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Can paternal preconceptional radiation account for the increase of leukaemia and non-Hodgkin's lymphoma in Seascale?

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Abstract

Objective—To determine if the excess of leukaemia and non-Hodgkin's lymphoma in Seascale is restricted to those born in the parish and whether it might be explained by the postulated relation with paternal preconceptional radiation.

Design—Comparison, separately for those born in the parish and those born elsewhere, of the numbers of these malignancies observed in Seascale with those expected on the basis of reference rates for England and Wales. Details of paternal radiation levels were sought for each case.

Setting—The parish of Seascale in west Cumbria.

Subjects—Residents of Seascale below age 25 years in the years 1951-91.

Main outcome measures—The observed and expected numbers of cases of leukaemia and non-Hodgkin's lymphoma within Seascale among those born there and among those born elsewhere. Also, the levels of any paternal preconceptional radiation associated with each case.

Results—A significant excess of leukaemia and non-Hodgkin's lymphoma at ages 0-24 was found in Seascale in those who were born there (ratio of observed to expected cases 8.6 and 20.2 respectively; $p < 0.01$). This also applied to those not born there (7.2 and 16.5; $p < 0.01$), a group often regarded as not showing an excess. The estimates were then conservatively recalculated so as to overestimate the risks among those born in Seascale and underestimate them among those born elsewhere. On this basis the six cases in those born in Seascale compare with 0.38 expected (15.8; $p < 0.001$), of which two were associated with paternal preconceptional life-time levels of 100 mSv or greater and three others with levels of 90-99 mSv. Among those born elsewhere, there were five cases (expected 0.74; ratio 6.7, $p < 0.01$), of which only one was associated with a high level of such radiation.

Conclusions—Paternal preconceptional radiation cannot be the sole cause of the excess in Seascale since it will not explain the excess among those born

outside Seascale. It follows that, unless two causes are to be postulated, any single cause must be a factor other than paternal preconceptional radiation. On this basis, the association found among those born there, if not partly due to chance, may reflect an indirect relation with the true cause. The recent hypothesis about such paternal radiation has originated in a subgroup of the excess cases that have aroused concern.

Introduction

An increased incidence of leukaemia and non-Hodgkin's lymphoma among young people in Seascale near the nuclear site of Sellafield in west Cumbria has been the subject of much study. Recent work has further strengthened the evidence of an excess, indicating its magnitude as well as its persistence into a recent period.¹ The suggested explanation for this excess attracting most attention is that concerning paternal preconceptional exposure to relatively high levels of radiation.² This association with leukaemia, which emerged from a study restricted to young people born in west Cumbria, is postulated to be causal and also to explain the excess in Seascale.² In fact, the relevant paternal exposure details have been reported only for those children born in Seascale—because no excess was considered to be present in young people who were born elsewhere.^{3,4} However, this view has been questioned, and the need for paternal details in cases of these malignancies among those born outside Seascale has been emphasised.⁵ These aspects are examined here.

Methods

LEUKAEMIA AND NON-HODGKIN'S LYMPHOMA

Cases of leukaemia and non-Hodgkin's lymphoma recurring below age 25 in Seascale from 1951 to 1991 were identified. The particulars of cases up to 1983 which are listed in the report of the Black Advisory Group⁶ have been supplemented by details obtained

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from a national series of death certificates, from relevant birth certificates, and from local clinicians. Cases diagnosed since 1983¹ have also been included.

SEASCALE POPULATIONS

Population details by five year age group up to age 24 for Seascale parish were obtained from the Office of Population Censuses and Surveys in the form of unpublished tables for the census years 1961, 1971, 1981, and 1991. The only age group below age 25 for which a 1951 census count is available is 0-14 years (383). Records of the local authority school in Seascale showed 181 children aged 5-15 on the roll for that year and this has been taken as approximating to the number of residents aged 5-14 years, implying a population of about 202 for the 0-4 age group. The proportion of the 1951 population aged 5-14 that were aged 5-9 and also the population aged 15-19 and 20-24 were derived using the levels recorded in these age groups in the three subsequent censuses. The age specific populations in intercensal years were derived by linear interpolation. In this way person years by age group could be assembled for 1951-5 and for subsequent quinquennia to 1981-5 and also for the final period 1986-91.

For children born in Seascale, populations by single years of age and single calendar years were estimated by using details of the numbers of births to residents in the years 1950-83 and of moves from the parish by members of this cohort by age and calendar period reported in a previous study.⁷ For the years before 1949 and after 1983 the numbers of births were assumed to be low—three per year before 1950 (when the school roll showed an average of around 40 children aged 5-15) and 15 per year after 1983. The levels of outward

movement from Seascale among those born there were taken to be slightly higher than those reported,⁷ thereby reducing the estimated numbers of those still resident there. These were calculated by rounding the fractions of those remaining in Seascale in each quinquennial calendar period in each age group (derived from table IVb in reference 7) downwards to the nearest 0.05 (for example, 0.79 became 0.75 and 0.74 became 0.70). More importantly, it was assumed that the percentage who left at, say, ages 0-4 all migrated below age 1. To further underestimate the populations in each single year of age and single calendar year, only the integer part of each number was used (for example, 12.9 was treated as 12).

Population estimates for those born elsewhere were derived by subtracting the details of those born in Seascale from the estimates for all residents of the parish. Because the numbers of those born within Seascale had been underestimated, the estimates for those born elsewhere would tend to be inflated, as would the corresponding expected numbers. Erring on the side of exaggerating the expected numbers for the group of special interest, namely those born elsewhere,⁵ would lead to a conservative estimate of any excess in this group. As a check on this method it was applied to the births in the years 1950-83 covered in the earlier study.⁷ Following up this group until mid-1986 by this method yielded a value of 7548 person years during residence in Seascale—appropriately smaller numbers than those published (8711).⁷

EXPECTED NUMBERS

The numbers of cases of leukaemia and non-Hodgkin's lymphoma observed in Seascale from 1951 to 1991 were compared with the numbers that would be expected. Expected numbers were calculated by applying national reference rates by age group and quinquennium to the corresponding population estimates for Seascale residents who were born there. A similar procedure was carried out for Seascale residents who were born outside the parish. For the period 1962-91, incidence rates for England and Wales from the national register of childhood cancers for ages 0-4, 5-9 and 10-14 and from the national cancer registration scheme for ages 15-19 and 20-24 were used. (Because of concern about incomplete registration of cases in those national schemes in the recent period it was judged prudent to use the rates for 1981-5 also for the period 1986-91.) For the earlier years 1951-61, for which reliable incidence data are not available, the corresponding national mortality rates were used both because incidence rates are not available for that period and because these malignancies were nearly always fatal.

RADIATION DETAILS

For the fathers of all individuals with leukaemia or non-Hodgkin's lymphoma, details were sought from the relevant nuclear bodies of any radiation exposures at Sellafield or elsewhere before the relevant conception, taken as 266 days (38 weeks) before the date of birth.

Results

The observed and expected numbers of leukaemia and non-Hodgkin's lymphoma in Seascale by age group and calendar period are shown in tables I and II, separately for those born in the parish and for those born outside. The use of different methods for estimating the age specific population for 1951 (consistent with the published census figure for the age group 0-14) had little effect on the expected numbers. No non-fatal case of either malignancy occurred in the years 1951-61, when national mortality was used as the

TABLE I—Leukaemia in young people in Seascale: observed and expected numbers by age group and calendar period 1951-91

Age group	1951-60	1961-70	1971-80	1981-91	Total	Ratio of observed to expected cases	p Value
Cases among those born in Seascale (expected values in parentheses are underestimates)							
0-4	1 (0.04)	1 (0.05)	1 (0.04)	0 (0.04)	3 (0.17)		
5-9	0 (0.01)	0 (0.02)	1 (0.02)	0 (0.02)	1 (0.07)		
10-14	0 (0.00)	0 (0.01)	0 (0.01)	0 (0.01)	0 (0.03)		
15-19	0 (0.00)	0 (0.00)	0 (0.01)	0 (0.01)	0 (0.02)		
20-24	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.01)	0 (0.01)		
0-24	1 (0.05)	1 (0.09)	2 (0.09)	0 (0.09)	4 (0.31)	12.9	<0.001
Cases among those born outside Seascale (expected values in parentheses are overestimates)							
0-4	0 (0.06)	0 (0.05)	0 (0.04)	0 (0.02)	0 (0.018)		
5-9	1 (0.04)	0 (0.05)	0 (0.04)	0 (0.02)	1 (0.15)		
10-14	0 (0.02)	1 (0.03)	0 (0.03)	0 (0.02)	1 (0.11)		
15-19	0 (0.01)	0 (0.02)	0 (0.03)	1 (0.03)	1 (0.09)		
20-24	0 (0.01)	0 (0.01)	0 (0.02)	0 (0.01)	0 (0.05)		
0-24	1 (0.15)	1 (0.16)	0 (0.16)	1 (0.11)	3 (0.58)	5.2	<0.05

TABLE II—Non-Hodgkin's lymphoma in young people in Seascale: observed and expected numbers by age group and calendar period 1951-91

Age group	1951-60	1961-70	1971-80	1981-91	Total	Ratio of observed to expected cases	p Value
Cases among those born in Seascale (expected values in parentheses are underestimates)							
0-4	1 (0.005)	0 (0.01)	0 (0.00)	1 (0.00)	2 (0.02)		
5-9	0 (0.00)	0 (0.01)	0 (0.01)	0 (0.00)	0 (0.02)		
10-14	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.01)		
15-19	0 (0.00)	0 (0.01)	0 (0.00)	0 (0.01)	0 (0.01)		
20-24	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.01)	0 (0.01)		
0-24	1 (0.01)	0 (0.02)	0 (0.02)	1 (0.02)	2 (0.07)	28.5	<0.01
Cases among those born outside Seascale (expected values in parentheses are overestimates)							
0-4	0 (0.01)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.02)		
5-9	0 (0.01)	0 (0.01)	0 (0.01)	1 (0.00)	1 (0.03)		
10-14	0 (0.01)	0 (0.01)	0 (0.01)	0 (0.01)	0 (0.03)		
15-19	0 (0.00)	0 (0.01)	0 (0.01)	0 (0.01)	0 (0.04)		
20-24	0 (0.00)	0 (0.01)	0 (0.01)	1 (0.01)	1 (0.03)		
0-24	0 (0.03)	0 (0.05)	0 (0.05)	2 (0.03)	2 (0.16)	12.5	<0.05

standard. There was a significant excess of leukaemia over the period 1951-91 both among those born in Seascale (4 v 0.31 expected; ratio 12.9, $p < 0.001$) and also in those born elsewhere (3 v 0.58; 5.2, $p < 0.05$) (table I). There was also a significant excess of non-Hodgkin's lymphoma both among those born in Seascale (2 v 0.07; 28.5, $p < 0.01$) and among those born elsewhere (2 v 0.16; 12.5, $p < 0.05$). If these expected numbers were not deliberately underestimated in those born in Seascale nor overestimated in the others (see Methods) then the observed to expected ratios for leukaemia become respectively 8.6 ($p < 0.01$) and 7.2 ($p < 0.01$). For non-Hodgkin's lymphoma the corresponding ratios are 20.2 ($p < 0.01$) and 16.5 ($p < 0.01$). All but one of the five born outside Seascale were born outside west Cumbria.

Details of the radiation exposures of the fathers of these young people before their conception are shown in table III, which uses the categories used by Gardner and his colleagues.² For completeness, corresponding details are shown for other malignancies as included in the recent study of Draper *et al.*¹ The cases of leukaemia and non-Hodgkin's lymphoma are far from confined to the subgroup associated with lifetime preconceptional radiation levels of 100 mSv or more—the dosage category found to be associated with an increased relative risk of 8.3 for leukaemia and non-Hodgkin's lymphoma.² Of a total of 11 cases diagnosed while resident in Seascale, only three were associated with such high levels (though a further three had levels

in the range 90-99 mSv). It is only if attention is restricted to those born in Seascale that a definite association with high levels of preconceptional radiation appears—shown by five of the six cases (table III). In contrast, in only one of the five cases among those born elsewhere is such an association present. Among the other four, only one father (of case No 4,¹ shown in table III) was recorded as having any radiation exposure before the relevant conception—namely, a lifetime preconceptional dose of 5.5 mSv, none of which was in the six months before conception. All radiation details given in the tables refer to external doses, as in the original study.² Inclusion of internal doses made only small absolute differences, though it moved one individual from the range 90-99 mSv to over 100 mSv.

Table IV summarises these details of leukaemia and non-Hodgkin's lymphoma. It would have been inappropriate to include in tables I, II, and IV the two cases of leukaemia that were diagnosed a few months after leaving Seascale. One is the case discovered in the birth cohort study in a child born in 1950 who died in 1954 aged 3.¹ The second was diagnosed at age 19 in 1978 but, as was recently pointed out,¹ was inaccurately included in the Black report and also in the case-control study² as a Seascale case. Details of these cases are shown in parentheses in table III. The first child died of leukaemia within five months of being registered in the NHS central register at an address away from Seascale, and the other within two months of such a change. Nevertheless these two cases associated with Seascale undoubtedly represent an excess and are therefore relevant to the overall picture of those malignancies in relation to this parish: even if all those who were born in Seascale in the years 1940-91 had left Seascale (after 1951) they would contribute, in the first six months after leaving, only about 600 person years. It can be deduced from the fact that the 8816 person years (among those born in Seascale) yielded an expected value of 0.31, that the expected numbers of cases of leukaemia based on 600 person years would be tiny. Of those two cases, one was associated with a paternal preconceptional radiation level above 100 mSv; the father of the other had not been exposed to radiation.

Discussion

This study shows that, despite the not infrequent assertions to the contrary, a significant excess of leukaemia and non-Hodgkin's lymphoma in Seascale is not restricted to young people who were born there. It was among these that the hypothesis largely originated about paternal preconceptional radiation and the subsequent risk of leukaemia and non-Hodgkin's lymphoma in their children.² The present findings also indicate that high levels of such radiation cannot explain the significant excess among young people who moved into the parish.

Our findings for Seascale residents who were born elsewhere may seem to conflict with the reported absence of any excess of these malignancies among children born elsewhere but attending schools in Seascale.³ A discrepancy is apparent, however, only if certain facts are overlooked. The previous study was not restricted to Seascale but to a group of individuals who were followed from a point when they attended school in that parish to a fixed point (mid-1986) when some had reached age 35, and long after many of them had moved away from Seascale. No less than 46% of those born outside Seascale who attended the local authority (the main) school had moved again (out of the parish) before reaching the age of 11 years.³ Inevitably, therefore, an appreciable contribution to the expected values for leukaemia and non-Hodgkin's lymphoma

TABLE III—Details of birthplace and paternal radiation in people aged 0-24 with malignancy who were resident in Seascale at diagnosis

Case No (Draper <i>et al.</i>)	Year of diagnosis	Age	Born in Seascale	Diagnosis	Paternal radiation category* (mSv)	Reference No in Black report
1	1954	6	No	Neuroblastoma	0	22
2	1955	7	No	Acute lymphatic leukaemia	0	1
†	1955	2	Yes	Non-Hodgkin's lymphoma	0	14
3	1960	2	Yes	Acute myeloid leukaemia	50-99 ^a	3
4	1968	11	No	Acute lymphatic leukaemia	0.1-49 ^a	2
5	1968	4	Yes	Acute lymphatic leukaemia	≥ 100	5
6	1971	2	Yes	Acute lymphatic leukaemia	≥ 100	6
7	1975	15	Yes	Rhabdomyosarcoma	0	26
8	1979	5	Yes	Acute lymphatic leukaemia	50-99 ^a	7
9	1983	9	No	Non-Hodgkin's lymphoma	0	16
10	1984	1	Yes	Non-Hodgkin's lymphoma	50-99 ^a	17
11	1985	18	No	Pinealoma	0.1-49 ^a	NA
12	1988	23	No	Non-Hodgkin's lymphoma (Burkitt-like lymphoma)	≥ 100	NA
13	1988	17	Yes	Hodgkin's disease	0.1-49 ^a	NA
14	1991	16	No	Acute lymphatic leukaemia	0	NA
15‡	1978	19	Yes	Chronic myeloid leukaemia	≥ 100	4
§‡	1954	3	Yes	Subacute lymphatic leukaemia	0	NA

^a=in range 90-99 mSv; ^b=5.5 mSv; ^c=5 mSv; ^d=0.5 mSv.

NA= Not applicable (diagnosed subsequently, etc).

*Father's lifetime paternal preconceptional (external) radiation.

†Inadvertently omitted initially and reported subsequently.¹⁴

‡Diagnosed a few months after leaving Seascale for another address.

§This case given by Gardner *et al.*¹

TABLE IV—Leukaemia and non-Hodgkin's lymphoma in Seascale residents aged 0-24 years: numbers observed by paternal preconceptional radiation levels in those born in Seascale and those born elsewhere

Paternal preconceptional radiation level (lifetime; mSv)	Leukaemia	NHL	Leukaemia and NHL	Expected No	p Value
Born in Seascale					
Unexposed	0*	1	1		
0.01-49.9	0	0	0		
50-99.9	2	1	3		
> 100	2*	0	2		
Total	4	2	6	0.37	<0.001
Born elsewhere					
Unexposed	2	1	3		
0.01-49.9	1	0	1		
50-99.9	0	0	0		
> 100	0	1	1		
Total	3	2	5	0.74	<0.01
All residents	7	4	11	1.11	<0.001

*In each of these categories there is an additional individual who developed leukaemia within a few months of leaving Seascale for another address.

came from periods spent outside Seascale. Furthermore, the expected numbers that were estimated for these malignancies (0.7) referred only to deaths. The only death (in 1956; case No 1 in the Black report) in a child born in 1947 was excluded as the study covered only children born since 1950. There were, however, also two non-fatal cases (case Nos 2 and 16 in the Black report¹), and a further two cases (case Nos 12 and 14 in Draper *et al*¹) have occurred more recently, both in people born outside Seascale.

The large scale of movement out of Seascale is a feature also of the children who were born there, 40% of whom did not stay long enough to attend a local school at the age of 4 or 5—similar to the proportion of parents coming off the electoral register within five years of their child's birth.⁷ Almost all the cases of leukaemia and non-Hodgkin's lymphoma among young people born in Seascale have occurred while they were living there. The only two exceptions (both leukaemia) were diagnosed within a few months of the children moving away. (The corresponding expected value cannot be calculated precisely for this period, but it is most unlikely to have been more than 0.05; $p < 0.01$.)

The calendar period covered by the present study (1951-91) is wider than that analysed in the recent study by Draper and his colleagues (1963-90 for ages 0-14, 1969-90 for ages 15-24).¹ For the latter periods, the present study found closely similar incidence rates to theirs, in keeping with the similar methods for calculating the populations: for the entire study period, the age standardised annual incidence for leukaemia (all types) and non-Hodgkin's lymphoma was 412.4 per million at ages 0-14 and 218.9 per million at ages 15-24.

Exposures in the high external radiation category occurred only to the fathers of three of the 11 cases in Seascale (or four of 13 if the cases associated with Seascale are included). Even if inspection of the data is allowed to widen the definition of high exposure from 100 mSv to 90 mSv or over, such cases represent only about half the total—namely, six out of 11, or seven out of 13 if the associated cases are included. If the remaining five cases without appreciable paternal preconceptional radiation had been the only cases in Seascale, they would still have represented a significant excess (expected 1.09, $p < 0.01$) and clearly one that cannot be explained on the basis of such radiation. A different explanation must therefore be invoked for these cases. Suggested explanations for the overall excess in Seascale include some unidentified chemical leukaemogen⁹ and an (infective) epidemic promoted by the unusual population mixing in an isolated area of high social class,¹⁰ though only for the latter does any independent evidence exist.¹⁰⁻¹⁴ While it is possible that two separate causes of leukaemia and non-Hodgkin's lymphoma have operated in Seascale, the appeal to scientific parsimony of searching for a single cause cannot lightly be dismissed.

The suggestion that paternal preconceptional radiation could explain the excess of leukaemia

and non-Hodgkin's lymphoma in Seascale² is not supported by the present study. If there is a single dominant cause for this excess, the association shown by a subgroup with paternal preconceptional radiation, unless partly due to chance, points to an indirect (or conceivably an interactive) relation with the true cause. Some commonality with the excess near Britain's other large remote nuclear site at Dounreay has been strongly suggested,¹⁵ so that the absence of any association there with paternal radiation^{14,16} makes an interactive relation¹⁷ most unlikely. If it had been clear from the outset that the association with paternal preconceptional radiation was present only in a subgroup of the excess cases, this association must inevitably have seemed less striking since hypotheses with such a basis are well known often to be unreliable.

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ONE HUNDRED YEARS AGO

"WE CALL IT SUBSTITUTION."

Several grocers were fined last week for selling "substitutes" for coffee and chicory without a label attached. There is something peculiarly pleasing about this word "substitute," and honest withal, for it is a confession that adulteration of the old style is going out of fashion; we no longer let things down with sand or water or what not, but we substitute some entirely different compound. Brewers have long thriven on the scientific use of substitutes for

malt, and all forms of adulteration of butter paled before the simple plan of selling margarine in its stead. Obviously, now that margarine has obtained a legal footing, what is wanted is a "substitute" for margarine, and no doubt it will come before long. Coffee seems already to have arrived at that second stage in its downward progress; it is bad enough to buy it adulterated with chicory, but now we find this itself replaced by a "substitute" which goes by the name of "German chicory."

(*BMJ* 1893;ii:141.)