Hodgkin’s lymphoma and infection: findings from a UK case–control study

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Between 1998 and 2003, 214 people with Hodgkin’s lymphoma and 214 controls randomly selected from population registers in the north of England (after matching for age and sex) were recruited and their primary care medical records examined for details of clinical diagnoses due to infectious and non-infectious conditions in the preceding 15 years. In the year before diagnosis of Hodgkin’s lymphoma, almost all cases (99%) visited their general practitioner (GP) at least once. In comparison with controls, the excess was evident both for visits with an infection (odds ratio (OR) = 2.1; 95% confidence interval (CI) 1.4–3.2) and for visits with non-infectious problems (OR = 17.2; 95% CI 6.7–43.9). During the rest of the 15-year period prior to diagnosis, the proportion of people visiting their GP with a non-infectious condition did not differ between cases and controls. In contrast, compared to controls, there was an excess of cases visiting the GP with an infection, a finding that was evident for at least a decade prior to diagnosis and increased linearly with time (P = 0.02). This excess was not due to a specific infection(s) and may reflect underlying immune abnormality. Alternatively, infection may cause B-cell proliferation from which a malignant clone may evolve.

METHODS

Unravelling any relationship between risk of Hodgkin’s lymphoma and previous infections is not straightforward. To investigate the patterns of infectious illness prior to diagnosis, as well as to identify specific infectious exposures, we systematically abstracted data compiled prior to diagnosis from primary health-care medical records. We report here, on the role of clinically diagnosed infections (as recorded in primary care medical records) in the aetiology of Hodgkin’s lymphoma.

The cause(s) of Hodgkin’s lymphoma are largely unknown, although various infectious and immune factors have been implicated. A proportion is thought to be related to infection with Epstein Barr virus (EBV), which is integrated clonally into tumour cells in as many as 40% of cases (IARC, 1997). Elevated titres of antibodies against EBV have been associated with subsequent risk of Hodgkin’s lymphoma, while infectious mononucleosis, known to be caused by EBV, is an established risk factor (Mueller et al., 1989; Jarrett et al., 1998; Hjalgrim et al., 2000, 2007). Elevated titres of antibodies against another human herpesvirus (type 6) have been found in some, but not in other studies (Clark et al., 1990; Jarrett et al., 1998; Berrington de González et al., 2006). Infection with human immunodeficiency virus (HIV) may account for a small proportion of cases, although the virus is not thought to have any direct oncogenic activity, but rather to facilitate tumorigenesis via its immune effects (IARC, 1996; Beral and Newton, 1998; Newton et al., 1999). Immunosuppression, whether related to HIV infection or drug treatment such as that experienced by transplant recipients, appears to be associated with a modest increase in risk of Hodgkin’s lymphoma – substantially less than that of non-Hodgkin’s lymphoma (Kinlen et al., 1979; Birkeland et al., 1995; International Collaboration on HIV and Cancer, 2000; Vajdic et al., 2006). No other specific infectious or immune factors have been consistently found.

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Table 1  Number of cases and controls visiting the general practitioner at least once for an infectious or non-infectious condition during each of the 15 years prior to diagnosis of Hodgkin’s lymphoma (or pseudo-diagnosis in controls)

| Years before diagnosis | All visits | Infectious diagnosis | Non-infectious diagnosis |
|------------------------|------------|----------------------|-------------------------|
|                        | Controls N (%) | Cases N (%) | Controls N (%) | Cases N (%) | Controls N (%) | Cases N (%) |
| 1                      | 164 (77)     | 212 (99)          | 69 (32)        | 106 (50)    | 153 (72)     | 209 (98)    |
| 2                      | 169 (79)     | 177 (83)         | 79 (37)        | 90 (42)     | 157 (73)     | 168 (79)    |
| 3                      | 177 (83)     | 180 (84)         | 77 (36)        | 89 (42)     | 166 (78)     | 164 (77)    |
| 4                      | 160 (75)     | 180 (84)         | 67 (31)        | 92 (43)     | 146 (68)     | 166 (78)    |
| 5                      | 160 (75)     | 171 (80)         | 72 (34)        | 91 (43)     | 151 (71)     | 156 (73)    |
| 6                      | 164 (77)     | 161 (75)         | 80 (37)        | 82 (38)     | 144 (67)     | 139 (65)    |
| 7                      | 164 (77)     | 159 (74)         | 70 (33)        | 78 (36)     | 147 (69)     | 148 (69)    |
| 8                      | 166 (78)     | 155 (72)         | 75 (35)        | 88 (41)     | 148 (69)     | 138 (64)    |
| 9                      | 168 (79)     | 161 (75)         | 80 (37)        | 77 (36)     | 140 (65)     | 148 (69)    |
| 10                     | 164 (77)     | 155 (72)         | 67 (31)        | 91 (43)     | 151 (71)     | 134 (63)    |
| 11                     | 156 (73)     | 153 (72)         | 66 (31)        | 91 (43)     | 143 (67)     | 133 (62)    |
| 12                     | 152 (71)     | 155 (72)         | 75 (35)        | 89 (42)     | 132 (62)     | 133 (62)    |
| 13                     | 144 (67)     | 157 (73)         | 76 (36)        | 72 (34)     | 123 (57)     | 143 (67)    |
| 14                     | 145 (68)     | 147 (69)         | 74 (35)        | 76 (36)     | 119 (56)     | 129 (60)    |
| 15                     | 137 (64)     | 138 (65)         | 64 (30)        | 68 (32)     | 120 (56)     | 119 (56)    |
there was an excess, which increased linearly from about 10 years prior to diagnosis \((P = 0.02)\). This excess among cases as compared to controls did not appear to be due to a specific infection. Data for the most frequently diagnosed infections, together with some that have been linked to Hodgkin’s lymphoma in previous studies (such as herpesvirus infections), are shown for the entire time period (excluding the year before diagnosis or pseudo-diagnosis) in Table 2. With the possible exception of herpesviruses and lower respiratory tract infections, no single infection was particularly associated with Hodgkin’s lymphoma. The analyses described in Table 2 were repeated, limiting to infections occurring within 10 years prior to diagnosis (but omitting the year before diagnosis) and it made no material difference to the findings (data not shown).

When analyses were restricted to CHL alone, there was no material difference in the results. Similarly, when analyses were stratified by age \((<40\) and \(40 +\) years), sex, and EBV status of the tumour, the findings remained essentially unchanged (data not shown).

**DISCUSSION**

Our analyses of contemporaneously acquired primary care medical data indicate that compared to matched controls, a substantially higher proportion of people who develop Hodgkin’s lymphoma visit the GP for an infection, a finding that is evident for at least a decade prior to diagnosis. In contrast, there was little difference between cases and controls in the proportion visiting for a non-infectious problem until about a year before diagnosis, even cases showed a marked increase. We cannot, however, determine whether the excess of clinically diagnosed infections is a consequence of underlying immune abnormality or indeed, whether the infections are playing a causal role. No single infection stood out as being specifically associated with Hodgkin’s lymphoma and no single event was identified within the 15 years prior to diagnosis that might be associated with disease onset. Although we cannot exclude the possible existence of a single causal agent (possibly acting more than 15 years prior to diagnosis), none was identified.

Large amounts of information on previous illnesses, including infections, are routinely collected by medical practitioners working in primary care. Although these data, which are principally collected with the aim of documenting and monitoring patient care, have been used in a limited way in a number of aetiological studies (McKinney et al, 1991; Mann et al, 1993; Chilvers et al, 1994; Ansell et al, 2005), their potential with respect to describing symptom profiles is yet to be fully realised. A critical advantage for aetiological and other studies – where the sequence and timing of events is important – is that information held in GP records is collected prior to the diagnosis of malignancy and so have the advantage of being unaffected by recall and reporting bias, having been recorded by the GP contemporaneously. The methods used for abstracting data from primary care records were originally developed by the investigators (PA and ER). Indeed, the use of clinical records permits a far more precise characterisation of events preceding diagnosis than is possible in studies that rely on self-report (Simpson et al, 2007).

As in other epidemiological studies, a fundamental but simplistic distinction is made between Hodgkin’s lymphoma and non-Hodgkin’s lymphoma which originates in concepts from the early twentieth century. From an epidemiological perspective, Hodgkin’s lymphoma appears to be distinctive, with an unusual bimodal age distribution peaking in young adults and in older people (www.hmrn.org). Hodgkin’s lymphoma also differs from other types of lymphoma in having a female predominance in the young adult age group. However, to examine the role of infectious and immune factors in relation to Hodgkin’s lymphoma stratified by age, sex or indeed by EBV status of the tumour, we would need substantially larger numbers of cases than were available for analysis here. Indeed, in this study as in many others, recruitment was limited to a specific age range \((16–69\) years), which means, because of the unusual age distribution of Hodgkin’s lymphoma, many of the available cases were excluded.

However, it is apparent that CHL is a B-cell malignancy derived from postgerminal centre cells. The defining feature of the tumour cells is the loss of a mature B-cell phenotype but failure to complete differentiation to plasma cells (Cossman et al, 1988, 1999; Stein et al, 2001; Fan et al, 2003). The association of CHL with other B-cell malignancies is emphasised by the occurrence of the so-called composite lymphoma where CHL occurs in association with follicular lymphoma, diffuse large B-cell lymphoma or B-chronic lymphocytic leukaemia, and where both tumours can be
shown to have a common clonal origin (Gonzalez et al, 1991; Cathcart-Rake et al, 1992; Jaffe et al, 1992; Kim, 1993; Kuppers et al, 2001). Recent gene-expression studies have also shown that at least some cases of CHL have a very similar pattern of gene expression to mediastinal B-cell lymphoma. Both CHL and mediastinal B-cell lymphoma affect the mediastinum and have a female predominance in young adults leading to the suggestion that they are derived from a specific population of thymic B cells (Addis and Isaacscon, 1986; Palanisamy et al, 2002; Rosenwald et al, 2003; Calvo et al, 2004). These studies demonstrate the importance of considering CHL in the context of the epidemiology of B-cell malignancies as a whole rather than as a separate entity. Ideally, nodular lymphocyte predominant Hodgkin’s lymphoma should be considered separately, although its rarity makes it difficult to recruit the numbers of cases required for epidemiological studies. In the future, high-quality, contemporaneously collected exposure data, together with modern concepts of disease and accurate diagnostic and demographic information, will play a key role in addressing questions of pathogenesis of haematological malignancies.

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Table 2: Number of cases and controls visiting the general practitioner at least once for a specific infection prior to diagnosis of Hodgkin’s lymphoma (or pseudo-diagnosis in controls)

| Infections                  | Cases N (%) | Controls N (%) | OR (95% CI) |
|-----------------------------|-------------|----------------|-------------|
| Total                       | 214 (100)   | 214 (100)      | 2.67 (1.01–7.09) |
| Upper respiratory tract     | 208 (97.2)  | 199 (93.0)     | 1.00 (0.59–1.51) |
| Skin                        | 164 (76.6)  | 166 (77.6)     | 0.94 (0.59–1.51) |
| Fungal                      | 81 (37.9)   | 68 (31.8)      | 1.31 (0.88–1.95) |
| Lower respiratory tract     | 63 (29.0)   | 44 (20.6)      | 1.58 (1.01–2.48) |
| Eye (H01,H01,H05.0)         | 61 (28.5)   | 45 (21.0)      | 1.50 (0.96–2.34) |
| Influenza (I1.1)            | 53 (24.8)   | 48 (22.4)      | 1.14 (0.73–1.78) |

CI = confidence interval; EBV = Epstein Barr virus; OR = odd’s ratio. *Includes ICD-10, codes A00-B99, H01, H05.0, H10, H66.9, L0, L42, J0–J2 & N39.0. **Data in parentheses KCD-10 code(s).
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