Risk Factors for Osteosarcoma in Young People in Cornwall: A Case-Control Study

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Abstract

A case-control study has been carried out in an attempt to identify risk factors that may be implicated in a group of cases of osteosarcoma in young people that have occurred over a nine year period in or near the West Cornish town of Helston. The incidence of osteosarcoma in the study area was substantially in excess of the national rate, but did not significantly exceed that found in the South-West region as a whole (chi² with continuity correction = 0.003; p = 0.956).

Data were obtained by postal questionnaire. In addition, domestic radon levels in the homes of cases and controls were obtained by direct measurement. Statistical analyses included tests of association (χ² tests, or Fisher’s Exact Test where appropriate) and the calculation of odds ratios for exposure. For continuous variables, Mann-Whitney tests of rank distribution were undertaken.

Much higher levels of domestic radon were found in the houses of cases compared with those of controls (Mann-Whitney rank distribution test: p = 0.000376). Other possible risk factors identified were diphtheria/tetanus/pertussis immunisation, difficulty coping at school, periods of low mood, and previous accidents. BCG immunisation appeared to have a protective effect. However, logistic regression analysis showed that these were unimportant in comparison with radon, and their role as possible risk factors for osteosarcoma is by no means proved.

The strength of association with radon exposure is remarkable and convincing. Other associations which are weaker, but nonetheless statistically significant, are consistent with previous published research. The study should, though, be repeated on a larger scale in order to replicate these findings.

Key Words: Environmental health; osteosarcoma, radon, risk factors.

Introduction

A case-control study has been carried out in an attempt to identify risk factors that may be implicated in a group of cases of osteosarcoma in young people that have occurred within the past decade in or near the West Cornish town of Helston. Recently, concern has been expressed there about the number of cases (BBC News 2004; Guardian Unlimited, 2004, the “Helston Packet”, 29th January and 26th February 2004). A total of seven cases has been identified, which were diagnosed with osteosarcoma in the period 1996 to 2003 inclusive. Data pertaining to six of these cases, three of whom were male and three female, are presented here. In every case, they were aged less than 20 when diagnosed with osteosarcoma. The public perception was that these cases constituted a cluster, and that the incidence of osteosarcoma was in excess of that normally to be expected in that area. There was concern that this might have resulted from exposure to a common risk factor, which remained unidentified.

Osteosarcoma, though a rare form of cancer, is the fourth most common cancer in people under 20 years of age (Homa et al., 1991), and the most common type of bone cancer in this age group. It is derived from primitive bone-forming mesenchyma (Kramarova and Stiller, 1996). It is bimodally distributed by age, with an initial peak at age 15-19 years (Fraumeni and Boyce, 1982).

Table 1.0 summarises the incidence of osteosarcoma in the study area (i.e. an area of radius 13 miles around Helston). It will be noted that, while the incidence of osteosarcoma was substantially in excess of the national rate, it did not significantly exceed that found in the

<table>
<thead>
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<th>Location</th>
<th>UK</th>
<th>SW</th>
<th>Study area</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cases</td>
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<td>210</td>
<td>7</td>
</tr>
<tr>
<td>Population &lt;25 (100,000s)</td>
<td>112.03</td>
<td>6.94</td>
<td>0.14</td>
</tr>
<tr>
<td>No. of years</td>
<td>6</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>Person/years at risk</td>
<td>672.18</td>
<td>41.64</td>
<td>1.26</td>
</tr>
<tr>
<td>Annual rate/100,000 population &lt;25</td>
<td>1.09</td>
<td>5.04</td>
<td>5.56</td>
</tr>
<tr>
<td>Rate ratio (UK = 1)</td>
<td>1.00</td>
<td>4.62</td>
<td>5.10</td>
</tr>
</tbody>
</table>

* Sources: Office for National Statistics 2000 and Stiller et al., 2004.
South-West region as a whole (chi² with continuity correction = 0.003; p 0.956).

Very little is known about the aetiology of osteosarcoma in humans. Following local representations, the South West Cancer Intelligence Service prepared a report on the alleged cluster (South West Cancer Intelligence Service, 2004). This states that the aetiology of osteosarcoma is generally poorly understood. The only aetiological factor that is unequivocally recognised is ionising radiation (Rowland et al., 1983), having first been described in female factory workers after World War One who were exposed to radium and mesothorium (Patterson and Harman, 2001). Similarly, treatment especially of children with external beam radiotherapy is known to be associated with an increased risk of osteosarcoma (Patterson and Harman 2001, Tabone et al., 1999), particularly in those with an inherited susceptibility. However, as the SWCIS report points out, there has been no published scientific evidence to date linking radon exposure to osteosarcoma in young people, in either the South West (Thorne et al., 1996) or nationally (Cartwright, 2002). It should be noted that parts of Cornwall have some of the highest levels of radon intensity in England and Wales (Green et al., 2002), particularly in Kerrier district, where 48% of properties were found to have unsafe levels (Spear, 2004). Henshaw et al., (1990) identified that, at an indoor level of 110Bq/m², radon may cause 23-43% of cancer, and noted that the existence of radon hot spots had implications for the clustering of childhood cancer in the UK.

Other factors suggested to be related to osteosarcoma include tall stature, previous bone trauma (Fraumeni, 1967, Miller, 1976, Scranton et al., 1975) and viruses (Finkel et al., 1975). Animal studies have demonstrated an excess risk of bone sarcomas among larger breeds of dogs which suggests that a relationship may exist between human bone cancer and a large body size at the time of diagnosis (Oerskalski et al., 1987, Benedict et al., 1988). Genetic factors have also been identified in a small percentage of cases. Hereditary factors are involved in some patients (Hansen MF 1991), and there is an increased risk in siblings of patients (Coley, 1970, Schimke et al., 1974). Genetic mutations, e.g. of the p53 gene, and an increased incidence in children with the Li-Fraumeni syndrome have been reported (McIntyre et al., 1994).

A number of antenatal environmental exposures such as infective agents, drugs and radiation are capable of altering the normal development of an embryo which could contribute to the development of osteosarcoma in young people. Parental occupation is also of interest because parents can bring home chemicals or dusts from their workplace on their clothes, thus exposing their children. Parental chemical exposures may be associated with increased risk of osteosarcoma in children. Schwartzbaum et al. (1991) identified a statistically significant odds ratio of 2.6 among 78 childhood osteosarcoma patients for parents who reported that they gardened with fertilisers, herbicides and pesticides in the perinatal period, compared with parents of other childhood cancer patients. A genetic predisposition has also been suggested (Buckley et al., 1998, Birch 1999).

Excess risk of bone sarcomas among larger breeds of dogs has also been suggested (Finkel et al., 1975). Animal studies have demonstrated an excess risk of bone sarcomas among larger breeds of dogs which suggests that a relationship may exist between human bone cancer and a large body size at the time of diagnosis (Oerskalski et al., 1987, Benedict et al., 1988).

The SWCIS report states that there was no statistically significant difference in incidence between West Cornwall and surrounding areas (South West Cancer Intelligence Service, 2004). However, this assessment was made at PCT level, so any local clusters would have been substantially diluted in a larger population. It concluded that there was no evidence of a single environmental or other risk factor causing osteosarcoma in the West of Cornwall Primary Care Trust area, and that public concern was therefore misplaced. However, the study conducted by the SWCIS was a descriptive study utilizing cancer registry data. It was not an analytical study, and was neither designed to establish causation of this group of cases, nor indeed could it as the requisite data on environmental exposures was unavailable. SWCIS itself has commented that the cancer registry does not hold data on lifestyle factors which may affect cancer risk, duration of residence, or occupational or environmental exposures (South West Cancer Intelligence Service Factsheet 18).

The SWCIS report further asserted that any additional investigation of this group of cases would be unethical, as any study of such a small number would necessarily be underpowered (South West Cancer Intelligence Service 2004). This is incorrect. It is true that type 2 errors are more likely in a study of a small sample, but whether or not it is underpowered depends on the effect size of...
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possible risk factors being examined. Thus, our power and sample size calculations indicate that a matched case-control study of six cases, with four controls per case, with an a-value of 0.05 and a power of 0.8, would produce a significant result where the exposure in the control population was 10%, and the odds ratio 15:1. The present study is thus designed to complement and extend the SWCIS study.

Methods

A case-control study was undertaken, in order to identify, where possible, differences in exposure to a range of risk factors between the six cases and a group of matched controls. The specific potential risk factors investigated include radon, antenatal exposures, a family history of cancer or congenital malformation, parental occupation and psychological disturbances. Ethical approval was granted by the Faculty of Applied Sciences Ethics Committee at the University of the West of England, which follows NHS governance procedures.

The cases were identified via third party introductions or from word of mouth and media interest (television, radio and press). A close relationship had developed between locally affected families since the high media interest and as such facilitated the task of case finding. The study area comprised some 531 square miles within a 13-mile radius of Helston. The area extended from Redruth to the North, to the Lizard to the South, and St. Ives to the West.

Four controls were selected per case. Some were neighbourhood controls introduced by cases' families, while others were voluntary participants from local schools who had heard about the study. Cases and controls were matched for age, sex and ethnicity. For both cases and controls, participation was on the basis of informed consent.

There were two sources of information regarding exposures of interest. For most exposures, data were obtained by postal questionnaire. In addition, domestic radon levels in the homes of cases and controls were obtained by direct measurement.

The questionnaire, which was piloted among 25 unaffected families, addressed events during the index pregnancy, past medical and social history of the subject and his or her parents and siblings and other family members. Risk factors examined included length of gestation, place and type of delivery, birth weight, condition at birth, neonatal events (e.g. phototherapy, breastfeeding), previous illnesses, drug use and abuse, previous medical treatments including radiotherapy, immunisation status, and familial exposure to chemicals.

Domestic radon measurements were made using the Pylon Radon Detector Model AB-5, which is an instrument validated by the NRPB and the United States Environmental Protection Agency. The tool was calibrated for efficiency, and a pilot study undertaken to ensure familiarity with the equipment. In order to ensure comparability of results, families were asked to keep windows and doors closed as much as possible for twenty-four hours prior to, and during, measurements, and to turn off all air exchange systems. Siting of the equipment, well away from outside walls and avoiding draughts, was important, as was avoidance of taking measurements during severe storms or strong winds. Calculations were made using an hourly interval method, and expressed in Bq/m³. All radon measurements were made between 1st September and 1st October 2004. Each assessment was undertaken over an 8 hour period. The first three hourly readings were ignored, allowing the instrument to acclimatise to its surroundings. Cases and controls were assessed sequentially, the sequence being determined by random allocation. The apparatus was set up in a bedroom of the occupants' choosing. Background readings were calibrated after each assessment and programmed into the detector. Because of the possible effect of variations in air pressure on radon measurements, local barometric readings were obtained from Culdrose, Cornwall at 12:00 GMT (at www.metoffice.gov.uk).

Results were calculated using the radon concentration formula:

\[ C = \frac{CPM - BG}{S} \]

Where:
- \( C \) is the concentration (units depend on sensitivity)
- \( CPM \) is the count per interval value expressed in counts per minute
- \( BG \) is the background level expressed in counts per minute
- \( S \) is the counting sensitivity value

Statistical analyses included tests of association (\( \chi^2 \) tests, or Fisher’s Exact Test where appropriate) and the calculation of odds ratios for exposure. For continuous variables, such as radon measurements, Mann-Whitney tests of rank distribution were undertaken.

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Results

Measured radon levels in the houses of cases and controls are summarised in Table 2.0. There was a marked difference, in relation to the NRPB domestic radon intervention level of 200 Bq/m³, between the homes of cases and of controls (p, by Fisher’s Exact Test = 0.0000117). These are summarised in Table 3.0. In order to examine possible meteorological factors that might have influenced radon measurements, possible correlations between radon measurements and wind speed, wind direction, rainfall, humidity, air temperature and atmospheric pressure were examined. The strongest correlation (r = 0.28) was with wind speed, i.e. only 7.8% of variation in radon measurements could be explained by variations in this.

Radon measurements ranged from 26 to 3484 Bq/m³. This latter measurement was very much higher than the second highest radon measurement, which was 352 Bq/m³. Consequently, a Mann-Whitney rank distribution test was conducted in order to avoid the possible distorting effect of this one extreme value. The cases occupied five of the top six ranks, while the remaining case was in rank 7. The probability of this distribution having arisen by chance was 0.000376. Similar tests were
undertaken in respect of other continuous variables, but no other significant results were obtained. Clearly, radon levels measured at a particular point in time are not a measure of total exposure. Accordingly, cases and controls were asked about duration of residence in their current addresses, and there were in fact no significant differences between them.

As regards categorical variables, 2x2 contingency tables were examined, and odds ratios and 95% confidence limits calculated. The results in respect of exposures experienced by cases and controls are summarised in Table 4.0.

Cases were much more likely than controls to have had diphtheria/tetanus/pertussis immunisation, and also to have had difficulty coping at school, periods of low mood, or previous accidents. However, BCG immunisation was much more frequent among the controls, and therefore appeared to have a protective effect. A logistic regression analysis was undertaken, which involved construction of a model incorporating those variables which individually were positively associated with the occurrence of osteosarcoma, viz. radon above intervention level, diphtheria/tetanus/pertussis immunisation, school difficulties, periods of low mood, and previous accidents. The model chi^2 for this five-variable model was 30.02 (p < 0.0001). An identical model chi^2 was found for a two variable model comprising radon above intervention level and diphtheria/tetanus/pertussis immunisation only, indicating that school difficulties, periods of low mood, and previous accidents had no impact at all on the predictive power of the model. For radon above intervention level alone, chi^2 was 24.64 (p < 0.0001, without continuity correction).

Other possible risk factors enquired about included factors related to the biological mother’s obstetric history, i.e. occupation before, during and immediately after the birth, and exposure to X-rays, medication and trauma during pregnancy. Parental occupations (particularly in horticulture and agriculture) were also enquired about, and exposures to chemicals and other external agents (i.e. dusts, fumes, X-rays, fertilisers, herbicides, pesticides, prescription medication, alcohol and tobacco), and serious illnesses in the extended family. Factors concerning the construction of buildings which might affect levels of domestic radon (presence of double glazing, cavity wall insulation, or draft exclusion, and construction date) showed no variation between cases and controls. There were no significant associations involving any of these factors, or with the existence of serious illnesses in other family members, except for genetic diseases in aunts, which cases reported more frequently than controls (odds ratio = 1.83; 95% confidence interval = 1.14 – 23.83). There would not appear to be any plausible biological mechanism to explain this, and it appears likely that it is simply a chance result arising as a consequence of multiple hypothesis testing.

Discussion

Summary of main findings

The number of cases identified was markedly higher than that which would have been found if national incidence rates applied, but was not significantly higher than the regional rate. The number of cases found in the Helston area during the study period cannot therefore be regarded as a cluster. Consequently, there is no need to postulate a specific localised exposure which may have been a risk factor for osteosarcoma. There is always a danger, in investigating an alleged cluster, of artificially designating a cluster by post hoc rationalisation (the so-called ‘Texas sharpshooter’ fallacy). We have not done this. Rather, we have investigated a group of cases which occurred in close proximity in space and time. Whether or not these cases constitute a cluster is a matter of semantics, and such labelling is not necessarily helpful in endeavouring to identify possible risk factors.

This study has shown a very strong association between levels of domestic radon and the development of osteosarcoma in the group of cases investigated (p = 0.000376). Radon levels throughout the South West of England are higher than in other parts of the country, and this may account for the relatively high incidence rate for osteosarcoma found in the region. Logistic regression analysis indicated that diphtheria/tetanus/pertussis immunisation may be a relatively minor risk factor for osteosarcoma, but this remains a hypothesis requiring further testing on a much larger scale. Other factors that were weakly associated with the development of osteosarcoma included difficulty coping at school, periods of low mood, and previous accidents, but these had no impact on the logistic regression model, so their possible roles as risk factors should also be regarded as hypotheses to be tested in much larger studies. Paradoxically, BCG immunisation appeared to have a protective effect. In conclusion, the association between domestic radon levels and developing osteosarcoma is very strong, and this suggests a causal relationship.
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<tr>
<th>History of:</th>
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<th>95% Confidence Interval</th>
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<td>9</td>
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<td>2</td>
<td>18</td>
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<td>BCG immunisation</td>
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<td>4</td>
<td>20</td>
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<td>X-ray exposure</td>
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Table 4.0
Strengths and the limitations of this study

The main limitation of this study arises from the small number of cases. Nevertheless, the strength of association with radon exposure is remarkable and convincing. Other associations which are weaker but nonetheless statistically significant are consistent with previous published research. The study should, though, be repeated on a larger scale in order to replicate these findings.

Conformity with existing research literature

The strong association with radon exposure is consistent with previous work implicating ionising irradiation in the aetiology of osteosarcoma (Rowland et al. 1983), though this particular finding is new information, for, as the SWCIS report (South West Cancer Intelligence Service, 2004) pointed out, there has been to date no published research evidence for the role of radon as a risk factor for osteosarcoma in young people.

Other factors that may constitute risk factors for osteosarcoma include diphtheria/tetanus/pertussis immunisation, difficulty coping at school, periods of low mood, and previous accidents. BCG immunisation, however, appeared to have a protective effect.

A recent collaborative analysis of data from 13 case-control studies of residential radon and lung cancer (Darby et al., 2005), involving over seven thousand cases with approximately two controls per case found a mean domestic radon concentration in the homes of cases of 97 Bq/m³ and in the homes of controls of 104 Bq/m³. This study has found proportionally much larger differences between cases and controls, suggesting that radon is more unequivocally important as a risk factor for osteosarcoma than for lung cancer.

The indication that immunisation status, particularly the apparent protective effect of BCG immunisation, may affect likelihood of developing osteosarcoma is consistent with previous work suggesting that children who had not been immunised were significantly more at risk of osteosarcoma than others (Hartley et al., 1988). As regards accidents, a possible role for trauma as a risk factor has previously been suggested (Fraumeni, 1967; Miller, 1976). In addition, our finding of the possible role as a risk factor of having had difficulty coping at school is consistent with a previous study indicating that children who experienced such difficulties were particularly at risk (Frentzel-Beyme et al., 2004).

Conclusions

A case-control study of risk factors for osteosarcoma in a group of cases in young people in and around Helston, in Cornwall, indicated a very strong association between domestic radon levels and the development of osteosarcoma. This is consistent with other research, though is the first time that this particular association has been demonstrated in this age group. The strength of the association (p = 0.000376, by Mann-Whitney rank distribution test) strongly suggests a causal relationship. Other associations, e.g. diphtheria/tetanus/pertussis immunisation, were much weaker, and more research is needed in larger scale studies to elucidate their possible role as causal factors.

Acknowledgements

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Our appreciation also goes to the participants and their families who took part, without which this study would not have come to fruition.

Finally, our thanks go to the Chartered Institute of Environmental Health who funded, and encouraged us to complete, the project.
Barometric Readings for Culdrose, Cornwall at 12:00GMT. www.metoffice.gov.uk [Accessed 07/10/04].


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