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A geographical study of thyroid cancer incidence in north-west England following the Windscale nuclear reactor fire of 1957

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Abstract

The Windscale nuclear reactor fire at Sellafield, United Kingdom, in October 1957 led to an uncontrolled release of iodine-131 (radioactive half-life, 8 days) into the atmosphere. Contamination from the accident was most pronounced in the counties of Cumbria and Lancashire, north-west England. Radioiodine concentrates in the thyroid gland producing an excess risk of thyroid cancer, notably among those exposed as children, which persists into later life. For an initial investigation of thyroid cancer incidence in north-west England, data were obtained on cases of thyroid cancer among people born during 1929-1973 and diagnosed during 1974-2012 while resident in England, together with corresponding populations. Incidence rate ratios (IRRs), with Poisson 95% confidence intervals (CIs), compared thyroid cancer incidence rates in Cumbria and in Lancashire with those in the rest of England. For those aged <20 years in 1958, a statistically significantly increased IRR was found for those diagnosed during 1974-2012 while living in Cumbria (IRR = 1.29; 95% CI 1.09-1.52), but the equivalent IRR for Lancashire was marginally non-significantly decreased (IRR = 0.91; 95% CI 0.80-1.04). This pattern of IRRs was also apparent for earlier births, and the significantly increased IRR in Cumbria extended to individuals born in 1959-1963, who would not have been exposed to iodine-131 from the Windscale accident. Moreover, significant overdispersion was present in the temporal distributions of the IRRs, so that Poisson CIs substantially underestimate statistical uncertainties. Consequently, although further investigations are required to properly understand the unusual patterns of thyroid cancer IRRs in Cumbria and Lancashire, the results of this preliminary study are not consistent with an effect of exposure to iodine-131 from the Windscale accident.

Keywords: cancer epidemiology, geographical analysis, cancer registration, thyroid cancer, radioactive iodine, reactor accidents

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1. Introduction

A fire in a nuclear reactor (the “Windscale Number 1 Pile”) at Sellafield, situated on the coast of the present-day county of Cumbria in north-west England, on 10-11 October 1957 (the “Windscale Fire”) released substantial quantities of radionuclides to atmosphere over a period of about 20 hours (Supplementary Figure S1) [1-4]. The discharges included 1800 TBq of iodine-131 (radioactive half-life, 8 days), and deposition in the vicinity of Sellafield produced concentrations of iodine-131 in cow’s milk that were sufficiently high for a local milk distribution ban to be established [1, 2]. The plume of radioactive material initially travelled to the north-east before a north-westerly wind carried the emissions to the south-east, over southern Cumbria and the neighbouring county of Lancashire (Figure 1 and Supplementary Figure S2), the rest of England and mainland Europe [2, 3, 5-11]. Doses estimated to have been received by the general population as a result of the Windscale accident have been presented by Crick and Linsley [11].

Iodine concentrates in the thyroid gland and it is well established that the thyroids of young children are particularly sensitive to radiation-induced cancer [12-15]. Evidence for this includes the marked excess incidence of thyroid cancer among those highly exposed as children in the former USSR to radioiodine released from the Chernobyl nuclear reactor accident in Ukraine in 1986, mainly through the consumption of heavily contaminated milk [16]. Radiation doses to the thyroids of children following the Windscale Fire were, in general, much less than those received by children in the neighbourhood of Chernobyl [11, 16, 17], and the milk distribution ban limited doses to predominantly low levels in the worst affected area of Cumbria [11]. However, during the late-1980s, the then Director of the UK National Radiological Protection Board estimated from assessed doses [11] and

radiation-induced thyroid cancer risk models available at the time that around 60 thyroid cancers would eventually result from exposure to iodine-131 released during the Windscale accident [17, 18].

The lifetime risk of radiation-induced thyroid cancer is greatest for those exposed as infants and young children, and falls away markedly with increasing age at exposure so that it is difficult to reliably detect any radiation-induced excess risk of thyroid cancer among those exposed beyond 20 years of age [12-15, 19-22]. Current radiation-induced thyroid cancer risk models predict that the excess risk is best expressed by the Excess Relative Risk (ERR, the proportional increase in risk over the background risk in the absence of the exposure) [12-15, 23, 24], which after a minimum latent period of around five years, remains approximately constant over the remaining lifetime of the exposed individual (Supplementary Figure S3) [23], although possibly with some attenuation with increasing time since exposure (or equivalently, increasing attained age) [24]. Consequently, most of the excess thyroid cancer cases among those exposed to radiation at young ages will occur when the background thyroid cancer risk is highest at older ages (Supplementary Figure S4) [25], so that the radiation-induced risk is predicted to be expressed mainly in later life.

From this understanding of radiation-induced thyroid cancer, any cases of thyroid cancer attributable to exposure to iodine-131 released during the Windscale Fire are most likely to occur among those with the highest exposures at the youngest ages, but incident many years after the accident at older attained ages. To date, no study has specifically investigated whether evidence exists for excess cases of thyroid cancer associated with the Windscale Fire, notwithstanding the continuing large excess incidence of thyroid cancer in the areas most affected by radioiodine

contamination from the Chernobyl accident [16], and the major release of iodine-131 from the damaged Fukushima Dai-ichi reactors in Japan during March 2011 [26].

The aim of the present study was to make a preliminary examination of the long-term rates of incidence of thyroid cancer in those groups of people living in areas of north-west England most contaminated by iodine-131 from the 1957 Windscale Fire who were young at the time of the accident.

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2. Materials and Methods

2.1 Study subjects

All patients were included in the study who were registered as diagnosed with thyroid cancer while resident in England during the period 1 January 1974 to 31 December 2012 and who were aged less than 85 years at the time of diagnosis. Comprehensive registration data for cancer incidence in England from 1971 are available at the National Cancer Registry [27]. However, the reorganisation of local government in 1974 led to boundary changes that affected both counties of primary interest in this study, Cumbria and Lancashire, so the first year of cancer registrations for this study was 1974; the final year was 2012, which was the last year for which registrations at the National Cancer Registry were considered complete at the time of data acquisition. The recording of cancer cases among the elderly is less reliable than at younger ages and so 84 years was taken as the upper attained age bound for the study. The period of birth of cases considered was 1929-1973, which includes those young at the time of the Windscale accident, together with individuals who were older, or not born, in 1957 for comparison purposes.

Since individuals were potentially identifiable from the cancer registration data, a Data Sharing Agreement was negotiated with the Public Health England Office for Data Release; this stipulated destruction of the original data on completion of the analysis and that published results would not permit identification of individuals. Individual case data (year of birth, year of diagnosis, sex, area of domestic residence at time of diagnosis) were provided for three areas of residence at diagnosis: (i) the post-1974 county of Cumbria; (ii) the post-1974 county of

Lancashire; and (iii) the Rest of England (that is, England excluding Cumbria and Lancashire).

2.2 Population data

Mid-year population estimates for each year from 1974 to 2012 were obtained from the Office for National Statistics (ONS) for Cumbria, Lancashire and the Rest of England. Population estimates were obtained separately for males and females for 17 five-year age groups: 0-4, 5-9, 10-14,..., 80-84.

2.3 Statistical Analysis

Case data were grouped into five-year calendar periods of birth: 1929-1933, 1934-1938,..., 1969-1973, for males and females for each of the three areas of residence at diagnosis (Cumbria, Lancashire and the Rest of England). Since the areas of birth of the cases and the corresponding populations were not available, an approximate method was used to obtain incidence rates by period of birth. First, annual population estimates for the 17 five-year attained age groups were used to construct sex- and age group-specific populations for each of the three areas for seven five-year calendar periods of diagnosis, 1974-1978, 1979-1983,..., 2004-2008, and one four-year period, 2009-2012; sex-specific age-period tables of population data were then constructed. Age group, period of diagnosis and period of birth are intrinsically related [28], so labelling age groups (i) as 1, 2,..., 17, corresponding to 0-4, 5-9,..., 80-84 years, and diagnosis periods (j) as 1, 2,..., 8, corresponding to 1974-1978, 1979-1983,..., 2009-2012, approximate ten-year overlapping birth periods (1929-1938, 1934-1943,..., 1964-1973) are defined as $k = 17 - i + j$. For example, a diagnosis at age 15-19 years during the period 1974-1978 corresponds to the ten-

year birth period 1954-1963. Each age-period population estimate was divided by two to obtain approximate five-year birth period populations for that age-period combination. For example, the ten-year birth period for those diagnosed aged 25-29 years during 1974-1978 is 1944-1953, so for this age-period combination, the populations for those born during 1944-1948 and 1949-1953 were estimated by dividing the age-period population by two. Using this approach, sex- and age group-specific incidence rates were calculated for each combination of diagnosis period and birth period. A sensitivity analysis was carried out after generating five-year birth period populations proportionally by weighting periods according to annual birth rates obtained from the ONS, but results were little changed and so are not reported here.

The primary focus of this study was the incidence of thyroid cancer among those who were less than 20 years of age in 1958 (that is, those young at the time of the accident in 1957, and allowing for those who were potentially exposed *in utero* to iodine-131). Most attention was given to the findings for males and females combined, but results for each sex were checked for consistency. Consequently, incidence rates were calculated for persons aged 0-19 years in 1958 (born in 1954-1958, 1949-1953, 1944-1948 and 1939-1943), and the younger subgroups of those aged 0-9 and 0-14 years of age in 1958, for the areas Cumbria, Lancashire, Cumbria plus Lancashire combined, and the Rest of England. Incidence rate ratios (IRRs), together with corresponding 95% confidence intervals (CIs) calculated by assuming that thyroid cancer incidence rates follow a Poisson distribution, were used to compare Cumbria, Lancashire, and Cumbria plus Lancashire, with the Rest of England providing reference rates. For comparison purposes, equivalent incidence rates and IRRs were calculated for those aged 20-29 years in 1958 (born in 1934-1938 and 1929-1933), and also for those born in 1959-1963, 1964-1968 and 1969-

1973 (i.e. after the Windscale accident). The assumption of Poisson distributed rates was examined by testing for overdispersion. Statistical analyses were performed using Stata and statistical significance was taken to be a two-sided $P < 0.05$.

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3. Results

During 1974-2012, among residents of England, 24,148 people (6679 (27.7%) males and 17,469 females) who were born during 1929-1973 were diagnosed with thyroid cancer. Of these, 304 people (83 (27.3%) males and 221 females) were resident in Cumbria at diagnosis, and 499 (134 (26.9%) males and 365 females) were resident in Lancashire.

Table 1 presents data for thyroid cancer cases and populations, and resulting incidence rates and incidence rate ratios (IRRs), for the study areas for people aged 0-19 years in 1958, i.e. for those born during 1939-1958 and diagnosed during 1974-2012. For Cumbria residents, there were raised IRRs (relative to the Rest of England) for those aged 0-9, 0-14 and 0-19 years in 1958, which were statistically significant for those aged 0-14 and 0-19 years, with IRRs increasing as age groups included those older in 1958 (Table 1). For 0-19 year olds, the IRR was 1.29 (95% CI 1.09, 1.52), the significantly raised IRR being primarily due to the IRR in females (male IRR, 1.07 (95% CI 0.76, 1.49); female IRR, 1.38 (95% CI 1.15, 1.67)), although the difference in the sex-specific IRRs was not significant. In contrast, for Lancashire residents, equivalent incidence rates did not differ significantly from those for the Rest of England, although for the 0-19 year age group the IRR was lowered to a marginally statistically non-significant extent, 0.91 (95% CI 0.80, 1.04), and IRRs decreased as older age groups were included (Table 1). For the combined counties of Cumbria plus Lancashire, the IRRs did not differ significantly from 1.0, the IRR for the 0-19 year age group being 1.03 (95% CI 0.93, 1.14). For comparison purposes, Table 1 also presents equivalent information for those aged 20-29 years in 1958 (born during 1929-1938); the IRR for Cumbria was significantly increased and that for Lancashire significantly decreased.

Table 2 presents data for cases and populations, and incidence rates and IRRs, for the study areas for the three successive 15-year periods of birth, 1929-1943, 1944-1958 and 1959-1973. These three birth periods represent people who were, respectively, beyond childhood, children or *in utero*, or not conceived at the time of the Windscale Fire in 1957. Supplementary Figure S5 shows the incidence rates by sex for the study areas for the three birth periods. For Cumbria residents, IRRs were significantly elevated for those born in 1929-1943 and 1944-1958, while for Lancashire residents, the IRR was significantly reduced for those born in 1929-1943 and non-significantly lowered in 1944-1958. The IRR for Cumbria and that for Lancashire for those born in 1959-1973 were unremarkable. Supplementary Figure S6 shows the IRRs by sex for Cumbria and Lancashire for these three periods of birth; the only notable difference in the sex-specific IRRs was for Cumbria residents for the 1944-1958 birth period, but the higher IRR for females was not significantly different from the IRR for males. Supplementary Figure S7 presents the variation of IRRs by attained age for Cumbria and Lancashire for the three periods of birth.

Table 3 and Figure 2 present IRRs by nine successive five-year periods of birth. For Cumbria, there were raised IRRs for all seven consecutive birth periods from 1929-1933 to 1959-1963 (the elevated IRRs for 1929-1933 and 1959-1963 being statistically significant), but not for those born during 1964-1968 and 1969-1973. The largest and most statistically significant IRR was for those born in 1959-1963, with the sex-specific IRRs being raised to a similar extent, significantly so for females (Supplementary Figure S8). For Lancashire, there were decreased IRRs for those born in the four consecutive periods 1929-1933 to 1944-1948 (the reduced IRR for 1929-1933 being statistically significant), but the IRRs for following birth periods were unexceptional. Broadly consistent temporal patterns of sex-specific

IRRs were seen for Cumbria and Lancashire (Supplementary Figure S8). For Cumbria plus Lancashire combined, IRRs did not differ significantly from 1.0 for any period of birth.

Testing for overdispersion demonstrated highly significant extra-Poisson variation in the temporal distributions of the IRRs for Cumbria and Lancashire presented in Table 3 and Figure 2. As a consequence, additional analyses were undertaken in which adjustments for extra-Poisson variation were made using the method proposed by Breslow [29]. The resulting IRRs and 95% CIs (equivalent to those shown in Tables 1 to 3) are presented in Supplementary Tables S1 to S3. None of the adjusted 95% CIs excluded unity. For those aged <20 years in 1958, the adjusted IRRs were 1.21 (95% CI 0.83, 1.76) and 0.90 (95% CI 0.62, 1.29) for residents of Cumbria and Lancashire, respectively.

4. Discussion

4.1 Interpretation of findings

This preliminary geographical study of thyroid cancer incidence was based on 24,148 registered cases of thyroid cancer, born during 1929-1973 and diagnosed aged 0-84 years while resident in England during 1974-2012. The analysis focussed on the two counties that were most contaminated by iodine-131 from the Windscale nuclear reactor fire in October 1957, namely Cumbria and (post-1974) Lancashire, and compared thyroid cancer incidence rates in residents of these counties with equivalent rates for those living in the remainder of England. Most attention was concentrated on those who were young at the time of the Windscale accident, since sensitivity to radiation-induced thyroid cancer is greatest when exposure occurs at the youngest ages (Supplementary Figure S3) [12-15, 19-24], but other ages and birth periods were considered to provide perspective.

The thyroid cancer IRR for people aged 0-19 years in 1958 was significantly increased for those diagnosed during 1974-2012 while resident in Cumbria, an IRR of 1.29 (95% CI: 1.09, 1.52), largely due to a significantly raised IRR in females; but the equivalent IRR for Lancashire was decreased to a marginally non-significant extent, an IRR of 0.91 (95% CI: 0.80, 1.04). Hence, although the raised thyroid cancer incidence rate among those born during 1939-1958 and diagnosed while living in Cumbria might be thought to suggest an effect of radioiodine released during the 1957 Windscale Fire, the decreased rate in Lancashire residents does not provide support for this inference. The IRR for Cumbria was raised, and that for Lancashire lowered, to larger extents for those aged 20-29 years in 1958 (Table 1), contrary to the greater effect at younger ages that would be predicted if radiation

exposure of the thyroid was to be involved [12-15, 19-24]. The need for caution in interpretation is reinforced by the patterns of thyroid cancer IRRs found in Cumbria and Lancashire among those born in successive five-year periods during 1929-1973 (Table 3 and Figure 2): for those born during 1954-1958, who were youngest at the time of the Fire and therefore at greatest potential risk of radiation-induced thyroid cancer [12-15, 19-24], for neither Cumbria nor Lancashire did IRRs differ significantly from 1.0. Moreover, Figure 2 shows a general tendency for increased IRRs in Cumbria that extends from those born in 1929-1933 to those born in 1959-1963, a tendency that is not repeated for Lancashire where those born in the earliest four five-year periods exhibit decreased IRRs (significantly so for those born during 1929-1933). Indeed, the Cumbrian IRR for those born in 1959-1963, 1.49 (95% CI: 1.10, 2.02), is the highest and most statistically significant of all the IRRs examined (with the IRRs being elevated to similar levels in both sexes), and relates to individuals who were not exposed to iodine-131 released during the 1957 Fire.

The difficulties of interpretation of the patterns of thyroid cancer IRRs are exacerbated by the highly significant extra-Poisson variation exhibited by the distributions. When appropriate adjustment is made to account for overdispersion, none of the IRRs differs significantly from 1.0. The extra-Poisson variation displayed in Figure 2 could be due to a non-uniform presence of major thyroid cancer risk factors, or shortcomings in the incidence data, or both.

4.2 Potential problems with registration data

What might be responsible for the observed patterns of thyroid cancer IRRs? One possibility is incompleteness of thyroid cancer registration that has varied geographically and temporally. In their study of the geographical distribution and temporal trends of thyroid cancer incidence in England and Wales during 1968-1985,

dos Santos Silva and Swerdlow [30] noted that the completeness of cancer registration was known to vary across England and Wales [31], and the degree of completeness will have varied geographically over time [27]. To address this problem, dos Santos Silva and Swerdlow [30] obtained for each county the ratio of the age- and sex-adjusted thyroid cancer registration rate to that for a weighted sample of other sites of cancer, and then compared this county ratio with the equivalent ratio for the rest of England and Wales. This approach attempts to correct for any differential cancer registration completeness at the county level. We did not have access to registration data for other types of cancer to adopt this approach, which does implicitly assume that the efficiency of registration for largely non-fatal thyroid cancer is the same as that for cancers with a greater lethality. A preliminary comparison of annual rates of registration of thyroid cancer and of all cancers during 1974-1989 in Cumbria, Lancashire and the Rest of England did not reveal any obvious shortcomings in thyroid cancer registration rates in Cumbria and Lancashire, but further investigations are required to make a full assessment of the patterns of IRRs present in Figure 2.

The rate of detection of thyroid cancer is also an issue of relevance. There is no doubt that the ability to detect smaller thyroid tumours has improved, which has led (at least in part) to increases in recorded thyroid cancer incidence rates in Great Britain (Supplementary Figure S9) and in other countries [25, 32, 33]. In some countries, such as South Korea, where ultrasonography screening has increasingly become used, the rise has been dramatic [34, 35]. It seems most unlikely that geographical variation in detection efficiency could account for the patterns in IRRs that we have observed, although this could have made some contribution, particularly if a high rate of benign thyroid diseases in an area has led to a higher

frequency of medical investigations that have then detected small malignant tumours.

dos Santos Silva and Swerdlow [30] point to the geographical distribution of benign thyroid diseases as being of potential relevance to the geographical distribution of thyroid cancer in England and Wales. In particular, they draw attention to county mortality rates for exophthalmic goitre in the first half of the twentieth century and the similarity of the geographical distribution of these rates to that of thyroid cancer incidence rates in their study. The pre-1974 county of Westmorland (now part of Cumbria) was notable for its high rate of exophthalmic goitre mortality, and this may be relevant to the increased rates of thyroid cancer incidence found in Cumbria, particularly for births in earlier periods; dos Santos Silva and Swerdlow [30] suggest that iodine deficiency might be a common factor underlying these raised rates of benign and malignant thyroid disease. While it is established that iodine deficiency increases the risk of benign thyroid disorders, its role in thyroid cancer is not so clear, although evidence suggests that it is a risk factor [36].

4.3 Limitations of the study

The study has a number of limitations, which bear upon the interpretation of its findings. Of fundamental relevance is that it is a geographical (“ecological”) study, dealing with groups of people, so rendering it susceptible to the “ecological fallacy” of erroneously making inferences about individuals from the findings for groups. It could not account for inward and outward migration in Cumbria and Lancashire, which may have led to the inclusion of people diagnosed with thyroid cancer while resident in these two counties who were living elsewhere at the time of the accident, and to the exclusion of those living in Cumbria and Lancashire in late-1957 who were resident outside these counties at diagnosis. The influence of migration upon the findings of

this study is dependent, not only upon the absolute numbers of migrants, but also, *inter alia*, upon their ages at the time of the Fire and at migration, which complicates an assessment of its impact. Birth period population estimates had to be obtained from attained age-period population data making certain assumptions, although the results do not appear to be especially sensitive to these assumptions.

The study deals with the whole counties of Cumbria and Lancashire, whereas iodine-131 deposition from the Windscale Fire was not geographically uniform within these counties (Figure 1). For example, in Cumbria contamination was greatest in the immediate vicinity of Sellafield and to the south-east of the site, while Carlisle, Workington and Maryport (to the north of Sellafield) were hardly affected [2, 5], but the study could not distinguish between thyroid cancer cases resident in areas of Cumbria contaminated at different levels of iodine-131 following the accident because only incidence data at the county level were made available to us. Potentially, thyroid cancer incidence in areas of north-west England smaller than counties could be examined if confidentiality requirements permitted such registration data to be made available, and incidence rates related to estimated doses received from iodine-131 in these smaller areas using methods such as those outlined by Crick and Linsley [11]; but such refinement could not overcome other limitations of a geographical study. For example, in a geographical study individual thyroid doses within a particular area are not estimated, but even in areas contaminated to a similar extent, intake of radioiodine will have been variable [11] (e.g. through the consumption of milk in differing volumes from a variety of sources).

Since exposure in childhood is predicted to lead to an increased risk of thyroid cancer throughout the remaining lifetime, excess cases among those exposed at a young age during 1957 may occur beyond the study end-date of 2012. In addition,

cases of thyroid cancer diagnosed before 1974 were not included in the study. However, the minimum latent period for radiation-induced thyroid cancer is around five years [12-15, 23, 24], and thyroid cancer data for the period 1959-1975 for mortality and 1961-1975 for incidence from the study of Cook-Mozaffari *et al* [37] for those areas of Cumbria and Lancashire most affected by iodine-131 contamination from the Windscale Fire demonstrate that thyroid cancer rates before 1974 in these areas are unexceptional (among those <25 years of age, there was only one incident case recorded during 1961-1975, and no death during 1959-1975), so the omission of cases incident before 1974 is most unlikely to have had a material impact upon our study (Supplementary Table S4).

Clarke [17, 18] suggested that around 60 additional cases of thyroid cancer would result from exposure to iodine-131 released during the accident. However, under the conventional assumption of a linear no-threshold dose-response, the predicted excess risk of thyroid cancer will be distributed geographically according to the areal distribution of the collective thyroid dose received by the affected population, so that although the highest individual thyroid doses will have occurred in Cumbria, followed by Lancashire, only about one-sixth of the collective thyroid dose was received by the population of Cumbria [11], the remainder being received principally by the population of the rest of England (composed of the sum of many very low individual thyroid doses) [11]. On this basis, only around 10 excess cases of thyroid cancer would be predicted to occur among those exposed to iodine-131 in Cumbria as children in the last three months of 1957, primarily incident at older attained ages many years after the accident. Consequently, the ability to detect any influence of the accident upon thyroid cancer risk in Cumbria and Lancashire is limited. Nonetheless, it should be borne in mind that Clarke [17, 18] performed these

calculations in the late-1980s, and factors such as revised radiation-induced thyroid cancer risk models, increasing background thyroid cancer incidence rates and increasing longevity will have modified the predicted number of thyroid cancers attributable to the Windscale accident, most probably in an upwards direction.

In this study, all thyroid cancer types have been considered together with no separation into the various types. Most thyroid cancers (~80%) are papillary and so cases of papillary thyroid cancer would be expected to dominate overall patterns of incidence [20]. However, the radiation dose-response for non-papillary thyroid cancers has been found to be statistically compatible with that for papillary thyroid cancers [20], so the combining of all thyroid cancer cases as a single grouping for analysis is unlikely to affect the findings of this investigation.

It has been assumed in this study that thyroid doses consequent to the Windscale Fire were dominated by the intake of short-lived iodine-131. However, other radionuclides with longer half-lives (e.g. polonium-210 and caesium-137) were also released; but the contribution of these other radionuclides to the thyroid dose was much less than that of iodine-131 [11]. Finally, thyroid doses from iodine-131 were assumed to result from the 1957 Windscale accident, but iodine-131 contamination will also have arisen from routine and other releases from Sellafield, and more generally from fallout from atmospheric nuclear weapons testing and the Chernobyl accident; these sources will be considered in more detail below.

4.4 Other sources of exposure to iodine-131

Wakeford [38] made a preliminary assessment of routine and inadvertent discharges of iodine-131 from early irradiated fuel reprocessing and reactor operations (other than the 1957 Fire) at Sellafield, and concluded that 62 TBq of iodine-131 may have been discharged to atmosphere during 1952-1966. This assessed level of discharge

is some 30 times less than the estimated release to atmosphere of 1800 TBq of iodine-131 during the 1957 Windscale Fire [3]. Annual thyroid doses received by young children from Sellafield discharges of iodine-131 during this period (other than the 1957 accident) are likely to have been around 1 mGy in the neighbourhood of the site [39]. Wakeford [38] emphasised that that this figure of 62 TBq of iodine-131 discharged during the first 15 years of nuclear operations at Sellafield is highly uncertain.

Atmospheric nuclear weapons testing, at its height in the late-1950s and early-1960s, also led to exposure to radioactive iodine produced in the explosions. Iodine-131 deposition will have depended on the direction of travel of the radioactive debris of a test explosion and on the level of local precipitation. The average annual thyroid dose from radioiodine in weapons testing fallout in the UK was about 1 mGy during the period of peak testing, with regional variations of around a factor of two [40]. Contamination from the Chernobyl nuclear reactor accident in 1986 affected Cumbria to a greater extent than the rest of England because of rainfall as the plume passed overhead [41]. Even so, thyroid doses received by young children living in Cumbria from iodine-131 deposition in 1986 were only a few milligray at most [42], and any effect of these doses on thyroid cancer risk would lag those of the Windscale Fire by around 30 years.

Thyroid doses from natural background radiation, largely from external sources, are around 1 mGy per annum and are rather uniform geographically [11]. The remaining major source of radiation exposure of the thyroid is from medical practice [43]. In individual instances (e.g. radiotherapy) doses can be high, but such doses received by children are rare, and it is unlikely that the population-based distribution of these doses will be materially non-uniform.

In summary, annual thyroid doses received by children living in north-west England in the mid- to late-1950s amounted to around 1 mGy from natural background radiation and generally approached 1 mGy from iodine-131 produced in atmospheric nuclear weapons testing, with some children receiving additional doses from medical exposures. Routine and unintentional discharges of iodine-131 from Sellafield (apart from the 1957 accident) may have led to thyroid doses of a few milligray close to the site, but doses would have attenuated with distance from Sellafield. Against this background, doses to thyroids of children measured soon after the Windscale Fire of 1957 occasionally exceeded 100 mGy within 20 km of Sellafield (possibly as a result of drinking locally sourced milk), but were generally around 10-20 mGy, and reduced with distance from the site in a manner that varied with the direction of travel of the plume [2, 11].

4.5 Review of studies of exposure to iodine-131

Following the explosion in a nuclear reactor at Chernobyl, Ukraine, in April 1986, 1800 PBq of iodine-131 was released to atmosphere (i.e. 1000 times greater than during the Windscale accident) [16]. Several tens of thousands of children in the worst affected areas of the former USSR received high thyroid doses (>1 Gy), mainly as a result of drinking heavily contaminated milk [16]. Excess cases of thyroid cancer among those highly exposed to radioiodine as children started to appear in 1990, and several thousand additional cases of thyroid cancer have now resulted [16], with several thousand future cases predicted on the basis of current radiation-induced thyroid cancer risk models [12-15, 23, 24]. The greatest risk of thyroid cancer has been experienced by those who received high thyroid doses at the youngest ages [16], and the level of this risk broadly conforms to what would be predicted based on evidence from the Japanese atomic-bomb survivors and those exposed to radiation

from external sources for medical reasons [44, 45]. Evidence of an excess risk of thyroid cancer in areas less contaminated by Chernobyl fallout is much less clear [16]. In Finland, which was one of the countries most affected by Chernobyl contamination outside the former USSR, no increased risk of thyroid cancer among those exposed while less than 21 years of age in 1986 was detected [46], although the average thyroid dose in Finland of a few milligray was far less than those received around Chernobyl [16].

Using data from the Northern Region Young Person's Malignant Disease Registry, Cotterill *et al* [47] suggested that an increased rate of thyroid cancer incidence among those <25 years of age in Cumbria during 1987-1997 might be attributable to contamination from the Chernobyl accident, and Magnanti *et al* [48] noted that this increased incidence rate for Cumbria persisted into 1998-2005; the incidence in Cumbria during 1987-2005 was entirely due to nine cases in females [48]. However, exposure to iodine-131 from the Chernobyl accident will have been effectively confined to May-July 1986, so any children conceived after this period will not have been so-exposed, and any such cases should be excluded from the analyses. Account should also be taken of the minimum latent period of about five years, and of the residence of the cases at the time of the accident in relation to the geographical distribution of the contamination levels in Cumbria. Consequently, the findings are not readily interpretable in terms of the potential role of iodine-131 fallout from Chernobyl. In any event, average thyroid doses received by children in Cumbria in 1986 were only around a milligray [42], i.e. comparable to those received from natural background radiation every year.

Iodine-131 has been released into the environment from other nuclear installations, both routinely and accidentally. Substantial quantities were released

during the Fukushima accident in Japan in 2011, although the largest consequent thyroid doses are assessed to have been considerably less than those received after the Chernobyl accident [26], and given a minimum latent period of around five years, the time that has elapsed since the Fukushima accident is too short for any increased risk of thyroid cancer to have become evident. Recent claims of a radiation-related increase of thyroid cancer cases in Fukushima Prefecture [49] are highly suspect [50].

From 1944 to 1957, the Hanford Nuclear Site in Washington State, USA, reprocessed nuclear fuel that had been stored for a comparatively short time after irradiation, and substantial quantities of iodine-131 (27 PBq) were released to atmosphere during this period [51]. Davis *et al* [51] conducted a historical cohort study of thyroid disease among almost 3500 people who had potentially been exposed as children to iodine-131 discharged from Hanford. Considerable efforts were made to reconstruct thyroid doses, and medical examinations of study subjects were carried out by thyroid specialists during 1992-1997. The maximum estimated individual thyroid dose was 2823 mGy, with a median of 97 mGy and a mean of 174 mGy, doses that are around an order of magnitude greater than those typically received locally from the Windscale Fire, but substantially less than the doses received after the Chernobyl accident in heavily contaminated areas of the former USSR. Davies *et al* [51] found no evidence of a relationship between the dose received from Hanford releases and the cumulative incidence of thyroid cancer (19 cases) or of any other thyroid disease. The authors stated that the study had sufficient statistical power to detect the increases of thyroid diseases that had been reported elsewhere following exposure to iodine-131, although others have pointed

to the low power of the study to detect the predicted excess risk of thyroid cancer [13, 52].

The Mayak nuclear complex in the Southern Urals of the Russian Federation commenced reactor operations in 1948 and started reprocessing irradiated nuclear fuel in 1949. During 1948-1972 about 38 PBq of iodine-131 was discharged to atmosphere from Mayak [53]. A child born in 1947 in the nearby closed city of Ozyorsk and living there until 1972 is estimated to have received a cumulative thyroid dose during this period of 2280 mGy. For young children five years of age living in Ozyorsk, the maximum annual thyroid dose was approaching 1000 mGy in 1949, with annual doses decreasing to around 10 mGy by the late-1950s. Koshurnikova *et al* [54] studied thyroid cancer incidence during 1948-2009 in Ozyorsk and the neighbouring city of Kyshtym, and compared rates based on registries in these cities with those derived from incidence data for the regional centre of Chelyabinsk during 1993-2006. They reported that thyroid cancer incidence rates in Ozyorsk and Kyshtym during 1948-2009 were 50% higher than the rate in Chelyabinsk during 1993-2006, although details of the Chelyabinsk data were not given, and it is difficult to interpret this finding from the information reported.

There have been reports of raised levels of thyroid cancer incidence around some nuclear installations that have discharged much lower levels of iodine-131. In Belgium, thyroid cancer incidence was reported to be raised to a marginally significant extent around the Mol-Dessel and Fleurus sites where a number of nuclear research and industrial facilities are located [55]. In 2008, 48 GBq of iodine-131 was accidentally released from the radioiodine production plant at Fleurus, but a conservative assessment of the maximum thyroid dose received by an infant as a consequence of this discharge was just 0.6 mGy [56], and a causal link is unlikely

[57]. Similarly, a report of an elevated incidence rate of thyroid cancer in the vicinity of the Three Mile Island nuclear power station in Pennsylvania [58], where 550 GBq of iodine-131 was released to atmosphere during the 1979 reactor accident (leading to an estimated maximum individual thyroid dose of <0.2 mGy [17]), is difficult to interpret given the background of high thyroid cancer incidence throughout Pennsylvania [59]. Kim *et al* [60] have reviewed, and conducted a meta-analysis of, studies of the risk of thyroid cancer and residence near nuclear power stations. Overall, they concluded that the evidence does not support an association, but noted various shortcomings in the studies available to their investigation.

Above-ground nuclear weapons test explosions led to locally raised deposition of radioiodine near the test sites, which frequently involved exposure to short-lived iodine-133 (half-life, 21 h) in addition to iodine-131. Studies of thyroid cancer incidence have been undertaken near the Nevada Test Site in the USA, the Semipalatinsk Nuclear Test Site in Kazakhstan (formerly part of the USSR) and in the Marshall Islands in the Pacific Ocean. Lyon *et al* [61] studied thyroid disease in a cohort of nearly 2500 people who were children in 1965 and living near the Nevada Test Site, who were medically examined in 1985-1986. The maximum assessed individual thyroid dose was 1.4 Gy and the mean 0.12 Gy [62]. Eight cases of thyroid cancer were found, but the dose-response was unremarkable, although the positive dose-response for benign thyroid disease was highly significant. Land *et al* [63] investigated thyroid disease among almost 2400 people who were resident downwind of the Semipalatinsk Nuclear Test Site during 1949-1962 while less than 21 years of age. The prevalence of thyroid nodules was assessed by ultrasound screening in 1998, and 35 cases of thyroid cancer were detected. Estimated thyroid doses ranged up to several gray, with a mean of 100-200 mGy, although

uncertainties were substantial. The dose-response for thyroid cancer was positive, but not significantly so. Residents of the Marshall Islands were exposed to radioiodine as a result of testing of nuclear weapons by the USA, and particularly so by inadvertent exposure from the Castle Bravo thermonuclear test explosion in 1954 that led to assessed thyroid doses of around 20 Gy for young children living on Rongelap Island [64]. Examination of nearly 6000 Marshallese during 1993-1997 found a high prevalence of thyroid cancer, especially among those alive at the time of the Castle Bravo test [65]. Finally, studies of thyroid cancer incidence throughout Scandinavia [66] and the USA [67] have suggested an increased risk of thyroid cancer among those exposed in childhood to nuclear weapons testing fallout, although the authors were cautious in their conclusions.

Three studies including more than 6000 children administered known amounts of iodine-131 for diagnostic purposes (giving a mean thyroid dose of 1 Gy) did not find an excess of thyroid cancer [68]. However, the numbers of children exposed while less than ten years of age, who would be at most risk, were small.

4.6 Other relevant studies in Cumbria

Bowlit and Tiplady [69] measured levels of long-lived iodine-129 (half-life, 16 million years) in 130 human thyroids from Cumbria and compared them with distance of residence from Sellafield; environmental levels of iodine-129 around Sellafield will be dominated by routine releases, not the 1957 accident [38]. Incidence rates of thyroid cancer in Cumbria during 1969-1986 (using data from the Northern Regional Cancer Registry for both sexes and all ages) were also examined. Levels of iodine-129 in thyroids decreased significantly, whereas the age- and sex-adjusted incidence rate of thyroid cancer increased significantly, with distance from Sellafield. Bowlit and Tiplady [69] reported that during 1969-1986 the thyroid cancer incidence rate for

Cumbria relative to the national rate, at 0.77, was significantly low, particularly so for Copeland District (0.49) containing Sellafield, but these ratios are not directly comparable with those obtained from our study – Bowlit and Tiplady [69] included cases incident at all ages during 1969-1986 whereas we included cases born in 1929-1973 and diagnosed during 1974-2012.

Recently, Bunch *et al* [70] have reported the findings of a cohort study of cancer incidence among those who were born in Cumbria during 1950-2006 and diagnosed while resident in the UK during 1971-2006, which included thyroid cancer among those born in the village of Seascale (adjacent to Sellafield), the rest of Copeland and Allerdale districts, and the remainder of Cumbria. Overall, 89 cases of thyroid cancer were observed: 0 in Seascale births (0.44 case expected), 30 in the rest of Copeland and Allerdale (34.7 expected), and 59 in the remainder of Cumbria (56.9 expected). It is not possible from the results as reported to infer much of substance about the incidence of thyroid cancer in relation to the 1957 Windscale accident, except that thyroid cancer incidence rates among those alive at the time of the accident have not made a notable impact upon the overall level of incidence of thyroid cancer among people born in Cumbria during 1950-2006. The Cumbrian birth cohort [70] potentially permits a study of thyroid cancer risk among those born during 1950-1958 with respect to individual thyroid doses assessed to have been received as a result of the radioiodine released during the Windscale Fire; such a study could address many of the limitations of the “ecological” study reported here, and would be preferable to attempts to refine the geographical approach to investigating thyroid cancer risk related to the Windscale accident.

5. Conclusions

The registration rate of incident thyroid cancer in Cumbria during 1974-2012 among those who were less than 20 years of age in 1958 was significantly raised in comparison to that in England excluding Cumbria and Lancashire. In contrast, the equivalent registration rate for neighbouring Lancashire was lower than that in the Rest of England to a marginally non-significant extent. Further, the high registration rates of thyroid cancer in Cumbria extend from births in 1929-1933 to births in 1959-1963; the individuals born in this latter period were unexposed to iodine-131 from the Windscale Fire, but had the highest and most statistically significant incidence rate ratio found in this study. Highly significant extra-Poisson variation in the thyroid cancer incidence rates implies that interpretation of these findings must take account of major underlying factors affecting these rates. This pattern of thyroid cancer incidence does not suggest that the raised rate in Cumbria among those born during 1939-1958 can reasonably be attributed to exposure to iodine-131 released during the 1957 Windscale nuclear reactor accident, and a review of the literature on thyroid cancer risk following exposure to radioactive iodine supports this conclusion. However, further investigation of the reasons for the patterns of thyroid cancer incidence found in this preliminary geographical study would seem prudent.

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R Wakeford advises the UK Compensation Scheme for Radiation-Linked Diseases, otherwise the authors declare no conflict of interest.

The study used routinely collected and collated data and no person was approached for additional information; for this type of study formal individual consent is not required. A Data Sharing Agreement was negotiated with the Public Health England Office for Data Release; this stipulated destruction of the original data on completion of the analysis and that published results would not permit identification of individuals. All procedures performed in the study were in accordance with the ethical standards of appropriate institutional/national research ethics committees and

with the 1964 Declaration of Helsinki and its later amendments, or comparable ethical standards.

ACCEPTED MANUSCRIPT

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Table Captions

Table 1: Thyroid cancer incidence registration and population data, and derived thyroid cancer incidence rates and incidence rate ratios (IRRs), for people aged 0-19 years in 1958 (born during 1939-1958) and age subgroups 0-9 and 0-14 years in 1958. For comparison purposes, the equivalent information for those aged 20-29 years in 1958 (born 1929-1938) is also presented. Cases were diagnosed during 1974-2012 while resident in the respective areas of England. Poisson 95% confidence intervals (CIs) are shown for IRRs.

Table 2: Thyroid cancer incidence registration and population data, and derived thyroid cancer incidence rates and incidence rate ratios (IRRs), for those born in three successive 15-year periods during 1929-1973, and diagnosed during 1974-2012 while resident in the respective areas of England. Poisson 95% confidence intervals (CIs) are shown for IRRs.

Table 3: Thyroid cancer incidence rate ratios (IRRs) and Poisson 95% confidence intervals (CIs), for cases diagnosed during 1974-2012 while resident in Cumbria, Lancashire, and Cumbria combined with Lancashire, for nine successive five-year calendar periods of birth during 1929-1973. Reference thyroid cancer incidence rates are those for the Rest of England for the respective periods of birth.

Figure Captions

Figure 1. Map of northern England, showing iodine-131 deposition in the counties of Cumbria and Lancashire following the Windscale nuclear reactor accident at Sellafield in October 1957. Contours of iodine-131 deposition are labelled in units of $\mu\text{Ci.m}^{-2}$ (37 kBq.m^{-2}) (after Chamberlain [5]). See also Supplementary Figure S2.

Figure 2. Thyroid cancer incidence rate ratios (IRRs), for cases diagnosed during 1974-2012 while resident in either Cumbria or Lancashire, for nine successive five-year calendar periods of birth during 1929-1973. Reference thyroid cancer incidence rates are those for the Rest of England for the respective periods of birth. Error bars are Poisson 95% confidence intervals.

Table 1. Thyroid cancer incidence registration and population data, and derived thyroid cancer incidence rates and incidence rate ratios (IRRs), for people aged 0-19 years in 1958 (born during 1939-1958) and age subgroups 0-9 and 0-14 years in 1958. For comparison purposes, the equivalent information for those aged 20-29 years in 1958 (born 1929-1938) is also presented. Cases were diagnosed during 1974-2012 while resident in the respective areas of England. Poisson 95% confidence intervals (CIs) are shown for IRRs.

Area of England	Age in 1958 (years)			
	0-9	0-14	0-19	20-29
Number of Registered Incident Cases of Thyroid Cancer				
Cumbria	69	113	147	68
Lancashire	130	188	231	79
Cumbria + Lancashire	199	301	378	147
Rest of England	5316	8259	10509	4557
Population at Risk (thousand person-years)				
Cumbria	2620	3922	5073	2011
Lancashire	5841	8728	11245	4301
Cumbria + Lancashire	8461	12650	16318	6312
Rest of England	247409	365152	467084	174835
Thyroid Cancer Incidence Rate (cases per million person-years)				
Cumbria	26.34	28.81	28.98	33.82
Lancashire	22.26	21.54	20.54	18.37
Cumbria + Lancashire	23.52	23.79	23.16	23.29
Rest of England (reference)	21.49	22.62	22.50	26.06
Incidence Rate Ratio with respect to the Rest of England (95% CI)				
Cumbria	1.23 (0.97,1.55)	1.27 (1.06,1.53)	1.29 (1.09,1.52)	1.30 (1.02, 1.65)
Lancashire	1.04 (0.87,1.23)	0.95 (0.82,1.10)	0.91 (0.80,1.04)	0.70 (0.56, 0.88)
Cumbria + Lancashire	1.09 (0.95,1.26)	1.05 (0.94,1.18)	1.03 (0.93,1.14)	0.89 (0.76, 1.05)

Table 2: Thyroid cancer incidence registration and population data, and derived thyroid cancer incidence rates and incidence rate ratios (IRRs), for those born in three successive 15-year periods during 1929-1973, and diagnosed during 1974-2012 while resident in the respective areas of England. Poisson 95% confidence intervals (CIs) are shown for IRRs.

Area of England	Born 1929-1943*	Born 1944-1958*	Born 1959-1973*
Number of Registered Incident Cases of Thyroid Cancer			
Cumbria	102	113	89
Lancashire	122	188	189
Cumbria + Lancashire	224	301	278
Rest of England	6807	8259	8279
Population at Risk (thousand person-years)			
Cumbria	3162	3922	4079
Lancashire	6818	8728	9444
Cumbria + Lancashire	9980	12650	13523
Rest of England	276766	365152	413831
Thyroid Cancer Incidence Rate (cases per million person-years)			
Cumbria	32.26	28.81	21.82
Lancashire	17.89	21.54	20.01
Cumbria + Lancashire	22.45	23.79	20.56
Rest of England (reference)	24.59	22.62	20.01
Incidence Rate Ratio with respect to Rest of England (95% CI)			
Cumbria	1.31 (1.08, 1.59)	1.27 (1.06, 1.53)	1.09 (0.88, 1.34)
Lancashire	0.73 (0.61, 0.87)	0.95 (0.82, 1.10)	1.00 (0.87, 1.16)
Cumbria + Lancashire	0.91 (0.80, 1.04)	1.05 (0.94, 1.18)	1.03 (0.91, 1.16)

* Those born during 1944-1958 were children or *in utero* at the time of the Windscale Fire in October 1957, those born during 1929-1943 were beyond their childhood years at the time of the accident, and those born during 1959-1973 were not exposed to iodine-131 released during the accident.

Table 3: Thyroid cancer incidence rate ratios (IRRs) and Poisson 95% confidence intervals (CIs), for cases diagnosed during 1974-2012 while resident in Cumbria, Lancashire, and Cumbria combined with Lancashire, for nine successive five-year calendar periods of birth during 1929-1973. Reference thyroid cancer incidence rates are those for the Rest of England for the respective periods of birth.

Period of Birth	Incidence Rate Ratio (95% CI)		
	Cumbria	Lancashire	Cumbria + Lancashire
1929-1933	1.44 (1.05, 1.99)	0.61 (0.43, 0.85)	0.87 (0.69, 1.10)
1934-1938	1.15 (0.80, 1.65)	0.80 (0.60, 1.08)	0.91 (0.73, 1.15)
1939-1943	1.34 (0.95, 1.88)	0.77 (0.57, 1.05)	0.95 (0.76, 1.19)
1944-1948	1.35 (1.00, 1.82)	0.80 (0.62, 1.04)	0.97 (0.80, 1.19)
1949-1953	1.32 (0.96, 1.81)	1.02 (0.80, 1.30)	1.11 (0.92, 1.35)
1954-1958	1.12 (0.78, 1.61)	1.05 (0.82, 1.35)	1.07 (0.87, 1.32)
1959-1963	1.49 (1.10, 2.02)	0.91 (0.70, 1.17)	1.09 (0.89, 1.32)
1964-1968	0.93 (0.64, 1.36)	0.97 (0.76, 1.24)	0.96 (0.78, 1.18)
1969-1973	0.80 (0.51, 1.25)	1.15 (0.90, 1.47)	1.04 (0.84, 1.30)

Figure 1. Map of northern England, showing iodine-131 deposition in the counties of Cumbria and Lancashire following the Windscale nuclear reactor accident at Sellafield in October 1957. Contours of iodine-131 deposition are labelled in units of $\mu\text{Ci.m}^{-2}$ (37 kBq.m^{-2}) (after Chamberlain [5]). See also Supplementary Figure S2.

Figure 2. Thyroid cancer incidence rate ratios (IRRs), for cases diagnosed during 1974-2012 while resident in either Cumbria or Lancashire, for nine successive five-year calendar periods of birth during 1929-1973. Reference thyroid cancer incidence rates are those for the Rest of England for the respective periods of birth. Error bars are Poisson 95% confidence intervals.