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Geographical analysis of thyroid cancer in young people from northern England: Evidence for a sustained excess in females in Cumbria

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ABSTRACT

A previous study found a thyroid cancer excess in Cumbria following the Chernobyl explosion, but did not analyse sex-specific effects. This study examines sex differences in the incidence of thyroid cancer. Ninety-five primary thyroid carcinomas (69 females, 26 males) diagnosed in those aged 0–24 during 1968–2005 were identified from the Northern Region Young Persons' Malignant Disease Registry. Age-standardised incidence rates (ASRs), rate ratios (RRs) and 95% confidence intervals (CIs) were calculated.

For males, the ASR was 0.6 per million person-years during the pre-Chernobyl period (1968–1986), and was 1.8 per million person-years during the post-Chernobyl period (1987–2005). For females, the ASR was 2.4 pre-Chernobyl and was 3.9 post-Chernobyl. The previously noted excess in Cumbria was entirely confined to females (Cumbrian females: RR for post-Chernobyl compared with pre-Chernobyl = 10.8; 95% CI: 1.4–85.3). These findings may be consistent with sex-specific differences in susceptibility to an environmental exposure, such as fallout from the Chernobyl nuclear accident.

1. Introduction

Exposure to ionising radiation in early life is a risk factor for thyroid cancer in children and young people,[1] and can be a risk even at low levels.[2] The nuclear accident in Chernobyl on 26th April 1986 released a radioactive cloud that affected a number of countries and reached northern England on 2nd May 1986. Numerous studies have shown the connection between radiation from Chernobyl and increased risk of childhood cancer in Belarus.[3–5] More widespread increases in the incidence of thyroid cancer have been reported from other parts of Europe.[6,7]

A statistically significant increase in the incidence of thyroid cancer in northern England during the immediate post-Chernobyl period, 1987–1997, has previously been found. The increase was particularly evident in Cumbria, which received especially high levels of radioactive fallout from Chernobyl.[8] The highest depositions in the region were found

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around the Solway estuary, a marshland which drains the rivers Wampool and Waver from the south and west of Cumbria. Measurements of radiocaesium at this site were up to 555 kilobecquerel/m^2, higher than the amount measured in Kiev and as high as some sites within 25–50 km of the accident itself,[9] and the initial prediction of a quick decline in caesium levels did not occur due to the acidic, peaty type of soil found in Cumbria, which was not binding the caesium.[10] Ground deposition of radioactive iodine was found to be at levels several hundred times those in southwest England.[11] Iodine measurements in grass were also elevated,[12] and environmental monitoring in the area around the nuclear installation at Sellafield before and after the accident showed peak concentrations in May 1986 to be 500 to 1000 times the values reported a year earlier, pointing to Chernobyl as the source of the contamination.[13]

Thyroid cancer exhibits a marked female excess, and this is true in cases among young people.[14] In England and Wales, the ratio of female to male cases is 2.5:1 for those aged 0–14.[15] The reasons for this excess are not clear, but are thought to be due to a greater female susceptibility to a triggering environmental exposure.

The aims of this study were to examine sex-specific differences in the incidence of thyroid cancer in northern England, and to specifically study sex differences in the post-Chernobyl period.

2. Patients and Methods

All cases of primary thyroid carcinoma in 0–24-year olds diagnosed in the Northern Region of England during the period 1968–2005 were obtained from the Northern Region Young Persons' Malignant Disease Registry (NRYPMDR). The Registry covers the counties of Northumberland, Tyne and Wear, Durham, Teesside and Cumbria (excluding Barrow-in-Furness) (Fig. 1). The entire region contains about 17% of the population of England aged less than 25 years. Tyne and Wear is the sixth largest conurbation in the country and the largest population centre in the study area. The population of the Northern Region is ethnically homogeneous, with fewer than 2% from ethnic minorities.[16–18] Less than 3% of its population was born outside the United Kingdom (UK), the lowest of any region in England and Scotland, and was similar to Wales.[19]

Cases with the site of diagnosis reported as the thyroid (ICDO C73.9) were considered.[20] Eight cases of multiple endocrine neoplasia (MEN), an autosomally dominant genetic syndrome related to a tumour suppressing gene MEN1,[21] were excluded. Ninety five cases of primary thyroid carcinoma were identified, where the patient had not been previously diagnosed with or treated for any cancer. There were no cases of non-syndromic thyroid cancer following any other type of previous cancer (such as Hodgkin lymphoma).

Incidence rates per million person-years were calculated based on mid-year population estimates for districts obtained from the Office for National Statistics. County populations for the years 1968–1970 were estimated using linear regression. Age-standardised rates (ASRs) were calculated based on a standard world population.[22] Trends were assessed using Poisson regression. Rate ratios (RRs) and 95% confidence intervals (CIs) were calculated to compare incidence during the post-Chernobyl periods 1987–1997, 1998–2005 and combined 1987–2005 with the pre-Chernobyl period of 1968–1986. Exact confidence intervals were calculated using the method described in Breslow and Day.[23]

3. Results

The study analysed a total of 95 cases (comprising 56 papillary carcinoma; 18 follicular carcinoma; 10 follicular variant of papillary carcinoma and 11 others). There were 26 males (7 cases diagnosed during 1968–1986, median age = 21; and 19 cases diagnosed during 1987–2005, median age = 19) and 69 females (28 cases diagnosed during 1968–1986, median age = 19; and 41 cases diagnosed during 1987–2005, median age = 20). There was one female case diagnosed at age 2 in 1968 and another at age 1 in 1974. There was also one male case diagnosed at age 8 in 1991 and another at age 8 in 2004; no other cases in the study were diagnosed under age 9.

Statistically significant excesses were observed in the risk of thyroid cancer during the period 1987–2005 compared with the period 1968–1986. For males (Table 1), the age-standardised rate (ASR) across the entire region for thyroid cancer was 0.6 (95% CI: 0.2–1.1) cases per million person-years in the pre-Chernobyl period, and was 1.8 (95% CI: 1.1–2.9) in the post-Chernobyl period (rate ratio = 3.3; 95% CI: 1.4–8.0). For females (Table 2), the ASRs were 2.4 (95% CI: 1.6–3.4) pre-Chernobyl and 3.9 (95% CI: 2.7–5.1) post-Chernobyl (rate ratio = 1.6; 95% CI: 1.0–2.7). A Poisson model showed that the incidence rate was higher for females (RR = 2.5: 95% 1.8–3.4) and higher in the post-Chernobyl period (RR = 1.9: 95% CI 1.4–2.7).

There were no male cases at all in Cumbria between 1968 and 2005 (expected number = 3.3. $P = 0.03$; Table 1), and the excess that was previously observed in Cumbria was entirely due to female cases (Table 2). For Cumbrian females, the rate ratio for the post-Chernobyl period compared with the pre-Chernobyl period was 10.8 (95% CI: 1.4–85.3) (Table 2). Address at birth was known for seven of nine female cases who were diagnosed in Cumbria post-Chernobyl. Four of these cases were born in Cumbria, and three were born elsewhere.

There was also an excess of females in Teesside in the post-Chernobyl period (rate ratio = 3.3; 95% CI: 0.9–12.5) (Table 2). Among males in Tyne and Wear, the rate ratio for the post-Chernobyl period compared to the pre-Chernobyl period was 6.5 (95% CI: 1.4–29.8) (Table 1). There was little migration from Cumbria to the more populous regions of Teesside or Tyne and Wear, and little immigration from outside the UK.

4. Discussion

This study has demonstrated that the previously noted marked excess of thyroid cancer in young people in Cumbria is entirely confined to females. The findings of this analysis are consistent with a possible sustained effect from exposure shortly after the Chernobyl accident limited to females in Cumbria, a county that had the highest recorded levels of exposure in the entire geographical region.

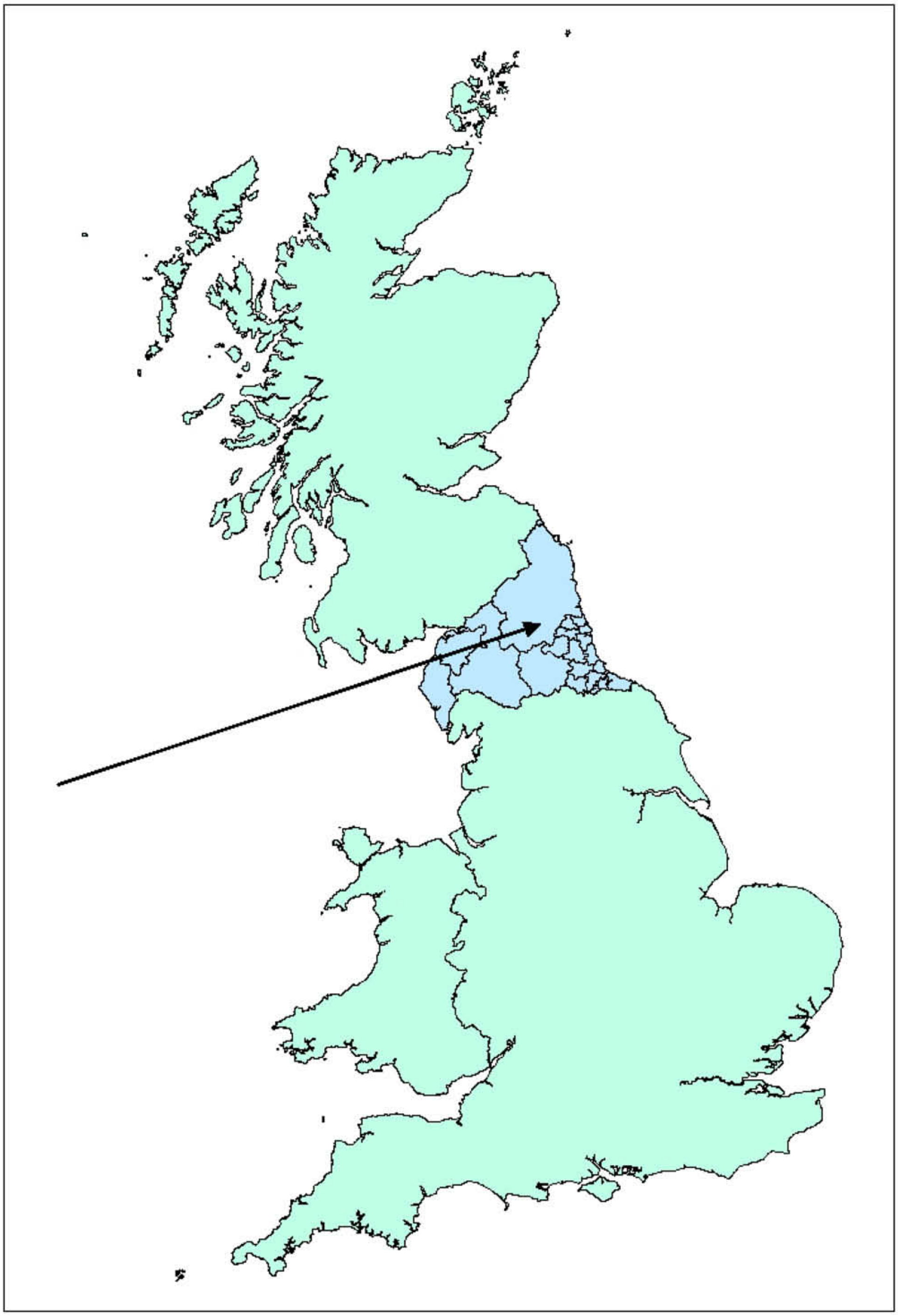

Fig. 1 – Great Britain with the Northern Region of England indicated.

The diagnoses were examined for histopathology subtype. While they may be caused by other agents, exposure to ionising radiation is especially associated with papillary thyroid carcinomas.[24] Over the entire region, the ratios of differentiated (papillary/follicular) carcinoma and medullary carcinoma were similar to those reported in the earlier study.[8] Also the frequency of types was similar to the recent findings reported from the Automated Childhood Cancer Information System (ACCIS) project,[14] although ACCIS data covered ages 0–19 rather than 0–24. The region of Cumbria, which showed excess cases, was very similar with regard to distribution of diagnosis type.

The female to male ratio of cases of 2.6:1 in the region for this time period is in agreement with the previous reports from other parts of England and Wales.[15] However, the distribution of the cases by sex displays heterogeneity throughout the Northern Region. A study of thyroid cancer in the region of Belarus within a 150 km radius of the Chernobyl accident

Table 1 – Incidence of male cases of thyroid cancer in 0–24-year olds in northern England by county at diagnosis and time period.

County	1968–1986		1987–1997		1998–2005		1987–2005	
	n	Rate (95% CI)	n	Rate (95% CI)	n	Rate (95% CI)	n	Rate (95% CI)
Age-standardised rates per million person- years								
Teesside	3	1.2 (0.3, 3.6)	1	0.8 (0.0, 4.3)	4	5.2 (1.4, 13.2)	5	2.5 (0.8, 5.8)
Cumbria	0	–	0	–	0	–	0	–
Durham	2	0.8 (0.1, 2.9)	1	1.0 (0.0, 5.4)	0	–	1	0.6 (0.01, 3.2)
Tyne and Wear	2	0.4 (0.05, 1.4)	7	2.9 (1.2, 6.0)	3	1.9 (0.4, 5.4)	10	2.5 (1.2, 4.6)
Northumberland	0	–	3	5.1 (1.0, 14.8)	0	–	3	3.0 (0.6, 8.8)
Total	7	0.6 (0.2, 1.1)	12	2.0 (1.0, 3.4)	7	1.7 (0.7, 3.5)	19	1.8 (1.1, 2.9)

	1987–1997 Rate ratio (95% CI)	1998–2005 Rate ratio (95% CI)	1987–2005 Rate ratio (95% CI)
Comparison of post-Chernobyl periods to pre-Chernobyl period (1968–1986)			
Teesside	0.6 (0.1, 6.0)	4.2 (0.9, 18.7)	2.0 (0.5, 8.4)
Cumbria	–	–	–
Durham	1.2 (0.1, 13.5)	–	0.7 (0.1, 8.0)
Tyne and Wear	7.6 (1.6, 36.8)	4.9 (0.8, 29.2)	6.5 (1.4, 29.8)
Northumberland	–	–	–
Total	3.6 (1.4, 9.1)	3.1 (1.1, 8.8)	3.3 (1.4, 8.0)

	1998–2005 Rate ratio (95% CI)
Comparison of later post-Chernobyl period (1998–2005) to earlier post-Chernobyl period (1987–1997)	
Teesside	6.7 (0.8, 59.8)
Cumbria	–
Durham	–
Tyne and Wear	0.6 (0.2, 2.5)
Northumberland	–
Total	0.9 (0.3, 2.2)

showed a heightened female effect, with a sex ratio of over 3:1,[4] and this is consistent with the Cumbrian results. It should also be noted that seven of the nine Cumbrian cases who were diagnosed during the post-Chernobyl period had been born prior to the Chernobyl accident. The other two cases were conceived within one year after the accident. The previous studies have produced mixed results as to whether sex affects radiation sensitivity.[25]

Stiller commented on possible limitations of the previously published analysis due to the small population of rural Cumbria.[26] However, a consistent excess in the incidence of thyroid cancer has been observed in Cumbria, both during 1987–1997 and during 1998–2005. The question must also be raised of whether the results in Cumbria represent a female excess, or a male deficit in cases. The eight excluded multiple endocrine neoplasia cases were examined as they were the only other cases with the thyroid reported as the primary diagnosis site. There were seven males and one female, but all were from Tyne and Wear or Teesside and do not account for any possible 'missing' or underascertained male thyroid cases in Cumbria. There is also the possibility of males from Cumbria moving out of the entire Northern Region before diagnosis, and therefore not being recorded in the Registry.

Stiller suggested that it was unlikely that many of the 1987–1990 cases in the Northern Region could have been attributed to Chernobyl given the latent period of the disease, and also suggested a cutoff date of 1991 as appropriate.[26] Considering the region as a whole, further statistical tests were applied to this adjusted before-and-after period. In some counties, such as Durham this did not change how the cases were designated and thus the only difference in the result was in confidence intervals. The results in other counties such as Tyne and Wear were comparable to the periods previously specified. In particular, for Cumbria the female post-Chernobyl excess remained statistically significant.

A female excess was also noted in Teesside, an area which received among the lowest levels of Caesium 137 deposition post-Chernobyl of anywhere in Europe (<1 kBq/m^2) and lower in general than the rest of the Northeast region.[6] Tyne and Wear also showed a similar excess that was apparent for males only, suggesting that there may be different aetiologies at work in these areas (although the plausible role of chance cannot be excluded). Examination of the types of thyroid cancers diagnosed by region did not illuminate the matter further. Radon emerging into households from cellars is also a source of ionising radiation, but a survey of England and Wales in 2002 showed very low levels in the Tyne and Wear and Teesside areas with less than 1% of sampled homes in the area having the Action Level of 200 Bq m^{-3} average per year.[27] While the Teesside area is known for its concentration of chemical production plants,[28] chemical exposures in themselves have not been shown to be risk factors for developing thyroid cancer.

Deprivation may be a contributing factor as it could affect both exposures and diets. According to the revised 2004 depri-

Table 2 – Incidence of female cases of thyroid cancer in 0–24-year olds in northern England by county at diagnosis and time period.

County	1968–1986		1987–1997		1998–2005		1987–2005	
	n	Rate (95% CI)	*n*	Rate (95% CI)	*n*	Rate (95% CI)	*n*	Rate (95% CI)
Age-standardised rates per million person-years								
Teesside	3	1.2 (0.3, 3.5)	6	4.9 (1.8, 10.7)	2	2.5 (0.3, 9.0)	8	4.0 (1.7, 7.8)
Cumbria	1	0.7 (0.02, 3.6)	6	7.3 (2.7, 15.8)	3	6.0 (1.2, 17.4)	9	7.0 (3.2, 13.2)
Durham	5	2.1 (0.7, 4.8)	3	2.4 (0.5, 7.0)	5	6.4 (2.1, 14.9)	8	4.0 (1.7, 7.9)
Tyne and Wear	16	3.5 (2.0, 5.7)	8	3.3 (1.4, 6.6)	5	2.8 (0.9, 6.7)	13	3.1 (1.6, 5.3)
Northumberland	3	3.2 (0.6, 9.4)	1	1.7 (0.04, 9.4)	2	5.9 (0.7, 21.3)	3	3.2 (0.7, 9.4)
Total	28	2.4 (1.6, 3.4)	24	3.7 (2.4, 5.6)	17	4.1 (2.4, 6.6)	41	3.9 (2.7, 5.1)

	1987–1997 Rate ratio (95% CI)	1998–2005 Rate ratio (95% CI)	1987–2005 Rate ratio (95% CI)
Comparison of post-Chernobyl periods to pre-Chernobyl period (1968–1986)			
Teesside	4.1 (1.0, 16.5)	2.1 (0.4, 12.4)	3.3 (0.9, 12.5)
Cumbria	11.2 (1.4, 93.4)	9.2 (1.0, 88.7)	10.8 (1.4, 85.3)
Durham	1.2 (0.3, 4.9)	3.1 (0.9, 10.7)	1.9 (0.6, 5.9)
Tyne and Wear	1.0 (0.4, 2.2)	0.8 (0.3, 2.2)	0.9 (0.4, 1.9)
Northumberland	0.5 (0.1, 5.2)	1.9 (0.3, 11.4)	1.0 (0.2, 5.2)
Total	1.6 (0.9, 2.7)	1.7 (1.0, 3.2)	1.6 (1.0, 2.7)

	1998–2005 Rate ratio (95% CI)
Comparison of later post-Chernobyl period (1998–2005) to earlier post-Chernobyl period (1987–1997)	
Teesside	0.5 (0.1, 2.5)
Cumbria	0.8 (0.2, 3.3)
Durham	2.7 (0.6, 11.3)
Tyne and Wear	0.9 (0.3, 2.6)
Northumberland	3.5 (0.3, 38.5)
Total	1.1 (0.6, 2.1)

vation index which considers quality of life factors,[29] the Super Output Areas (SOAs) of Middlesbrough, Hartlepool, Redcar and Stockton-on-Tees which comprise Teesside rank 10th, 14th, 44th and 75th, respectively, most deprived of 354 SOAs. Middlesbrough and Hartlepool are in the top 5% most deprived SOAs, and all areas of Teesside are within the most deprived quartile. Overall Teesside is, by this measure, the most deprived area as a whole in the region covered by the Registry. Tyne and Wear contains pockets of deprivation, but on the whole has a more mixed socioeconomic profile. By comparison, only one district in Cumbria is in the lowest quartile, one is in the highest, and the rest fall in the middle 50%. Our results suggest that the possible contribution of socioeconomic factors and the urban/rural divide may affect the aetiology of the disease in males and be worthy of future investigation.

The latent period between exposure and subsequent development of a thyroid tumour is unknown, but may have a highly variable duration. A study of childhood thyroid cancer in Gomel, Belarus, showed the average latency period as 5.6 years,[30] although the average latency was bound to be short since there was less than 10 years of follow-up. However, other studies suggest much longer lag times between exposure and subsequent diagnosis with increasing risk, peaking between 20–29 years after exposure, and subsequently with declining risk.[31,32] An age at exposure effect, with a higher risk accorded to earlier exposure, has been shown.[32] The continued elevated risk of thyroid cancer in Cumbria is consistent with such an effect. Nearly all the cases of thyroid cancer occurring in the earlier post-Chernobyl period (1987–1997) were exposed to Chernobyl-related radiation at young ages, indicating that the trend might continue in Cumbria and the rest of the Northern Region for another decade but emerging in age groups not covered by the Northern Region Young Persons' Malignant Disease Registry. However, another recent study, from Finland, following a similar age group has not shown a long-term trend.[33] The highest depositions of 420 kilobecquerel/m^2 were comparable to the highest in Cumbria (555 kilobecquerel/m^2). It will be necessary to follow up incidence in Cumbria in several years' time to see whether the risk shown in this study falls as the Chernobyl-exposed cohort moves out of the under-25 age group.

In conclusion, we have found a continued marked excess of thyroid cancer in Cumbria, which was entirely confined to females. This finding may be consistent with a sex-specific susceptibility to an environmental exposure, such as fallout from the Chernobyl accident. There is no known bias in the accurate and full reporting of data on thyroid cancer to the Registry. However, the role of chance and other unknown confounders cannot be dismissed. Although geographical variation in major cancers has been examined in a recent cancer atlas of the UK and Ireland, this did not include thyroid cancer.[34] To our knowledge, the most recent national study of temporal and geographical variation in thyroid cancer only included cases up to 1984.[35] Further research should examine trends and geographical variability in the incidence of thyroid cancer in other geographical regions and also older age groups using recent data.

Conflict of interest statement

None declared.

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