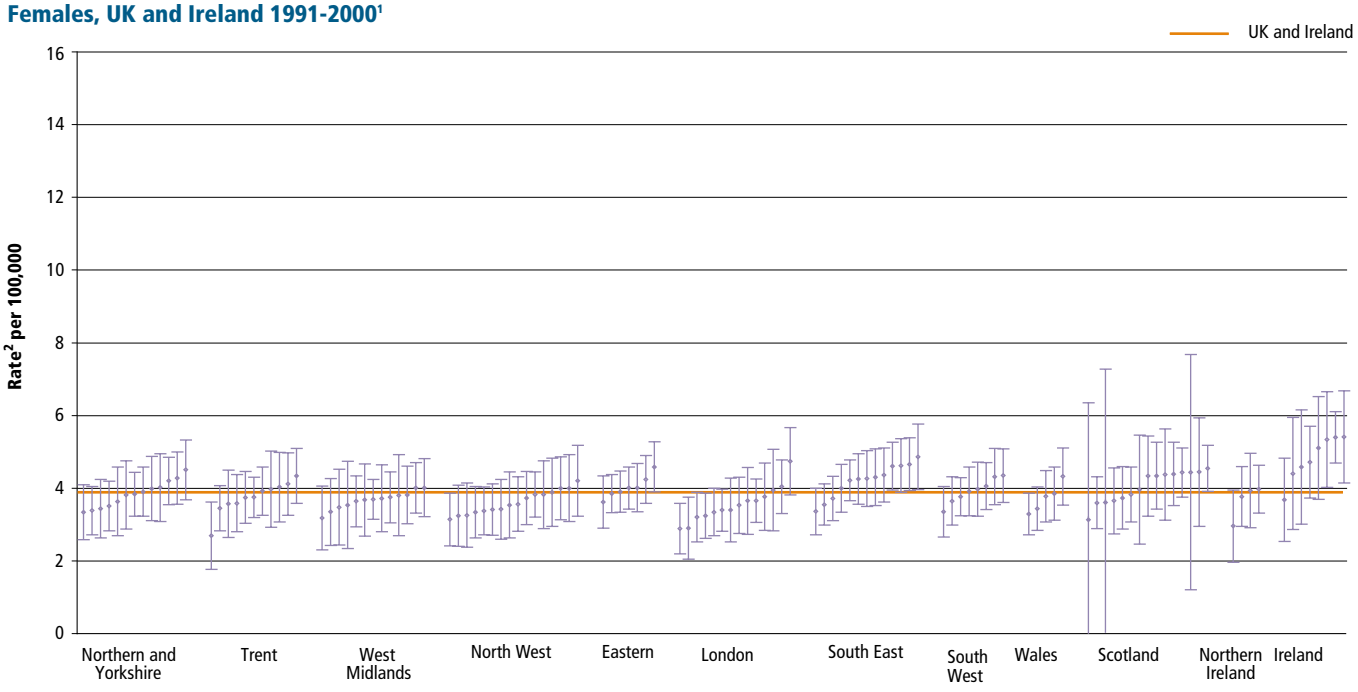


1 Scotland 1991-99, Ireland 1994-2000

2 Age standardised using the European standard population, with 95% confidence interval

Figure 4.4b

Brain: mortality by health authority within country, and region of England
Females, UK and Ireland 1991-2000[1]

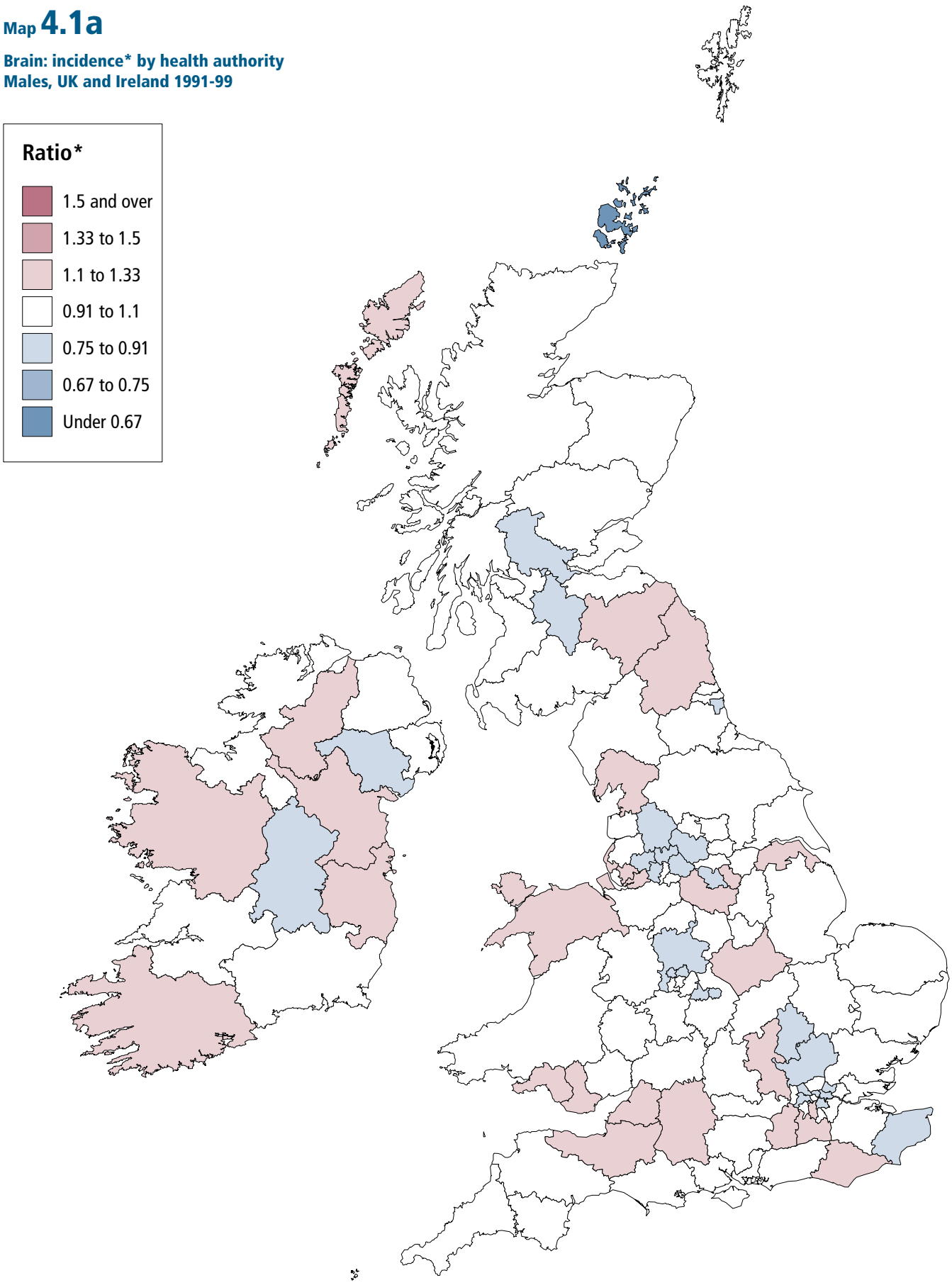


1 Scotland 1991-99, Ireland 1994-2000

2 Age standardised using the European standard population, with 95% confidence interval

Map 4.1a

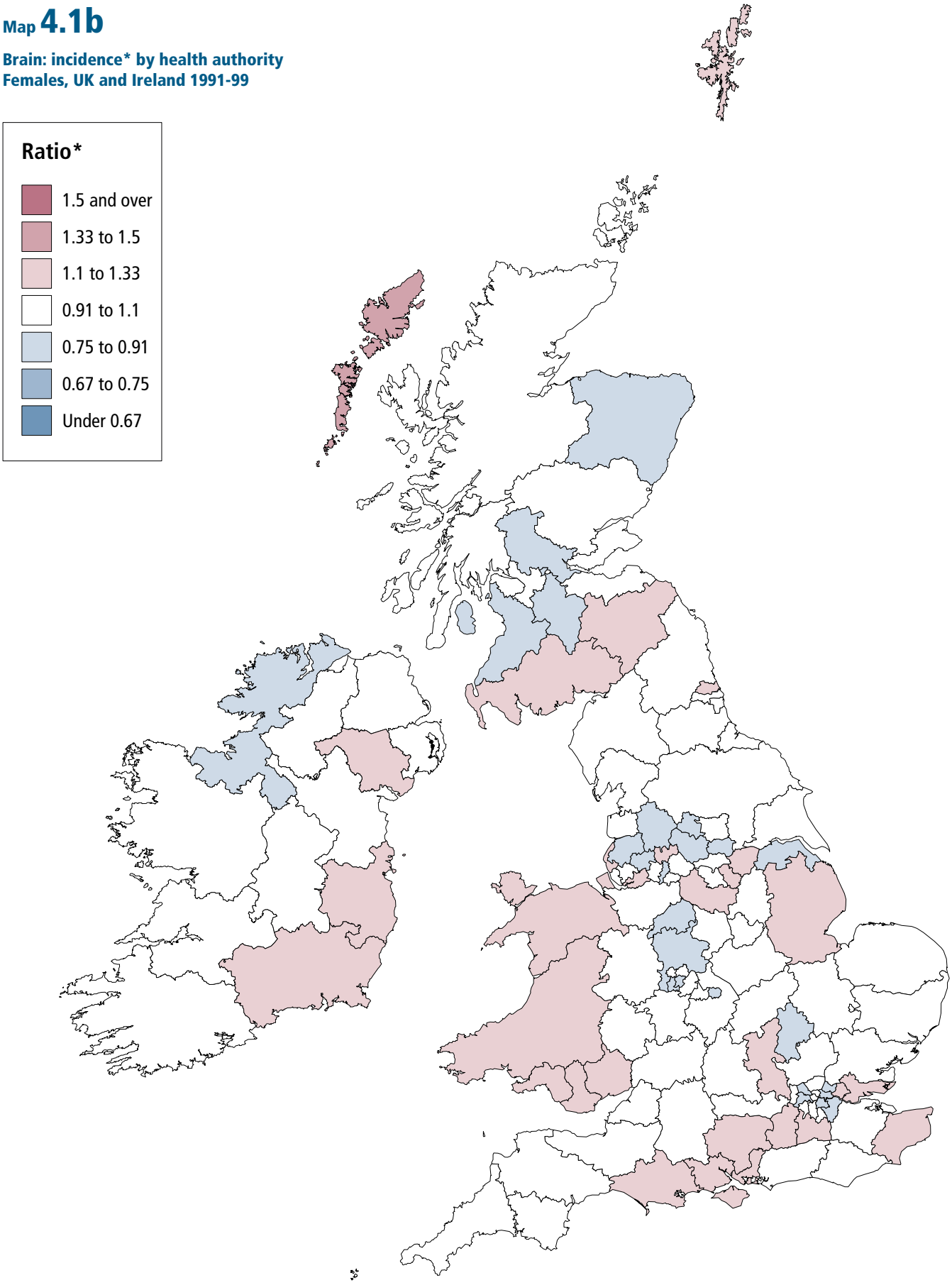
Brain: incidence* by health authority
Males, UK and Ireland 1991-99



Ratio of directly age-standardised rate in health authority to UK and Ireland average

Map 4.1b

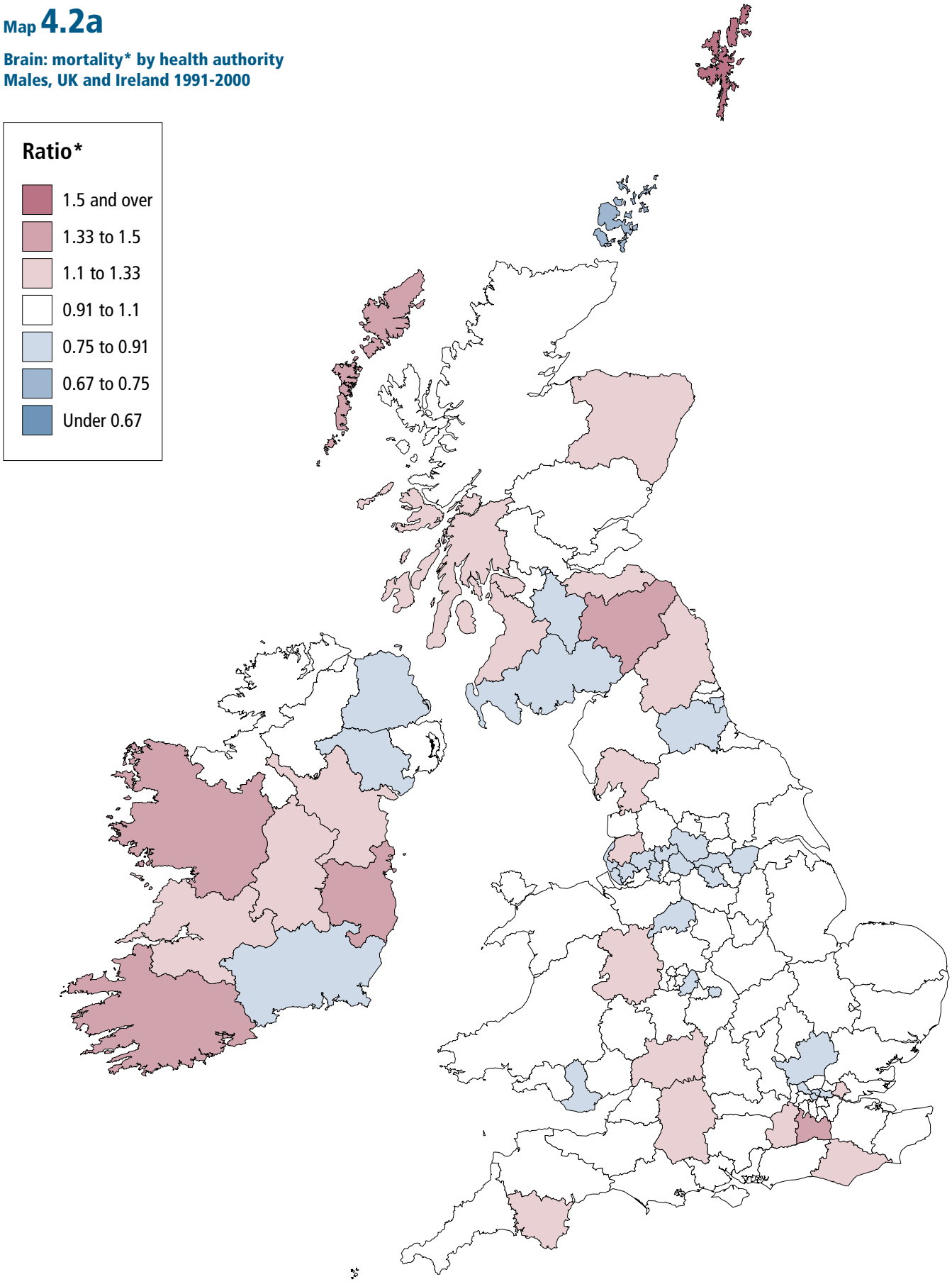
Brain: incidence* by health authority
Females, UK and Ireland 1991-99



Ratio of directly age-standardised rate in health authority to UK and Ireland average

Map 4.2a

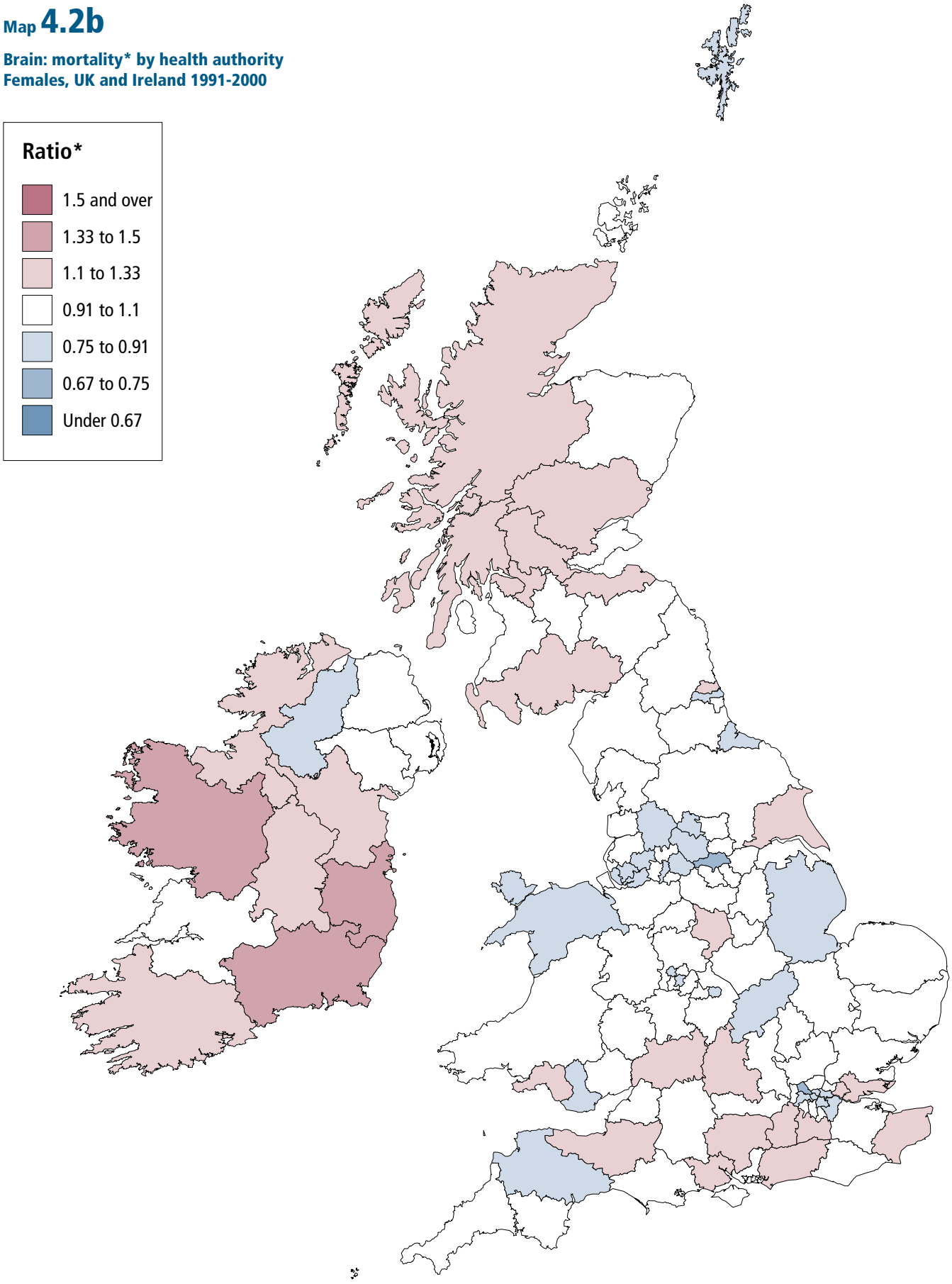
Brain: mortality* by health authority
Males, UK and Ireland 1991-2000



Ratio of directly age-standardised rate in health authority to UK and Ireland average

Map 4.2b

Brain: mortality* by health authority
Females, UK and Ireland 1991-2000



Ratio of directly age-standardised rate in health authority to UK and Ireland average

The link with radiation has been established through studies of children irradiated for medical conditions such as ringworm, thymic enlargement and tonsil hypertrophy, dental X-rays and of atomic bomb survivors. However, the risk estimates are inconsistent and uncertain compared with the evidence relating to other cancers.[16] The relative risk is greater for benign than malignant tumours, and such exposure is rare.

Studies of international variations in incidence show that incidence rates are higher in western Europe, the USA, Australia and Canada, and lower in eastern Europe, Japan and India. Studies of migrants suggest that lifestyle may be important, since incidence in people who have migrated from countries with low rates to countries with high rates is higher than in the country of origin. However, this relationship is confounded by access to diagnostic facilities.[15]

The role of genetics in the aetiology of brain cancer is becoming better understood.[17] People with certain heritable conditions such as von Recklinghausen's neurofibromatosis have an increased risk of developing central nervous system tumours, including astrocytomas.[18] A case-control study of gliomas revealed that a family history of brain cancer was a risk factor but a history of chickenpox or shingles in the previous three years appeared to be protective.[19] To summarise, less than 5 per cent of brain cancer cases can be attributed to inherited syndromes. However, evidence is emerging that genetic factors in the sense of an inherent predisposition to specific environmental factors might eventually explain a greater proportion than this.[20]

Evidence from occupational studies has suggested a higher risk in various groups including agricultural, electrical, petrochemical and rubber workers, and health professionals. In all these studies there is often a misclassification bias in relation to occupational history and even when this is known the exact exposure may be difficult to assess.[16] There is a slight excess in incidence in rural compared to urban areas, which some have linked to the use of pesticides. A New Zealand study showed a raised risk in livestock farmers.[21] Small case-control studies have made tentative links between householders' use of pesticides and brain cancer incidence. Organophosphate can certainly reduce the effectiveness of the immune system.

The occupational associations with petroleum have suggested that exposure to petrochemicals could be a risk factor, and there have been reports of clusters in workers and residents. However, the evidence is weak and inconsistent and no specific carcinogen has been identified. A recent meta-analysis of cohort studies in petroleum workers failed to find an effect.[22] Evidence from animal experiments has suggested other possible carcinogens, but this does not seem to be supported by the available epidemiological evidence on humans.[23]

The higher risk in health professionals seems to be greatest in those involved in diagnostic services and others with potential exposure to radiation such as dental nurses. Electrical workers have high levels of occupational exposure to electromagnetic fields but electromagnetic radiation is non-ionising and therefore in itself not mutagenic. The evidence linking employment as an electrician or utility worker with brain cancer is also weak and inconsistent. However, some recent work has produced evidence for an interaction between electromagnetic fields and chemicals.[24]

In the general population of England and Wales, exposure to power frequency electromagnetic fields (50 Hz) – for example, domestic appliances and wiring – increased 4.5 fold from the 1950s to a peak around 1970, since when levels of exposure seem to have been relatively constant. Mobile phone use (as measured by number of subscribers) rose exponentially from a negligible number in 1985 to about 19 million in 1999. There is at present no strong evidence to link this with the trend of increasing incidence of brain cancer.[25,26]

There have also been studies examining brain cancer incidence in children living close to electrical power lines and a recent review concluded that there is evidence for an effect, but it is probably not causal (there may be higher incidence in children living close to electrical power lines, but this exposure is not the cause of the cancer).[27] There are difficulties in measuring actual electromagnetic field exposure. One large UK population-based case-control study that attempted to do this, failed to find evidence for an effect of exposure on the incidence of brain cancer.[28]

The evidence for lifestyle factors such as tobacco and alcohol consumption having any association with brain cancer incidence is weak and inconsistent. There is weak evidence for a link with diet, particularly N-nitroso compounds (which have also been linked with stomach cancer).[16]

Socio-economic deprivation

In England and Wales, age-standardised incidence and mortality are both slightly higher in more affluent groups.[1] Survival is also slightly higher in affluent groups[13,29] but the possibility cannot be ruled out that these gradients simply reflect access to diagnostic services and lead-time bias. Although there was relatively little geographical variability in either incidence or mortality for cancer of the brain, in England and Wales the weak inverse relationships with deprivation were reflected in slightly lower than average rates in parts of London and former heavily industrialised areas in the midlands and north; the small numbers of areas with higher rates were predominantly rural and/or in the south. Deprivation,

particularly an area-based measure such as the Carstairs index,[30] is of course only a marker for some possible underlying, but unknown, factor(s).

There is no obvious link between the geographical pattern of brain cancer incidence and mortality, as illustrated by the maps (Maps 4.1 and 4.2), and any of the risk factors discussed in the aetiology section.

References

1. Quinn MJ, Babb PJ, Brock A, Kirby L et al. *Cancer Trends in England and Wales 1950-1999.* Studies on Medical and Population Subjects No. 66. London: The Stationery Office, 2001.
2. Swerdlow AJ, dos Santos Silva I, Doll R. *Cancer Incidence and Mortality in England and Wales: Trends and Risk Factors.* Oxford: Oxford University Press, 2001.
3. Legler JM, Ries LA, Smith MA, Warren JL et al. Cancer surveillance series [corrected]: brain and other central nervous system cancers: recent trends in incidence and mortality. *Journal of the National Cancer Institute* 1999; 91: 1382-1390.
4. McKinney PA, Parslow RC, Lane SA, Bailey CC et al. Epidemiology of childhood brain tumours in Yorkshire, UK, 1974-95: geographical distribution and changing patterns of occurrence. *British Journal of Cancer* 1998; 78: 974-979.
5. Smith MA, Freidlin B, Ries LA, Simon R. Trends in reported incidence of primary malignant brain tumors in children in the United States. *Journal of the National Cancer Institute* 1998; 90: 1269-1277.
6. Nishi M, Miyake H, Takeda T, Hatae Y. Epidemiology of childhood brain tumors in Japan. *International Journal of Oncology* 1999; 15: 721-725.
7. ONS. Cancer Survival: England and Wales, 1991-2001. March 2004. Available at *http://www.statistics.gov.uk/statbase/ssdataset.asp?vlnk=7899.*
8. Fitzpatrick D, Gavin A, Middleton R, Catney D. *Cancer in Northern Ireland 1993-2001: A Comprehensive Report.* Belfast: Northern Ireland Cancer Registry, 2004.
9. Black R, Brewster D, Brown H, Fraser L et al. *Trends in Cancer Survival in Scotland 1971-1995.* Edinburgh: Information and Statistics Division, 2000.
10. Sant M, Areleid T, Berrino F, Bielska Lasota M et al. EUROCARE-3: survival of cancer patients diagnosed 1990-1994 - results and commentary. *Annals of Oncology* 2003; 14 Suppl 5: v61-v118.
11. World Health Organisation. *Pathology and Genetics of Tumours of the Central Nervous System.* Lyon: IARC Press, 2000.
12. Souhami R, Tobias J. *Cancer and its Management, fourth edition.* Oxford: Blackwell Science, 2003.
13. Coleman MP, Babb P, Damiecki P, Grosclaude P et al. *Cancer Survival Trends in England and Wales, 1971-1995: Deprivation and NHS Region.* Studies on Medical and Population Subjects No. 61. London: The Stationery Office, 1999.
14. International Agency for Research on Cancer. *International Incidence of Childhood Cancer Volume II.* IARC Scientific Publication No. 144. Lyon: IARC Press, 1999.
15. Preston-Martin S, Mack W. Neoplasms of the Nervous System. In: Schottenfeld D, Fraumeni JF, Jr. (eds) *Cancer Epidemiology and Prevention, second edition.* New York: Oxford University Press, 1996.
16. Savitz D, Trichopoulos D. Brain Cancer. In: Adami HO, Hunter D, Trichopoulos D (eds) *Textbook of Cancer Epidemiology.* Oxford: Oxford University Press, 2002.
17. Preston-Martin S. Epidemiology of primary CNS neoplasms. *Neurologic Clinics* 1996; 14: 273-290.
18. Li FP, Dreyfus MG, Russell TL, Verselis SJ et al. Molecular epidemiology study of a suspected community cluster of childhood cancers. *Medical and Pediatric Oncology* 1997; 28: 243-247.
19. Wrensch M, Lee M, Miike R, Newman B et al. Familial and personal medical history of cancer and nervous system conditions among adults with glioma and controls. *American Journal of Epidemiology* 1997; 145: 581-593.
20. Malmer B, Iselius L, Holmberg E, Collins A et al. Genetic epidemiology of glioma. *British Journal of Cancer* 2001; 84: 429-434.
21. Reif JS, Pearce N, Fraser J. Occupational risks for brain cancer: a New Zealand Cancer Registry-based study. *Journal of Occupational Medicine* 1989; 31: 863-867.
22. Wong O, Raabe GK. A critical review of cancer epidemiology in the petroleum industry, with a meta-analysis of a combined database of more than 350,000 workers. *Regulatory Toxicology Pharmacology* 2000; 32: 78-98.
23. Collins JJ, Strother DE. CNS tumors and exposure to acrylonitrile: inconsistency between experimental and epidemiology studies. *Neuro-Oncology* 1999; 1: 221-230.
24. Navas-Acien A, Pollan M, Gustavsson P, Floderus B et al. Interactive effect of chemical substances and occupational electromagnetic field exposure on the risk of gliomas and meningiomas in Swedish men. *Cancer Epidemiology Biomarkers and Prevention* 2002; 11: 1678-1683.
25. Cook A, Woodward A, Pearce N, Marshall C. Cellular telephone use and time trends for brain, head and neck tumours. *New Zealand Medical Journal* 2003; 116: U457.
26. Lonn S, Ahlbom A, Hall P, Feychting M. Mobile phone use and the risk of acoustic neuroma. *Epidemiology* 2004; 15: 653-659.
27. Ahlbom IC, Cardis E, Green A, Linet M et al. Review of the epidemiologic literature on EMF and Health. *Environmental Health Perspectives* 2001; 109 Suppl 6: 911-933.
28. Skinner J, Mee TJ, Blackwell RP, Maslanyj MP et al. Exposure to power frequency electric fields and the risk of childhood cancer in the UK. *British Journal of Cancer* 2002; 87: 1257-1266.
29. Coleman MP, Rachet B, Woods LM, Mitry E et al. Trends and socioeconomic inequalities in cancer survival in England and Wales up to 2001. *British Journal of Cancer* 2004; 90: 1367-1373.
30. Carstairs V, Morris R. Deprivation and mortality: an alternative to social class? *Community Medicine* 1989; 11: 213-219.