Short Communication

Childhood infections, orchitis and testicular germ cell tumours: a report from the STEED study and a meta-analysis of existing data

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BACKGROUND: Similarities between the age-specific incidence pattern of testicular germ cell tumours (TGCTs) and the age-specific incidence pattern of cancers of viral origin prompted us to evaluate the relationship between common infections occurring during childhood or young adult life and TGCT using existing data from the US Servicemen’s Testicular Tumor Environmental and Endocrine Determinants (STEED) case-control study.

METHODS: TGCT cases diagnosed between 2002 and 2005 (n = 767) were matched on age, race and serum draw date to at least one control (n = 929).

RESULTS: None of the infections evaluated were associated with TGCT risk. Further, a meta-analysis of mumps and mumps orchitis or orchitis infection did not support an association with TGCT (mumps pooled odds ratio (OR): 1.03, 95% confidence interval (CI): 0.89–1.20; mumps orchitis or orchitis pooled OR: 1.80, 95% CI: 0.74–4.42).

CONCLUSION: Based on our evaluation of childhood and early life infections and meta-analyses of mumps and mumps orchitis and/or orchitis, TGCT does not appear to be associated with common childhood infections.

Keywords: testicular germ cell tumours; childhood infections; mumps; orchitis; case-control

Testicular germ cell tumours (TGCTs) are the most common cancer among young men in many countries (Chia et al, 2010). There are few established risk factors beyond age, race/ethnicity, adult height, history of cryptorchidism and family history of TGCT (McGlynn and Cook, 2009). The great majority of TGCTs arise in young men between the ages of 15 and 40 years. Although there has been much interest in a possible perinatal aetiology of these young adult tumours, non-perinatal factors may also have a role. In addition, the age-specific incidence pattern of TGCT resembles that of some cancers with viral aetiology, such as young-adult non-Hodgkin’s lymphoma (NHL) (Newell et al, 1984; Algood et al, 1988).

Mumps, a viral disease, is manifested by inflammation of the salivary glands (Plotkin and Rubin, 2008). In the absence of vaccination, most persons will be infected by this disease in young adulthood (Plotkin and Rubin, 2008) and up to 37% of post-pubertal males will develop orchitis. A number of studies support an association between post-pubertal mumps and/or orchitis and TGCT (Mills et al, 1984; Brown et al, 1987; Swerdlow et al, 1987), whereas evidence linking TGCT and childhood mumps is largely null (Henderson et al, 1979; Loughlin et al, 1980; Goldman et al, 1982; Moss et al, 1986; Brown et al, 1987; Haughey et al, 1989; Stone et al, 1991; UK Testicular Cancer Study Group, 1994; Petridou et al, 1997).

Using existing data from the US Servicemen’s Testicular Tumor Environmental and Endocrine Determinants (STEED) study, we evaluated the association between common childhood infections and TGCT. In addition, using published reports in the literature, we conducted a meta-analysis of mumps and/or orchitis and risk of TGCT.

MATERIALS AND METHODS

Study population

Participants in the STEED study were enrolled between 2002 and 2005 (McGlynn et al, 2007). Briefly, men between 18 and 45 years of age who had at least one serum sample stored in the US Department of Defense Serum Repository (DoDSR, Silver Spring, MD, USA) were eligible for the study. Men who developed TGCT while on active duty were eligible to participate as cases, whereas men who did not develop TGCT were eligible to participate as controls. TGCT diagnoses were limited to classic seminoma or nonseminoma (embryonal carcinoma, yolk sac carcinoma, choriovucarcinoma, teratoma and mixed germ cell tumour). Eligible controls (n = 928) were individually matched to cases (n = 767) based on age at diagnosis (within 1 year), ethnicity (white, black and other) and date when serum was donated (within 30 days). Informed consent was obtained from all the participants. The study was approved by the institutional review boards of the National Cancer Institute (Bethesda, MD, USA) and the Walter Reed Army Institute of Research (Silver Spring, MD, USA).
The study questionnaire elicited information on risk factors for TGCT, as well as self-reported history of common childhood infections and age at onset (mumps, chicken pox including varicella or shingle, measles, roseola or Sixth disease and mononucleosis). The questionnaire also ascertained a self-reported history of orchitis and TGCT (OR: 1.34; 95% CI: 0.71–2.51) with self-reported age at infection within 1 year of the reference age. The consistent fixed- and random-effects models yielded a pooled OR of 1.80 (95% CI: 0.74–4.42). The disparate fixed- and random-effects pooled ORs and $I^2$ of 6.1% indicate very little heterogeneity among the six studies ($P$-value: 0.38).

**Meta-analysis**

The pooled summary OR based on the random-effects model for mumps was 1.03 (95% CI: 0.89–1.20); suggesting no association with TGCT (Figure 1). The consistent fixed- and random-effects pooled ORs and $I^2$ of 6.1% indicate very little heterogeneity among the six studies ($P$-value: 0.38).

For mumps orchitis or orchitis, the random-effects model yielded a pooled OR of 1.80 (95% CI: 0.74–4.42). The disparate fixed- and random-effects pooled ORs and $I^2$ of 6.1% suggested considerable heterogeneity across study-specific ORs for the five studies. Bajou’s plot indicated that the two recent studies contributed most to the heterogeneity (Moller and Skakkebaek, 1999 and the current study). When these studies were removed, the $I^2$ value dropped to 0.0% ($P$-value: 0.91) and the pooled ORs for fixed- and random-effects models became

| Table 1 Characteristics of study participants stratified by case-control status and TGCT histology, STEED Study, 2002–2005 |
|---------------------------------|
| Controls | All TGCT | Seminoma | Nonseminoma |
| (n = 928) | (n = 767) | (n = 324) | (n = 442) |
| Age (years) | | | |
| <25 | 318 | 34.3 | 278 | 36.2 | 61 | 18.8 | 216 | 48.9 |
| 25–29 | 277 | 29.8 | 217 | 28.3 | 97 | 29.9 | 120 | 27.1 |
| 30–34 | 174 | 18.8 | 137 | 17.9 | 78 | 24.1 | 59 | 13.3 |
| 35–39 | 120 | 12.9 | 101 | 13.2 | 64 | 19.8 | 37 | 8.4 |
| 40+ | 39 | 4.2 | 34 | 4.4 | 24 | 7.4 | 10 | 2.3 |
| Race | | | |
| White | 788 | 84.9 | 647 | 84.4 | 260 | 80.2 | 387 | 87.6 |
| Black | 35 | 3.8 | 22 | 2.9 | 12 | 3.7 | 10 | 2.3 |
| Other | 105 | 11.3 | 98 | 12.8 | 52 | 16.0 | 45 | 10.2 |
| Reference height (cm) | | | |
| <172.73 | 260 | 15.3 | 157 | 9.3 | 62 | 3.7 | 95 | 5.6 |
| 172.73–177.80 | 257 | 15.2 | 223 | 13.2 | 98 | 5.8 | 125 | 7.4 |
| 177.81–182.88 | 240 | 14.2 | 197 | 11.6 | 87 | 5.1 | 110 | 6.5 |
| >182.88 | 171 | 10.1 | 188 | 11.1 | 77 | 4.5 | 110 | 6.5 |
| Cryptorchidism | | | |
| Yes | 16 | 1.7 | 41 | 5.3 | 11 | 3.4 | 30 | 6.8 |
| No | 912 | 98.3 | 726 | 94.7 | 313 | 96.6 | 412 | 93.2 |
| First- or second-degree family history of testicular cancer | | | |
| Yes | 14 | 1.5 | 33 | 4.3 | 17 | 5.2 | 16 | 3.6 |
| No | 915 | 98.5 | 734 | 95.7 | 307 | 94.8 | 426 | 96.4 |

Abbreviations: STEED = Servicemen’s Testicular Tumor Environmental and Endocrine Determinants; TGCT = testicular germ cell tumour. *Percent may not sum to 100 because of missing values.

**RESULTS**

The distributions of selected characteristics of the study population are provided in Table 1. Cases were more likely than controls to report a history of cryptorchidism (adjusted OR: 3.31; 95% CI: 1.84 – 5.97).

**Mumps and orchitis**

There was no association between history of mumps without orchitis and TGCT (OR: 0.98; 95% CI: 0.76 – 1.27) (Table 2). Overall history of orchitis was associated with an increased risk of TGCT (OR: 2.38; 95% CI: 1.56 – 3.63), however, this association was limited to orchitis diagnosed within one calendar year of the reference date (OR: 23.16; 95% CI: 5.53 – 96.99). Orchitis diagnosed more than 1 year prior to the reference age was not associated with risk (OR: 1.17; 95% CI: 0.71 – 1.94).

We further evaluated mumps and orchitis occurring around puberty (≥10 years of age) as the testes undergo maturation and peripubertal infection accompanied with inflammation may be an aetiologically relevant event. Orchitis at ≥10 years of age (OR: 1.12; 95% CI: 0.67 – 1.90) and mumps infection at ≥10 years of age were not associated with TGCT (OR: 1.34; 95% CI: 0.71 – 2.51) (Supplementary Table 1).

**Common childhood infections, genital conditions and genital tract infections**

History of measles, chicken pox, roseola/sixth disease and mononucleosis were not associated with TGCT overall or by histological type (Supplementary Table 2). Similarly, self-reported inflammation in the groyne area and sexually transmitted infections were associated.

With the exception of results presented above for orchitis infection where the age at diagnosis of orchitis was within 1 year of reference age, the ORs for association between infection and TGCT remained unchanged in sensitivity analyses excluding participants with self-reported age at infection within 1 year of the reference age.

**Meta-analysis of the association between mumps, orchitis and TGCT**

The pooled summary OR based on the random-effects model for mumps was 1.03 (95% CI: 0.89 – 1.20); suggesting no association with TGCT (Figure 1). The consistent fixed- and random-effects pooled ORs and $I^2$ of 6.1% indicated very little heterogeneity among the six studies ($P$-value: 0.38).

For mumps orchitis or orchitis, the random-effects model yielded a pooled OR of 1.80 (95% CI: 0.74 – 4.42). The disparate fixed- and random-effects pooled ORs and $I^2$ of 6.1% indicated very little heterogeneity across study-specific ORs for the five studies. Bajou’s plot indicated that the two recent studies contributed most to the heterogeneity (Moller and Skakkebaek, 1999 and the current study). When these studies were removed, the $I^2$ value dropped to 0.0% ($P$-value: 0.91) and the pooled ORs for fixed- and random-effects models became
### Table 2: Association of mumps, orchitis and testicular germ cell tumours according to histology; STEED Study 2002–2005

| Author/year/location | %Exp cases | %Exp controls | OR (95% CI) | Weight (D+L) |
|-----------------------|------------|---------------|-------------|--------------|
| Mills* (94) US        | 2.3        | 0.3           | 8.16 (1.02, 65.60) | 12.56 |
| Brown (97) US         | 2.2        | 0.4           | 5.80 (0.26, 129.70) | 6.66 |
| Swerdlow (87) UK      | 1.9        | 0.2           | 12.70 (1.42, 113.60) | 11.72 |
| Moller (99) DK        | 6.6        | 8.8           | 0.65 (0.37, 1.13) | 34.06 |
| Trabert* (12) US      | 4.4        | 3.7           | 1.17 (0.71, 1.94) | 34.80 |
| D+L Subtotal (I² = 69.0%, P = 0.012) | 1.80 (0.74, 4.42) | 100.00 |
| I-V Subtotal         |            |               | 1.05 (0.73, 1.51) |

### Discussion

History of orchitis, mumps and other childhood infections were not risk factors for TGCT in this study.

As summarised in the meta-analysis of mumps orchitis or orchitis, increased risk of TGCT was observed in three prior studies (Mills et al, 1984; Brown et al, 1987; Swerdlow et al, 1987) and a null association was observed in the current study and another recent study conducted by Moller and Skakkebaek (1999). These earlier studies, however, are based on small sample sizes (n = 8, 6 and 5 exposed cases, respectively), whereas the latter studies included 32 and 34 exposed cases, respectively. Not included in the meta-analysis were three studies that did not provide case/control counts or risk estimates, two of which reported an increased risk with orchitis (Beard et al, 1977) and one reported a null association (Stone et al, 1991).
Common childhood infections, inflammation in the groin area, history of urinary tract infection and sexually transmitted infections were not associated with TGCT. The lack of association with childhood infectious diseases, including mumps, was consistent with most published reports (Henderson et al., 1979; Loughlin et al., 1980; Goldman et al., 1982; Moss et al., 1986; Brown et al., 1987; Haughey et al., 1989; Stone et al., 1991; UK Testicular Cancer Study Group, 1994; Petridou et al., 1997). Our meta-analysis of mumps included six studies in addition to the current study (Henderson et al., 1979; Loughlin et al., 1980; Brown et al., 1987; Swerdlow et al., 1987; UK Testicular Cancer Study Group, 1994; Petridou et al., 1997); all of these studies reported a null association. Four additional studies also reported a null association, however, these studies were not included in the meta-analysis because of the lack of case/control counts or risk estimates (Coldman et al., 1982; Moss et al., 1986; Haughey et al., 1989; Stone et al., 1991). Most authors reported, as we do, a lack of association between sexually transmitted infections and TGCT (Coldman et al., 1982; Moss et al., 1986; Brown et al., 1987; Swerdlow et al., 1987).

Strengths of the current study include the large sample size, high response proportion (91% of cases and 81% of controls), and that cases and controls were drawn from the same well-defined population (McGlynn et al., 2007). Further, the study included only pathologically confirmed TGCT. As with all case-control studies, however, limitations include the reliance on participant recall, which may be more selective among cases. We attempted to address this issue with sensitivity analyses that excluded self-reported infection that occurred in the calendar year prior to the reference date.

As hypothesised in the introduction, we evaluated infectious agents and risk of TGCT based on similarities in age-specific incidence patterns for TGCT and cancers with infectious etiologies. Specifically, NHL also occurs in young men, and studies have shown that some cases are the result of an infectious agent following the paralytic polio model. Given the epidemiologic similarities between TGCT and NHL, Newell et al. (1984) hypothesised that the paralytic polio model may be relevant to TGCT aetiology (Newell et al., 1984). However, our data suggest that, unlike NHL, TGCT does not appear to be associated with common childhood infections.

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Conflict of interest

The authors declare no conflict of interest.

Supplementary Information accompanies the paper on British Journal of Cancer website (http://www.nature.com/bjc)

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