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Thyroid cancer in children and young adults in the North of England. Is increasing incidence related to the Chernobyl accident?

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Abstract

Population-based data on thyroid carcinomas was obtained from the Northern Region Young Person's Malignant Disease Registry to analyse the incidence of thyroid cancers in young people (<25 years) in the North of England for the period 1968 and 1997 and to assess if changes in incidence were consistent with the spatial and temporal distribution of the fallout from the Chernobyl nuclear accident. We compared incidence rates for differentiated (papillary or follicular) thyroid carcinomas 1968–1986 with those for 1987–1997. There were 75 cases of thyroid carcinoma diagnosed over the study period, of which 63 were differentiated carcinoma and 12 were medullary carcinoma. There were 26 young adults (15–24 years) diagnosed with differentiated thyroid carcinoma in the 19-year period 1968–1986 and 30 in the subsequent 11 years 1987–1997, Age standardised rate (ASR) 3.0 versus 6.5, respectively (rate ratio 2.2, 95% confidence interval (CI): 1.3–3.6). There were three children (aged <15 years) diagnosed with differentiated carcinoma in the period 1968–1986 and four in the period 1987–1997, ASR 0.2 versus 0.6 (rate ratio 2.7, 95% CI: 0.6–12.1). Regression models showed a significant increase in the incidence of thyroid cancer after the Chernobyl accident ($P=0.002$). In Cumbria, the area receiving the heaviest fallout in the UK, the increase in incidence was much greater (rate ratio 12.19, 95% CI 1.5–101.2). These temporal and spatial changes in incidence are consistent with a causal association with the Chernobyl accident although a greater effect in the younger rather than the older age group would have been anticipated. However, factors including improvements in ascertainment and earlier detection of tumours may also have contributed to the increasing incidence. Further collaborative international studies are needed to investigate changes in the incidence of thyroid cancer in children and young adults.

Keywords: Thyroid neoplasms; Childhood cancer; Young adults; Iodine radioisotopes; Nuclear accidents

1. Introduction

The thyroid gland in children is very sensitive to the tumorigenic effects of ionising radiation [1,2]. Risk of radiation-related thyroid cancer decreases with increasing age at exposure, with little risk apparent among persons exposed as adults [1]. Following the nuclear accident in Chernobyl on 26 April 1986 there have been reports of increased incidence of thyroid cancers in children in the regions around the reactor [3–5]. It has recently been reported that in the Ukraine there has been a 10-fold increase in the incidence of thyroid cancers in children and a 6-fold increase in the 15–18-year age group when comparing the periods 1981–1985 and 1986–1997 [6].

The radioactive cloud reached the North of England, approximately 2000 km distant from Chernobyl, on 2 May 1986. Deposition of radionuclides including I^{131}, C^{134} and C^{137} was highest in areas experiencing heavy rainfall during the passage of the cloud. Parts of the northern region of England, particularly in Cumbria received some of the highest levels of radioactive fallout from Chernobyl in the UK [7–9] (Fig. 1). We therefore investigated incidence rates for thyroid cancers in children and young adults (age <25 years) in the North of England using population-based data from the Northern Region Young Person's Malignant Disease Registry (NRYPMDR) [10,11].

2. Patients and methods

Children and young adults (aged <25 years at diagnosis) with primary thyroid carcinoma in the Northern

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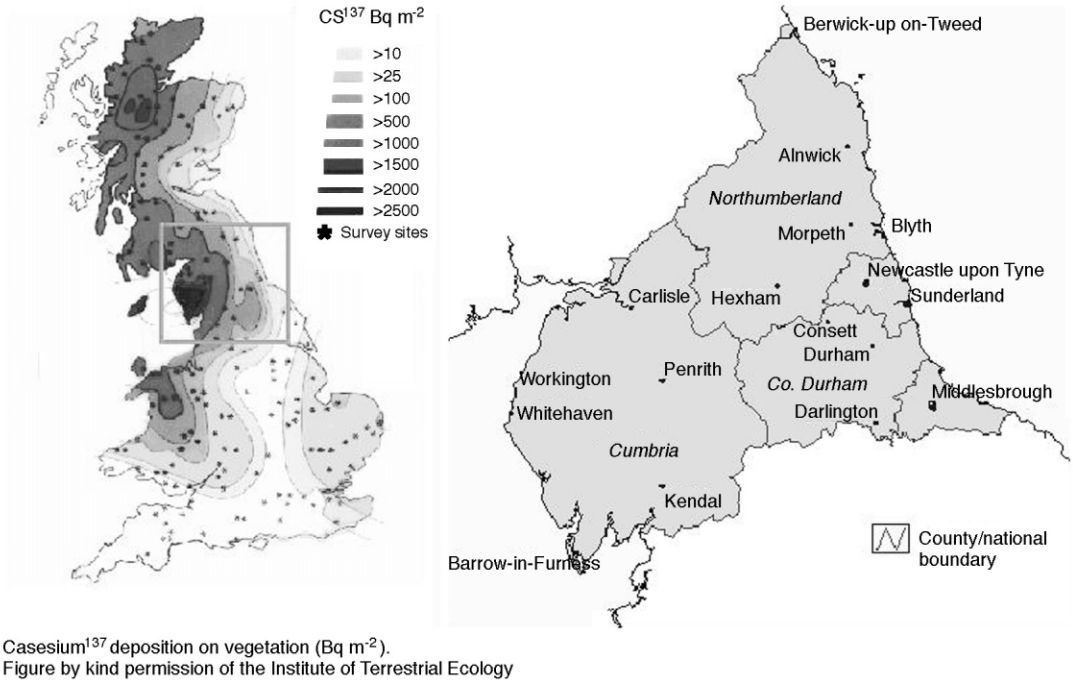

Fig. 1. Estimated distribution of radioactive fallout from the Chernobyl accident for the UK and map of the study region covered by the North of England Young Person's Malignant Disease Registry.

Region of England diagnosed between 1968–1997 were identified from the NRYPMDR. Case notes were reviewed and patients were classified for histological sub-type, duration of symptoms prior to diagnosis and clinical details. Those with differentiated carcinoma (papillary and/or follicular tumours) were analysed separately from those with medullary carcinoma or familial thyroid cancers as these tumours are known to have different aetiologies and clinical behaviour. 2 additional cases of primary thyroid tumours in women aged 19 and 24 years were excluded from this study: 1 had a nodular sclerosing Hodgkin's lymphoma of the thyroid and the other had a benign thyroid adenoma. Incidence rates were calculated using mid-year population estimates and age-standardised rates (ASR) were based on a standard world population [12]. Incidence rates for children were calculated for patients who were under 15 years and rates for young adults were for those between 15 and 24 years at diagnosis. Survival and relapse-free survival were calculated using Kaplan–Meier estimations.

In order to formally test the hypothesis that the incidence of differentiated thyroid carcinoma has increased following exposure to radioactive fallout from the Chernobyl accident, we compared incidence rates for 1968–1986 with those for 1987–1997 by calculating rate ratios with 95% confidence intervals (CI). Linear regression models were applied to annual incidence rates using (1) a model assuming constant incidence rates up to 1986, followed by a period of increasing incidence (the slope of which was estimated from the regression model), and (2) a bilinear 'broken-stick' model allowing different slopes for rates in the two time periods [13]. In addition, incidence rates were calculated for each of the 15 local health authority areas (based on the 1974 boundaries) for the two periods to assess if changes in incidence were consistent with the spatial distribution of the fallout.

3. Results

Seventy-five children and young adults (age <25 years) were diagnosed with primary thyroid carcinoma over the period 1968–1997. Of these, 63 were diagnosed with differentiated (papillary and/or follicular) tumours and 12 with medullary carcinoma. Overall, 11 children (aged 0–14 years) were diagnosed with thyroid cancer with an incidence of 0.55 cases per million children, per year (95% CI 0.29–0.94). Sixty-four young adults (ages 15–24 years) were diagnosed with an incidence of 4.7 cases per million young adults, per year (95% CI 3.7–6.0).

3.1. Differentiated (papillary and/or follicular carcinoma)

Over the 30-year study period, there were seven children (male:female ratio (M:F) 3:4) and 56 young adults (M:F 15:41) diagnosed with differentiated thyroid car-

cinoma. Clinical details are summarised in Table 1. The ASR for patients under 15 years at diagnosis was 0.31 per million children per year. The ASR for the young adults was 4.2 per million 15–24 year olds, per year, the ASR for males and females were 2.2 and 6.3 per million per year, respectively. All patients with differentiated tumours were alive at the time of analysis (median follow-up 11.4 years, range 2–32 years). 8 patients experienced a recurrence giving a 10-year relapse-free survival (RFS) rate of 87% (95% CI 77–96) (Fig. 2). Of the 8 patients who relapsed, all but 1 were in remission at the time of analysis.

3.2. Changes in the incidence of differentiated thyroid carcinoma

There were three children diagnosed in the period of 1968–1986 and four in the period of 1987–1997, ASR 0.2 versus 0.6 (rate ratio 2.7, 95% CI 0.6–12.1). In the young adults, the rates for the two periods were 3.0 and 6.5, respectively (rate ratio 2.2, 95% CI 1.3–3.6). Comparing patient details for the two periods, there was no demonstrable statistically significant difference in the gender ratios, age distribution, histological sub-type, proportion with metastases at diagnosis, tumour size, or duration of symptoms (Table 1). As the latency period for thyroid cancers is uncertain we also compared the periods 1987–1990 and 1991–1997. There were four children diagnosed over the two periods, ASRs were 0.87 versus 0.48, respectively (rate ratio 0.5, 95% CI 0.8–3.9). For the 30 young adults, the ASRs were 4.47 and 8.11, respectively (rate ratio 1.81, 95% CI 0.81–4.07). For those diagnosed after the Chernobyl accident, the median age at exposure was 14 years (range 3.4–22.9), 1 patient was <4 years.

The regression models showed a significant increase in the incidence of differentiated thyroid cancer after the Chernobyl accident. Assuming a constant rate up to 1986, the risk increased significantly after this time ($P=0.002$), the modelled increase is shown in Fig. 3a. Similarly the estimated increase in incidence from the bilinear 'broken-stick' model, with a break at 1986 is shown in Fig. 3b.

The number of cases (aged <25 years) by local health authority and county for the two periods 1968–1986 and 1987–1997 are shown in Table 2. In Cumbria, the area receiving the heaviest fallout, there was a substantial increase in incidence (rate ratio 12.19, 95% CI 1.5–101.2). Non significant increases were observed in Teeside (rate ratio 2.84), Northumberland (rate ratio 2.85) and Tyne and Wear (rate ratio 2.01), while the rate in County Durham was unchanged (rate ratio 0.99).

3.3. Medullary cancer and familial thyroid cancers

Over the 30-year period, 12 young people were diagnosed with medullary thyroid carcinoma in the study region. In children (aged <15 years), the rate for medullary thyroid cancer was 0.20 per million, per year (95% CI 0.06–0.47) and in young adults (aged 15–24 years), the rate was 0.52 (95% CI 0.22–1.00). Overall, 5 cases were diagnosed between 1987 and 1997, of which 3 were detected by screening for multiple endocrine neoplasia.

Table 1
Summary of clinical features at diagnosis of young people with differentiated thyroid carcinoma by study period

	Year of diagnosis	
Characteristics at diagnosis	1968–1986	1987–1997
Age (years)	20.6	20.5
Median (range)	(9–24)	(8–24)
Duration of symptoms (years)		
Median (range)	0.4 (0–5)	0.5 (0–3)
Gender		
Male	7 (24%)	11 (32%)
Female	22 (76%)	23 (68%)
Histology		
Papillary	18 (62%)	28 (82%)
Follicular/mixed[a]	11 (38%)	6 (18%)
Metastases		
Yes	14 (56%)	16 (48%)
No	11 (44%)	17 (52%)
Unavailable	4 –	1 –
Tumour size/foci		
<1.5 cm^2 and unifocal	5 (23%)	3 (10%)
$\geqslant 1.5$ cm^2 and/or multifocal	17 (77%)	27 (90%)
Unavailable	7 –	4 –

[a] Mixed, mixed papillary–follicular carcinoma.

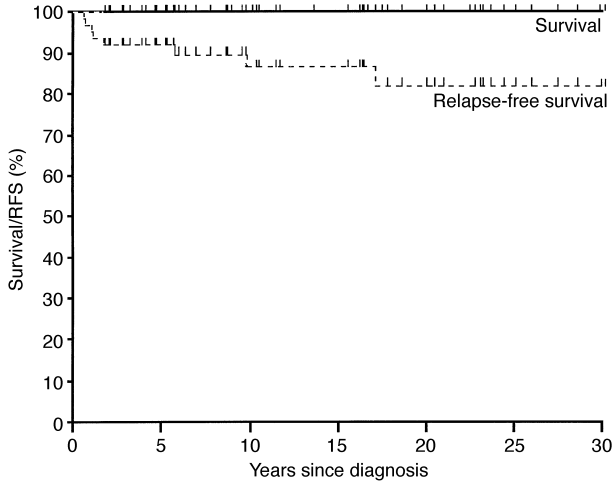

Fig. 2. Survival and relapse-free survival (RFS) in young people with differentiated thyroid carcinoma ($n=63$).

4. Discussion

There were 75 cases (M:F 25:50) of thyroid cancer in children and young adults diagnosed in the North of England during the period 1968–1997. 63 cases had differentiated (papillary/follicular) carcinomas and 12 had medullary carcinoma. 3 of the cases of medullary thyroid carcinoma were detected by screening in families with multiple endocrine neoplasia. No other cases were diagnosed by screening. This highlights the need to study medullary and differentiated thyroid carcinomas separately.

The findings of this population-based study are consistent with a hypothesis of increasing incidence of differentiated thyroid cancer in young people following the Chernobyl accident. Incidence of thyroid cancer in children and young adults in the North of England was significantly higher during 1987–1997 than 1968–1986 (rate ratio 2.33, 95% CI 1.4–3.8). In addition, geographically the greatest increase in incidence occurred in Cumbria (rate ratio 12.19, 95% CI 1.5–101.2), where radioactive contamination was highest (Fig. 1).

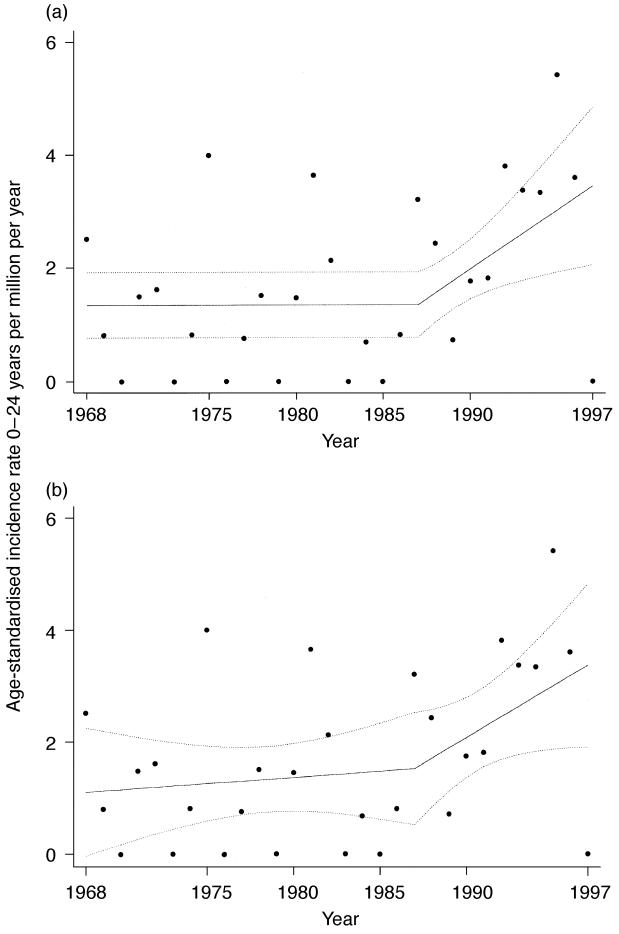

Fig. 3. (a) Regression model of age-standardised incidence rates with a breakpoint at 1987; (b) 'broken-stick' model of age-standardised incidence rates with a breakpoint at 1987 (··· 95% CI).

However, other potential explanations for these apparent temporal and spatial changes in incidence for the North of England cannot be entirely excluded. Earlier detection of tumours consequent to advances in medical imaging technologies and greater awareness of thyroid cancers in young people might contribute to the observed increase in incidence. However, there was no evidence of differences in duration of symptoms between the two periods, as might be expected with better detection. Therefore, this is unlikely to be a major reason for the observed increase in incidence. In addition, the clinical characteristics for the later period (Table 1) (i.e. a trend for a higher proportion of papillary histologies and larger tumour size) would be consistent with reports of more aggressive tumour types from regions near Chernobyl following the accident. Changes in diagnostic technologies and procedures might explain the differences in clinical characteristics in this study, however, they do suggest that the observed increase in incidence is not driven by better detection of less aggressive tumour types.

Another potential explanation for the apparent changes in incidence is that there may have been under-ascertainment of cases in the earlier period. In particular, malignancies in young adults (15–24 years) were ascertained retrospectively for 1968–1986 and then prospectively from 1987. However, the retrospective case ascertainment was a comprehensive exercise using regional cancer registries [14]. Since then, ascertainment has been an ongoing process using multiple sources including records from radiotherapy centres and national registry data. The records of the regional medical physics service were checked, but no additional cases were found. In addition, the trend for increasing incidence post-1986 (Fig. 3) is consistent with a causal association with exposure to radionuclides following the Chernobyl incident. In addition, the increase in incidence of thyroid cancers in young adults is of a similar magnitude to that observed in children, for whom cases have been ascertained prospectively since the onset of the registry in 1968. There may possibly have been better reporting associated with greater centralisation of treatment of thyroid cancers in recent years, however, throughout the study period there have been only a very limited number of hospitals with facilities for administering radio-iodine which is used in the treatment and monitoring of thyroid cancer. Ascertainment of cancers in young adults diagnosed in 1997 may not be complete, however, any additional cases would increase the strength of the findings of increasing incidence.

The incidence of thyroid cancer in children in the North of England over the entire period was 0.55 per million children per year. This is at the lower end of the reported range observed in Western Europe (range 0.3–1.7) [15], but is consistent with nationally reported rates (0.5 per million, 1974–1987) [16,17]. There is consider-

Table 2
Incidence of differentiated thyroid cancer in children and young adults (aged <25 years) by health authority district at diagnosis and time period[a,b]

County	Health authority	1968–1986		1987–1997		Total *n*	Rate ratio (95% CI)
		n	Rate	*n*	Rate		
Teeside	Total	5	1.13	7	3.21	12	2.84 (0.9–8.9)
	Hartlepool	0	–	2	5.82	2	–
	South Tees	4	1.68	4	3.44	8	2.04 (0.5–8.2)
	North Tees	1	0.76	1	1.49	2	1.96 (0.1–31.3)
Cumbria	Total	1	0.36	6	4.36	7	12.19 (1.5–101.2)
	East Cumbria	1	0.86	3	5.00	4	5.85 (0.6–56.2)
	West Cumbria	0	–	2	4.08	2	–
	South Cumbria[c]	0	–	1	1.88	1	–
Durham	Total	6	1.39	3	1.38	9	0.99 (0.3–4.0)
	Durham	3	1.69	2	2.25	5	1.33 (0.2–7.9)
	NW Durham	1	1.67	0	–	1	–
	Darlington	0	–	1	2.34	1	–
	SW Durham	2	1.82	0	–	2	–
Tyne and Wear	Total	15	1.80	15	3.62	30	2.01 (0.9–4.1)
	Gateshead	2	1.32	3	4.17	5	3.16 (0.5–18.9)
	Newcastle	8	3.84	6	5.65	14	1.47 (0.5–4.2)
	North Tyneside	3	2.19	2	2.99	5	1.37 (0.2–8.2)
	South Tyneside	2	1.69	2	3.61	4	2.14 (0.3–15.2)
	Sunderland	0	–	2	1.75	2	–
Northumberland	Total	2	1.01	3	2.88	5	2.85 (0.5–17.0)
Total	–	29	1.33	34	3.11	63	2.33 (1.4–3.8)

95% CI, 95% confidence interval.
[a] Areas defined by 1974 health authority districts.
[b] Cases were residents of the specified areas at diagnosis, but not necessarily treated in that health authority district.
[c] Excludes Barrow-in-Furness.

able variation in the rates of thyroid cancer in children [15] and the lower rate in the UK might relate to the relative iodine sufficiency compared with other countries. The UK National Registry of Childhood Tumours is well established, uses multiple sources and consequently has high rates of ascertainment [13]. The incidence rates for thyroid cancer in young adults in the North of England were also very similar to those for England and Wales [18].

An increase in incidence of differentiated thyroid carcinomas in the North of England is consistent, though of considerably less magnitude, with reports from the regions around the Chernobyl reactor. In Belarus, a 100-fold increase in incidence of childhood thyroid cancer has been reported with a national rate of 30.6 cases per million children for 1991–1994 compared with rates of 0.3 for 1981–1985 [5]. In the Gomel region of Belarus immediately north of Chernobyl, the rate was 96.4 for 1991–1994. In the Ukraine, a 10-fold increase in the incidence of thyroid cancers in children and a 6-fold increase in the 15–18 year group has been reported when comparing the periods 1981–1985 and 1986–1997 [6]. A further study compared I^{131} dose to incidence in two areas which received the highest rates of fallout, Belarus and the Brynsk district of the Russian Federation [19]. However, there is debate as to the extent to which the reported increase in the number of cases of childhood thyroid cancer in Belarus is real and attributable to radiation exposure from the Chernobyl nuclear incident, or is an artefact of more complete case reporting and mass screening of children after the accident and/or incorrect histological diagnosis of benign thyroid conditions [20]. However, the magnitude of the increase is so large that the component which is causally related to radiation exposure must be substantial.

There have been reports of incidence of thyroid cancer in regions more geographically distant from Chernobyl, where fallout radiation doses were smaller. Data from Connecticut in the United States suggested an increased incidence of thyroid cancers (all ages) albeit non-significant, with ASRs for 1985–1989 and 1990–1992 of 34.6 to 42.9 per million population per year. The levels of I^{131} in milk peaked at 2.0 Bq/l in June 1986 compared with a state average of 0.07 Bq/l for 1983–1990 [21]. A study of childhood differentiated thyroid carcinoma in the Provence-Alps-Cote d'Azure and Corsicas regions of France where the received dose was about 3 mSv following the Chernobyl accident reported rates of 1.12 and 1.77 for 1984–1986 compared with 1987–1994 [22]. They conclude there is no demonstrable variation in rates that could correspond with the radioactive fallout from Chernobyl. However, the earlier period is limited to 3 years in which just three children were diagnosed and rates in both periods are amongst

the highest rates of childhood thyroid cancer reported in Europe [14]. An International Union against Cancer (UICC) review of cancer consequences of the Chernobyl accident by Sali and colleagues included studies of the incidence of thyroid cancer for Greece, Croatia, Poland and Turkey (all ages) [23]. In Greece, there was no increase in the proportion of thyroid cancers detected during thyroid examinations for adults over the period 1982–1992. In Croatia, for the period 1982–1990, there was an increase in incidence of thyroid cancers in adults, but not in children. In Poland, there were increases in the incidence of thyroid cancer in adults, but not in children, for the periods 1976–1992. In Turkey over the period 1983–1992, significant increases in thyroid cancers (all ages) were seen in three of the six most contaminated provinces, but this was not related to the levels of contamination. Rates fell 6 years after the accident. Follow-up is short in all these studies resulting in low statistical power.

The spatial changes in incidence in the North of England reported in this study provide evidence in support of the hypothesis that exposure to radioactive fallout from Chernobyl, even in geographically distant regions has caused an increase in incidence of thyroid cancer in young people. The largest increase in incidence was seen in Cumbria which received the highest doses of radioactive fallout in England. Concentrations of I^{131} in rainwater as high as 784 Bq/l and in goat's milk as high as 1040 Bq/l were recorded in parts of Cumbria [24]. Livestock restrictions enforced in Cumbria immediately after the Chernobyl accident covered 1670 farms in the county, and in 1999, a small number of sheep farms were still under restrictions as radiocaesium levels had not fallen to consistently below 1000 Bq/kg [25]. Just 1 case of thyroid cancer in young people aged <25 years was diagnosed in Cumbria in the 19-year period 1968–1986, while 6 cases were diagnosed in the subsequent 11 years. There were more modest increases in incidence in other areas in the North of England (Table 2).

The biological plausability of thyroid carcinogenesis due to radiation exposure from the nuclear accident in areas distant from Chernobyl needs to be addressed. Young age at exposure to external X-ray radiation is associated with risk of thyroid cancer [1,26]. Relatively little is known about the effects of chronic internal exposure to I^{131}. Most studies on thyroid cancer following Chernobyl do indicate that the largest increase in incidence was seen in those aged $\leqslant 5$ years at the time of the accident. Only 1 case in the NRYPMDR data was <4 years of age at exposure. However, most other studies only report rates for children so the effect of I^{131} on young adults is uncertain. Population differences in iodine deficiency status, dose of I^{131}, length of chronic exposure and use of countermeasures, for example iodine supplements, might potentially influence age-related thyroid cancer risk. In the study from the Ukraine [6] only 4 cases were *in utero* at time of the accident and 58% of cases were aged >5 years at the time of the accident. While the largest increase in incidence in the Ukraine was observed in those aged $\leqslant 5$ years at the time of the accident there was also a 3-fold increase in incidence in young people aged 15–18 years at diagnosis.

Survival rates for young people with thyroid cancer are high compared with other types of cancer. One of the most important prognostic factors for thyroid cancer is age, with those under 45 years at diagnosis having higher survival rates [27]. In this study, no deaths have been reported in those diagnosed with differentiated carcinoma (median follow-up 11.4 years). For those with medullary carcinomas the 10 year relapse-free survival rate was 67%. Survivors require lifetime endocrine monitoring and most require thyroxine supplements following thyroidectomy. Thus, while increasing incidence rates should have little consequence for mortality in young people, the lifetime care required clearly has important implications for patients' quality of life and health service resources.

In conclusion, this study indicates increasing incidence of differentiated thyroid carcinomas in children and young adults in the North of England. The temporal and spatial changes in incidence are consistent with a causal association with radionuclide exposure following the Chernobyl accident. However, other factors such as improved case ascertainment may also have made a contribution to the higher number of cases identified in the later time period and thus the magnitude of a Chernobyl effect, if any, is difficult to estimate. The major limitation of this study is the small sample size. As thyroid cancers represent only a small proportion of cancers in children and young adults, larger international collaborative studies utilising I^{131} dose estimates are needed to provide a more definitive answer.

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