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Risk of benign tumours of nervous system, and of malignant neoplasms, in people with neurofibromatosis: population-based record-linkage study

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Background: The neurofibromatoses (NF) are genetic disorders. Increased risks of some cancers in people with NF are well recognised, but there is no comprehensive enumeration of the risks across the whole range of site-specific cancers. Our aim was to provide this.

Methods: A linked data set of hospital admissions and deaths in England was used to compare rates of tumours in an NF cohort with rates in a comparison cohort, with results expressed as rate ratios (RR).

Results: The RR for all cancers combined, in people with both types of NF combined, was 4.3 (95% confidence interval (CI): 4.0–4.6), based on 769 cases of cancer in 8003 people with NF. Considering only people with presumed NF1 (as defined in the main article), the RR for all cancers excluding nervous system malignancies remained elevated (2.7, 95% CI: 2.4–2.9); and risks were significantly high for cancer of the oesophagus (3.3), stomach (2.8), colon (2.0), liver (3.8), lung (3.0), bone (19.6), thyroid (4.9), malignant melanoma (3.6), non-Hodgkin's lymphoma (3.3), chronic myeloid leukaemia (6.7), female breast (2.3) and ovary (3.7).

Conclusion: Neurofibromatosis was associated with an increased risk of many individual cancers. The relationships between NF and cancers may hold clues to mechanisms of carcinogenesis more generally.

Neurofibromatosis type 1 (NF1) and neurofibromatosis type 2 (NF2) are inherited, autosomal-dominant, tumour predisposition syndromes (Ferner *et al*, 2007). Neurofibromatosis type 1 is the more common, with a prevalence in the United Kingdom of about 1 in 4560 people. Neurofibromatosis type 2 is a relatively rare disorder affecting about 1 in 56 160 people (Evans *et al*, 2010). Neurofibromatosis type 1 and NF2 have distinct genetic characteristics, and each disease is associated with mutations in a different gene. Neurofibromatosis type 1 is caused by mutation on chromosome 17q11.2 (Viskochil *et al*, 1990; Wallace *et al*, 1990). This genetic abnormality affects synthesis of a tumour suppressor protein, neurofibromin, which in unaffected individuals is expressed in high levels in the nervous system. Its deficit is associated with the development of both benign and malignant tumours (Johannessen *et al*, 2005, 2008; Jouhilahti *et al*, 2011). Each of the two diseases has its distinct pathogenesis, clinical features and prognosis, although the current 10th revision of the International Classification of Diseases (ICD) does not distinguish between them (World Health Organisation, 1992).

Patients with NF are at increased risk of neoplasia of several types (Zöller *et al*, 1995; Rasmussen *et al*, 2001; Walker *et al*, 2006; Evans *et al*, 2011). The majority of NF1 patients develop benign cutaneous neurofibromas (Ferner, 2010), and there is also an elevated risk of malignant peripheral nerve sheath tumours and

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connective tissue malignancies (Evans *et al*, 2002, 2011; Walker *et al*, 2006). Well-documented neoplastic risks in people with NF2 are largely those of benign vestibular schwannomas or meningiomas (Ferner *et al*, 2004; Ferner, 2010). There are data suggesting increased risks of other cancers, including breast cancer and leukaemia, among patients with NF1 (Stiller *et al*, 1994; Sharif *et al*, 2007). The possibility that NF may be associated with an increased risk of other malignant neoplasms, in addition to the already recognised NF-associated cancers mentioned above, is not well documented.

Because of the known tumour-prone nature of NF, it is important to have comprehensive estimates for the risk of different individual malignant neoplasms, both for documented and for hitherto undocumented tumour risks. This is important, both to understand prognosis and risk in people with NF and to boost further research into the relationship between NF and neoplasia.

Our aim was to quantify the risk in people with NF of neoplasms of the nervous system, and of malignant tumours outside the nervous system, systematically across the whole range of cancer sites and types. We analysed data on hospitalisation of people with NF, in the whole of England from 1999 to 2011, and their risk of cancer.

MATERIALS AND METHODS

Populations and data sets. We used a linked English national data set of hospital admissions (Hospital Episode Statistics (HES)) and mortality. Hospital Episode Statistics comprises routinely collected administrative data on all hospital admissions and day cases in all NHS hospitals in England, with brief statistical records for every admission. The HES data were provided by the NHS Information Centre, and the mortality data were derived from death registration data provided by the Office for National Statistics. All records of hospitalisation for each individual person, and the individual's death record in the event of death, were linked together as a single record of cumulative events for each person. The linkage was undertaken by the Oxford Record Linkage group (Gill and Goldacre, 2003). The data set spanned 1 January 1999 to 28 February 2011.

Construction of cohorts. The 'exposure' cohort of people with NF was constructed by identifying the first hospitalisation or day case care for NF in the linked data set. We defined NF as code Q 85.0 (termed 'Neurofibromatosis') in the 10th revision of ICD. The coding system used in England does not distinguish between NF1 and NF2. We made the assumption that people with any record of schwannoma, meningioma, acoustic neuroma and sensorineural deafness had NF2 and defined a second cohort excluding them.

We constructed a reference cohort, comprising people hospitalised with a range of mainly minor medical conditions, a range of surgical procedures and a range of injuries (see footnote to Table 1). These conditions and operations, both individually and in combination, were selected as conditions that were considered very unlikely to be associated with either an atypically high or low risk of cancers. We also have experience in using the reference cohort in other studies of cancer risk in people with non-malignant chronic conditions and know that they do not give atypical values (Goldacre *et al*, 2007, 2009; Fois *et al*, 2010). We included all eligible patients in the reference cohort. We stratified patients in the exposure and reference cohorts by age, sex, region of residence, calendar year of first hospitalisation and Index of Multiple Deprivation (a standard English metric for socioeconomic status, analysed by us in quintiles). All calculations of expected and observed cancers (see below) were undertaken within these strata (i.e., they were based on people who were the same, in respect of age group, gender, etc) and were then summed across strata to give overall expected and observed cases of each cancer.

The data set was searched for any subsequent hospital admission for, or death from, malignant neoplasms. We used the ICD-10 codes C00–C75, C80–C97 for all cancers, and their equivalents in ICD-9. We estimated the risk of malignant neoplasm for every type of cancer, and the risk of benign tumours of nervous system, at the three-digit level in the ICD. We excluded those patients who had a record of cancer before their first recorded admission for NF (468 cases), and we excluded people with a first record of NF on the same admission record as a cancer (833 cases). We did this to avoid surveillance bias, since cancer could have been diagnosed as a result of admission for NF, or, alternatively, NF could have been recorded because the patient needed care for cancer.

We repeated all analyses on the cohort of presumed NF1 cases only.

Statistical methods. Separate analyses were done for each cancer as described using the example of malignant brain tumour. Rates of malignant brain tumour were calculated based on person years. The 'date of entry' into the NF cohort, or the reference cohort, was the date of first admission for NF, or the reference condition. The 'date of exit' was the date of subsequent admission for malignant brain tumour (if any occurred), or death, or the end of the data file (28 February 2011), whichever was the earliest. Patients were censored from further follow-up on the exact day of first admission for malignant brain tumour or death.

We used the indirect method of standardisation, taking the combined NF and reference cohorts as the standard population. The stratum-specific rates in the standard population were applied first to the NF cohort, and then, separately, to the reference cohort, in order to obtain the 'expected' number of cases of cancers in each individual cohort based on the stratum-specific rates in the two cohorts combined. The ratio of the standardised rate of occurrence of malignant brain tumour in the NF cohort was calculated relative to that in the reference cohort using the formula $(O^{NF}/E^{NF})/(O^{ref}/E^{ref})$, where O is the observed and E is the expected number of cases of malignant brain tumour in each cohort. This follows the methods described in detail by us elsewhere (Fois *et al*, 2010), and by Breslow and Day (1987). The analysis was done using a suite of programs developed 'in house' using SAS 9 software (SAS Institute, Cary, NC, USA).

RESULTS

There were 8003 people hospitalised with NF over the study period. There were 6739 people in the cohort of presumed NF1. Their age and sex distributions are given in Supplementary Appendix 1 and 2 (online only), which also show the ratio of the number of people in the reference cohort per person in the NF cohort. There were generally about 1000 people in the reference cohort for each person in each 5-year age stratum in the NF cohort, that is, there were ample numbers to ensure adequate stratification and standardisation.

The rate ratio (RR) of cancers in the total NF cohort relative to the reference cohort was 4.3 (95% confidence interval (95% CI): 4.0–4.6), based on 769 observed cases in the NF cohort. In the cohort of people with presumed NF1, that is, after excluding all patients with schwannomas, meningiomas, acoustic neuromas and sensorineural deafness, the RR remained elevated at 4.0 (95% CI: 3.7–4.3, based on 697 observed cases).

The RRs for individual malignant and benign neoplasms of the nervous system in the whole NF cohort, and in the NF1 cohort, are shown in Table 1. The RRs of hospital admission for malignant

Table 1. Risk of all cancers combined, and of malignant and benign neoplasms of nervous system, in patients with neurofibromatosis (all NF) and neurofibromatosis type 1 (NF1): observed (O) and expected (E) number of each cancer, ratio of rate[a] (RR) in the NF and NF1 cohort to that in the reference cohort[b], and 95% confidence intervals (95% CI) with *P*-value

	All NF				NF1			
Cancers (ICD codes)[c]	***O***	***E***	**RR (95% CI)**	***P*-value**	***O***	***E***	**RR (95% CI)**	***P*-value**
All cancers (C00–C75, C81–C97)	769	178.4	4.3 (4.0–4.6)	<0.001	697	174.2	4.0 (3.7–4.3)	<0.001
All cancers, excluding nervous system and brain (C00–C46, C48–C68, C73–C75, C81–C97)	489	180.6	2.7 (2.5–3.0)	<0.001	459	174.9	2.7 (2.4–2.9)	<0.001
Malignant neoplasm								
Peripheral nerves (C47)	231	0.5	1047 (858–1280)	<0.001	204	0.3	1394 (1133–1716)	<0.001
Meninges (C70)	6	0.1	50.1 (18.3–110.5)	<0.001	0			
Brain (C71)	164	4.0	41.8 (35.5–48.8)	<0.001	134	3.6	37.9 (31.7–45.0)	<0.001
Spinal cord, cranial nerves and other parts of central nervous system (C72)	136	0.6	332 (271–405)	<0.001	105	0.4	377 (300–471)	<0.001
Eye and eye adnexa (C69)	14	0.7	21.5 (11.7–36.2)	<0.001	11	0.6	20.0 (9.7–35.2)	<0.001
Benign neoplasm								
Meninges (D32)	73	2.4	31.0 (24.2–39.0)	<0.001	0			
Brain, central nervous system, spinal cord (D33)	158	1.6	105 (89–123)	<0.001	20	0.5	42.7 (26.0–66.4)	<0.001
Eye and eye adnexa (D31)	16	0.9	18.1 (10.3–29.5)	<0.001	11	0.9	11.9 (5.9–21.3)	<0.001

Abbreviation: ICD = International Classification of Diseases.

[a]Adjusted for age in 5-year bands, time period in single calendar years, region of residence and deprivation score associated with patients' area of residence, in quintiles.

[b]Conditions used in reference cohort, with Office of Population, Censuses and Surveys (OPCS) code edition 4 for operations and ICD-10 code for diagnosis (with equivalent codes used for other coding editions): appendectomy (OPCS4 H01–H03), adenoidectomy (E20), dilation and curettage (Q10–Q11), hip replacement (W37–W39), knee replacement (W40–W42), squint (ICD-10 H49–H51),cataract (H25), otitis (H60–H67), upper respiratory tract infections (J00–J06), varicose veins (I83), haemorrhoids (I84), deflected septum, nasal polyp (J33 + J34.2), impacted tooth and other disorders of teeth (K00–K03), inguinal hernia (K40), head injury (S06), in-growing nail, toenail and other diseases of nail (L60), contraceptive management (Z30), internal derangement of knee (M23), bunion (727.1), dislocations, sprains and strains (S03, S13, S23, S33, S43, S53, S63, S73, S83, S93), selected limb fractures (S42, S52, S62, S82, S92), superficial injury and contusion (S00, S10, S20, S30, S40, S50, S60, S70, S80, S90). From analyses of colorectal cancers, we excluded appendectomy, haemorrhoids and inguinal hernia from the reference cohort. From analysis of uterine cancer we excluded dilation and curettage.

[c]ICD-10 codes for each cancer.

and benign neoplasm of peripheral nerves, spinal cord, cranial nerves, central nervous system and eye were very high. Table 2 shows the data for individual malignant tumours in the NF1 cohort. For most, the RRs were very similar in the NF1 and the total NF cohort (for the latter, see Supplementary Appendix 3). Of the other tumours, risks were very high for cancers of the 'heart mediastinum and pleura', 'retroperitoneum and peritoneum', 'bone and cartilage', 'connective and other soft tissue', small intestine and adrenal gland (Table 2). These are all cancers that are very uncommon in the general population and the ICD coding structure is such that their precise nature cannot be identified from the coding, except that all cases of adrenal cancer were cancers of the adrenal medulla. Considering cancers that are more common in the general population, and the NF1 cohort, we found significantly elevated risks for cancers of the oesophagus (RR: 3.3; see Table 2 for CIs), stomach (2.8), colon (2.0), liver (3.8), biliary tract (8.2), pancreas (3.4), lung and bronchus (3.0), malignant melanoma (3.6), non-melanoma skin cancer (1.6), thyroid gland (4.9), female breast (2.3), ovarian cancers (3.7) and several others (Table 2). There were elevations of risk of haematological cancers, notably diffuse non-Hodgkin's lymphoma (RR: 3.3), other and unspecified non-Hodgkin's lymphoma (2.3), lymphoid leukaemia (2.5), acute (4.2) and chronic myeloid leukaemia (6.7). Some of these cancers were identified from a subsequent hospital admission that was fairly close in time after the admission for NF; others were first identified more than a year after the NF admission (Supplementary Appendix 3).

Additionally, we estimated RRs for breast cancer in women aged under 50 years (i.e., younger than the age at which women in England are routinely invited for mammographic screening) and 50 plus. Younger women with NF had a high risk of breast cancer at RR 3.6 (95% CI: 2.5–5.0, based on 34 observed cases). In women aged ≥50, RR was 1.5 (95% CI: 1–2.2) based on 24 cases. After excluding the first year following hospital admission for NF, the risk remained high (RR: 3.3, 2.2–4.8) in younger women, but not in those aged 50 and older.

DISCUSSION

Principal findings. We have systematically documented and quantified the risk of each individual malignant neoplasm at the three-digit level of the ICD in patients hospitalised with NF in a large defined population. Over the 13-year period, with mean follow-up ~6 years, 697 out of 6739 patients with NF1 (10.3%) developed subsequent neoplasms. As expected, the highest rates, compared with rates in the reference population, were for tumours of the nervous system, brain and eye. Overall, there was a four-fold increase in risk of tumours. After excluding the well-known risks of the nervous system tumours, the RR remained high at 2.7. Some of the highest RRs, besides those relating to nervous system sites, were in relation to cancers that are very uncommon in the general population. We cannot interpret this finding; but it may signify that the mechanisms that generally protect against these cancers need a very specific set of circumstances (e.g., a genetic disorder like NF) to affect them. We also found that many common cancers have an elevated risk, with RRs of around two to four, in people with NF.

Limitations of the study. An important limitation is that there are no separate codes for NF type 1 and type 2 in the version of ICD used in English medical coding. We contacted the two English national data custodians, the NHS Information Centre for hospital statistics, and the Office for National Statistics for mortality statistics, to ask if they have unofficial codes (i.e., beyond the standard ICD codes) to distinguish the two types of NF. Both

Table 2. Risk of malignant neoplasm in patients with neurofibromatosis type 1 compared with the reference cohort[b], number of each observed (O) and expected (E) cancer, ratio of rate[a] (RR) with 95% confidence intervals (95% CI) and *P*-values

	All years				Excluding first year			
Cancers (ICD-10 codes[c])	***O***	***E***	**RR (95% CI)**	***P*-value**	***O***	***E***	**RR (95% CI)**	***P*-value**
Oesophagus (C15)	18	5.4	3.3 (2.0–5.3)	<0.001	12	4.5	2.7 (1.4–4.7)	0.001
Stomach (C16)	13	4.7	2.8 (1.5–4.7)	<0.001	7	3.8	1.8 (0.7–3.8)	0.174
Small intestine (C17)	12	0.8	14.5 (7.5–25.3)	<0.001	6	0.7	9.2 (3.4–20.0)	<0.001
Colon (C18)	26	13.2	2.0 (1.3–2.9)	0.001	14	11.0	1.3 (0.7–2.1)	0.446
Rectosigmoid junction (C19)	7	2.9	2.4 (1.0–4.8)	0.042	[d]			
Rectum (C20)	9	6.4	1.4 (0.6–2.7)	0.434	8	5.3	1.5 (0.7–3.0)	0.340
Liver (C22)	10	2.7	3.8 (1.8–6.8)	<0.001	7	2.2	3.1 (1.3–6.5)	0.004
Unspecified malignancies of biliary tract (C24)	5	0.6	8.2 (2.7–19.3)	<0.001	[d]			
Pancreas (C25)	16	4.7	3.4 (2.0–5.6)	<0.001	8	3.8	2.0 (0.9–4.1)	0.062
Other digestive organs (C26)	10	2.1	4.8 (2.3– 8.8)	<0.001	8	1.7	4.7 (2.0–9.3)	<0.001
Lung/bronchus (C34)	66	21.4	3.0 (2.4–3.9)	<0.001	39	17.2	2.3 (1.6–3.1)	<0.001
Heart, mediastinum and pleura (C38)	7	0.4	19.0 (7.6–40.0)	<0.001	5	0.3	16.6 (5.4–39.0)	<0.001
Retroperitoneum and peritoneum (C48)	10	0.7	14.5 (6.9–26.6)	<0.001	[d]			
Malignant skin melanoma (C43)	19	5.3	3.6 (2.2–5.6)	<0.001	12	4.3	2.8 (1.5–4.9)	<0.001
Non-melanoma skin cancer (C44)	53	34.0	1.6 (1.2–2.0)	0.002	43	27.9	1.5 (1.1–2.1)	0.006
Bone and cartilage of limbs (C40)	5	0.3	15.6 (5.1–36.7)	<0.001	5	0.2	23.1 (7.5–54.5)	<0.001
Bone and cartilage of other sites (C41)	17	0.9	19.6 (11.4–31.5)	<0.001	7	0.6	11.3 (4.5–23.4)	<0.001
Other connective and soft tissue (C49)	65	1.6	42.1 (32.4–53.8)	<0.001	28	1.2	23.8 (15.8–34.5)	<0.001
Thyroid gland (C73)	7	1.4	4.9 (2.0–10.2)	<0.001	6	1.2	5.1 (1.9–11.1)	<0.001
Adrenal gland (medulla) (C74.1)	12	0.1	304 (148–572)	<0.001	6	0.1	192 (67–451)	<0.001
Diffuse non-Hodgkin's lymphoma (C83)	11	3.3	3.3 (1.7–6.0)	<0.001	[d]			
Unspecified non-Hodgkins lymphomas (C84)	14	6.2	2.3 (1.2–3.8)	0.004	7	4.6	1.5 (0.6–3.2)	0.361
Multiple myeloma (C90)	7	2.9	2.4 (1.0–4.9)	0.036	[d]			
Lymphoid leukaemia (C91)	9	3.6	2.5 (1.1–4.6)	0.011	5	2.4	2.1 (0.7–4.9)	0.172
Acute myeloid leukaemia (C92.0)	8	1.9	4.2 (1.8–8.2)	<0.001	6	1.5	4.0 (1.5–8.6)	0.001
Chronic myeloid leukaemia (C92.1)	5	0.7	6.7 (2.2–15.8)	<0.001	[d]			
Breast (women) (C50)	58	25.7	2.3 (1.7–2.9)	<0.001	43	20.9	2.1 (1.5–2.8)	<0.001
Body of uterus (C54)	5	4.9	1.0 (0.3–2.4)	0.867	[d]			0.679
Ovary (C56)	14	3.8	3.7 (2.0–6.2)	<0.001	10	3.0	3.3 (1.6–6.1)	<0.001
Prostate (C61)	17	23.1	0.7 (0.4–1.2)	0.247	14	17.7	0.8 (0.4–1.3)	0.444

Abbreviation: ICD = International Classification of Diseases.

[a]Adjusted for age in 5-year bands, time period in single calendar years, region of residence and deprivation score associated with patients' area of residence, in quintiles.

[b]Conditions used in reference cohort, with Office of Population, Censuses and Surveys (OPCS) code edition 4 for operations and ICD-10 code for diagnosis (with equivalent codes used for other coding editions): appendectomy (OPCS4 H01–H03), adenoidectomy (E20), dilation and curettage (Q10–Q11), hip replacement (W37–W39), knee replacement (W40–W42), squint (ICD-10 H49–H51),cataract (H25), otitis (H60–H67), upper respiratory tract infections (J00–J06), varicose veins (I83), haemorrhoids (I84), deflected septum, nasal polyp (J33 + J34.2), impacted tooth and other disorders of teeth (K00–K03), inguinal hernia (K40), head injury (S06), in-growing nail, toenail and other diseases of nail (L60), contraceptive management (Z30), internal derangement of knee (M23), bunion (727.1), dislocations, sprains and strains (S03, S13, S23, S33, S43, S53, S63, S73, S83, S93), selected limb fractures (S42, S52, S62, S82, S92), superficial injury and contusion (S00, S10, S20, S30, S40, S50, S60, S70, S80, S90). From analyses of colorectal cancers, we excluded appendectomy, haemorrhoids and inguinal hernia from the reference cohort. From analysis of uterine cancer we excluded dilation and curettage.

[c]ICD-10 codes for each cancer.

[d]Data are not shown for fewer than five observed cases.

confirmed that they did not; and both confirmed that we were the first to raise this with them. The Office for National Statistics offered to review some of its death certificates that included NF. It reported that, on the majority of them, the type of NF had not been provided by the certifying doctor. Thus, the issue in routine medical information systems is not just one of ICD coding; it is one of encouraging certifying clinicians to record the type of NF. It is likely that other studies of NF, using routine data systems, have encountered similar issues. We made an attempt to restrict a subset of the NF cohort to just those people with NF1. We did so by excluding people with schwannomas, meningiomas, acoustic neuromas and sensorineural deafness, which are clinical features of NF2. They were identified by record linkage to all the individuals' records before, during and after the first admission for NF. This may not have identified all people who should have been excluded: some may have had admissions for these exclusion conditions before or after the timespan covered by the record-linkage study. Accordingly, and also because others may not be able to distinguish types 1 and 2 in their own studies, for the record we give the full data on all NF in Supplementary Appendix 3. We advocate that concerns about the recording and coding of NF1 and NF2 should be raised with clinicians treating NF patients

(to record the type) and with organisations that manage national statistics (to code the two types separately).

We can partially address the question of whether we are likely to have identified a majority of patients with NF in England through the hospitalisation data. At a prevalence of 1 in 4560 in a population of 50 million, there would be about 10 965 people with NF1; we identified 6739 people in the NF cohort, and a further 1301 before or at the same time as entry to the NF cohort, that is, about 73% of the likely total in England. The great majority of people with cancer are likely to be admitted and so reliance on hospitalisation and death should not miss many cases of the 'outcome' diseases. Although it is possible that some cases of NF were misdiagnosed, for example with lypomatosis or shwannomatosis, it is unlikely that the proportion misdiagnosed was big enough to affect the results materially. Our analysis is based on information recorded in hospital settings and the majority of diagnoses, if not all, would have been made by clinical specialists. Diagnostic coding in routine hospital statistics in England is generally accurate (Burns *et al*, 2011) and it is likely that the majority of common malignant tumours were accurately recorded. However, some misclassification is possible for less common tumours: for example, some cases of retroperitoneal malignancies or submucosal small bowel tumours might in fact have been malignant peripheral nerve sheath tumours.

We studied a large number of associations between diseases. The effect of making multiple comparisons should be considered. It is possible that some of the associations that are significant at conventional levels of significance may result from making multiple comparisons and the play of chance, but where the *P*-value is 0.001 or lower as seen in Tables 1 and 2, it is unlikely to be attributable to chance alone.

A further limitation is that the NF cases are prevalent, not incident, cases. We do not have the individuals' full history; and someone whose first admission for NF, as recorded in the data set, may have already had the condition, manifested clinically, for many years (i.e., prior to the establishment of the data set). The age distribution (Supplementary Appendix 1, 2) should be considered bearing this in mind.

Information on possible confounding factors, including smoking, diet and treatment, was not available, and neither was any genetic history.

Strengths. This was a population-based study with a large sample size and a 13-year period of coverage. The number of patients with NF in this study was larger than in any previously published work. The coding of the diagnosis of NF (apart from type) and the cancers is likely to have been reliable – the coding is very straightforward. However, current privacy regulations preclude sampling medical case notes to check.

Existing literature. Among patients with NF, increased mortality associated with malignant neoplasm has been reported in studies conducted in Sweden (Zöller *et al*, 1995), the United Kingdom (Evans *et al*, 2011), the United States (Rasmussen *et al*, 2001) and several other countries (Imaizumi, 1995; Duong *et al*, 2011; Masocco *et al*, 2011). Our findings, on elevated overall risk of cancer, are consistent with the literature (Rasmussen *et al*, 2001; Walker *et al*, 2006; Evans *et al*, 2011). Findings similar to our four-fold increase in the risk of malignancy have been reported by groups from Denmark and Sweden (Sorensen *et al*, 1986; Zöller *et al*, 1997). A recent study of cancer incidence in NF1 in the United Kingdom also showed an increased overall risk of cancers (Walker *et al*, 2006), similar in magnitude to our reported risk. In the UK study, the authors suggested that elevation of cancer risk in NF1 patients was mainly attributable to the high risk of malignancies of connective tissue, central and peripheral nerve tissue, and did not demonstrate an increased risk of cancers of other sites. However, their study was based on only 448 individuals with NF1, identified through the Neurofibromatosis Association UK, with 36 people who had developed malignant tumours and it would not have had the statistical power to identify risks of different individual malignancies.

Sharif *et al* (2007) reported an increased risk of breast cancer among female patients with NF1. We show a similarly high risk of breast cancer, notably a three-fold risk in women under 50, and consideration could be given to lowering the age at which breast cancer screening is offered to women with NF.

Our study showed a RR of more than two for non-Hodgkin's lymphoma and leukaemia, in line with that reported by Stiller in the United Kingdom and Matsui in Japan (Matsui *et al*, 1993; Stiller *et al*, 1994). Although NF1-associated skeletal problems and abnormal bone metabolism have been reported (Tucker *et al*, 2009), an increased risk of bone cancer in people with NF has not previously been reported. Phaeochromocytoma is known to be more common in patients with NF1 than in the general population (Zinnamosca *et al*, 2011). We found 12 cases of malignant neoplasm of the adrenal medulla, where most cases of phaeochromocytoma arise, and none coded as cancer of the adrenal cortex. To the best of our knowledge, we are the first to report on the increased risk of several gastrointestinal cancers, lung cancer, skin malignancies, thyroid cancer, a number of haematological malignancies and cancer of ovary (Table 2). Johannessen *et al* (2005) described NF1 as a 'familial cancers syndrome' and provided a robust genetic explanation for the increased risk of malignant tumours in people with NF1. Our findings on the elevation of risk of a wide range of cancers have biological plausibility.

CONCLUSIONS

First, we have shown associations between NF and a wide range of individual malignancies. If our findings on risks of individual cancers that are not already well documented are confirmed elsewhere, they have implications for understanding prognosis in people with NF, and, where appropriate, for the possibility of anticipatory care and screening. Second, the clinical recording and ICD coding of NF is suboptimal and should be improved. Third, large-scale epidemiological studies based on nationwide data sets that accumulate a large number of observations offer opportunities for studying the epidemiology of rare conditions, like NF, that would be difficult to study on such a scale in other study designs.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ETHICAL APPROVAL

Ethical approval for analysis of the record-linkage study data was obtained from the Central and South Bristol Multi–Centre Research Ethics Committee (04/Q2006/176).

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