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Clinical Study

Growth hormone treatment and risk of recurrence or development of secondary neoplasms in survivors of pediatric brain tumors

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ABSTRACT

Growth hormone (GH) is increasingly used for treatment of pediatric brain tumors. However, controversy remains over its safety. This meta-analysis assessed whether GH treatment was associated with risk of recurrence or development of secondary neoplasm for brain tumors in children. Systematic computerized searches of PubMed and Web of Knowledge were performed. Pooled relative risks (RR) with 95% confidence interval (CI) for recurrence and/or secondary neoplasm in children who were treated with GH *versus* those who did not receive GH were calculated. Ten studies were included. The pooled recurrence rates were 21.0% and 44.3% in the GH-treated group and non-GH-treated group, respectively. The pooled RR for recurrence was 0.470 (95% CI 0.372–0.593; z = 6.33, $p = 0.000$). Begg's test ($p = 0.060$) and Egger's test ($p = 0.089$) suggested there was no significant publication bias. The pooled RR in sensitivity analysis was 0.54 (95% CI 0.37–0.77; z = 3.32, $p = 0.001$), which showed the result was robust. The pooled RR for secondary neoplasm was 1.838 (95% CI 1.053–3.209; z = 2.14, $p = 0.032$). Begg's test ($p = 1.000$) and Egger's test ($p = 0.553$) suggested there was no significant publication bias. We found no evidence that GH therapy is associated with an increased risk of recurrence for pediatric brain tumors. However, because of our small sample size, the association of GH therapy with an increased risk of secondary neoplasm is uncertain. Further prospective cohorts are needed.

1. Introduction

Brain tumors are the second most common type of pediatric cancer after leukemia and are the leading cause of childhood cancer-related mortality [1–2]. The estimated incidence in children aged 0–15 years ranges from 29.9–47.1 cases per million children [2]. With the increasingly widespread availability of MRI, the incidence of childhood brain tumors seemed to rise after the 1980s [2–3]. The treatment of childhood brain tumors often incorporates multimodal approaches involving surgery, irradiation and chemotherapy. However, treatment often results in hypothalamic-pituitary function suppression, which includes growth hormone (GH) deficiency. Long-term human GH replacement therapy is needed to counteract growth impairment [4].

It is recognized that GH has mitogenic and anti-apoptotic activities. Using *in vitro* cells, Bogazzi et al. reported that GH exerts a direct anti-apoptotic effect on colonic cells through an increased expression of signal transducer and activator of transcription (STAT) 5b and a reduction of Bax and PPARgamma [5]. Zeitler et al. reported antagonism of endogenous GH-releasing hormone leads to reduced proliferation and apoptosis in MDA231 breast cancer cells [6]. Barabutis et al. found knocking down gene expression for GH-releasing hormone inhibited proliferation of human cancer cell lines [7]. Using *in vivo* animal studies, Stangelberger et al. reported antagonists of GH-releasing hormone had an inhibitory effect for intra-osseous growth and invasiveness of PC-3 human prostate cancer in nude mice [8]. Since GH is mitogenic, there is a theoretical risk that GH treatment may be associated with tumor recurrence or new tumor development.

Some studies have investigated GH replacement therapy in pediatric brain tumor treatment, but to our knowledge none have shown an increased risk of tumor recurrence [9–12]. However, controversy remains over its safety. This meta-analysis assessed whether GH treatment was associated with risk of recurrence or development of a secondary neoplasm in children who had survived brain tumors.

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2. Methods

2.1. Database and literature search

Systematic computerized searches of the PubMed and Web of Knowledge were performed from their inception to 10 December 2013. The following search terms were used: "growth hormone", "recurrence", "relapse", "second neoplasm", "brain tumor", "brain cancer", "glioma", "pediatric", and "children". The search detail in PubMed was ("growth hormone" title/abstract OR "GH" title/abstract) AND ("recurrence" title/abstract OR "relapse" title/abstract OR "second* neoplasm*" title/abstract OR "second* tumor*" title/abstract) AND ("brain tumor*" text word OR "brain cancer*" text word OR "glioma" text word) AND ("pediatric" text word OR "child*" text word). In the Web of Science citation database, we selected the Science Citation Index Expanded database and Conference Proceedings Citation Index Science database. The search detail used was as follows: (Topic [TS] "growth hormone") AND (TS "recurrence" OR TS "relapse" OR TS "second* neoplasm*" OR TS "second* tumor*") AND (TS "brain tumor*" OR TS "brain cancer*" OR TS "glioma") AND (TS "pediatric" OR TS "child*"). The references of all relevant studies were also manually reviewed to supplement our searches. Only studies published in English were included.

2.2. Study selection

The following inclusion criteria had to be fulfilled: (1) the studies permitted assessment of GH treatment and risk of recurrence or development of secondary neoplasm of brain tumors in children; and (2) the studies provided relative risk (RR), or provided sufficient data to construct the two-by-two contingency tables to calculate RR, or provided adjusted RR and the corresponding 95% confidence interval (CI). We excluded case reports, case series, and reviews.

2.3. Data extraction

We used a standardized data collection form to extract the following information: first author, publication year, study location, age at brain tumor diagnosis, follow-up, brain tumor types, number of patients with recurrence or secondary neoplasm and total number of patients in the GH-treated group and non-GH-treated group, crude RR with 95% CI, adjusted RR with 95% CI, and the main confounding or mediating factors for statistical adjustment. Data extraction was independently carried out by two reviewers. Disagreements were resolved by discussion between the two.

2.4. Qualitative assessment

The quality of studies was assessed according to the Newcastle–Ottawa Scale (NOS) [13]. The NOS contains eight items, categorized into three dimensions including Selection (four items), Comparability (one item), and Exposure (three items). A high quality study can be awarded a maximum of one star for each item within the Selection and Exposure categories, and a maximum of two stars can be given for Comparability, thus NOS results range between zero and nine stars.

2.5. Statistical analysis

Statistical heterogeneity was explored by χ^2 and inconsistency (I^2) statistics; $p < 0.05$ for χ^2 or an I^2 value of $\geqslant 50\%$ represented substantial heterogeneity [14]. In the absence of significant heterogeneity, studies were pooled using a fixed-effects model. If heterogeneity was observed, a random-effects model was used. Overall effects were determined using the Z test. Visual inspection of a funnel plot, the Egger's regression test, and Begg's adjusted rank correlation test were performed to assess publication bias. Subgroup analyses were conducted for different tumor types, and sensitivity analysis was conducted by using adjusted RR and 95% CI from original studies. Two-sided $p < 0.05$ was considered statistically significant. All statistical analyses were performed with Stata software, version 12.0 (Stata Corp, College Station, TX, USA).

3. Results

3.1. Eligible studies

We identified 10 studies that met our inclusion criteria for meta-analysis [9–12,15–20]. The detailed steps of our literature search are shown in Figure 1. Of the 10 studies, four were conducted in the USA, four in the UK, and one each in Canada and Germany. The quality rating of the included studies ranged from six to eight stars out of nine on the NOS scale. Table 1 shows the main characteristics of the 10 included studies.

3.2. Pooled analysis for GH treatment and recurrence risk in children with brain tumors

Nine studies assessed GH treatment and recurrence risk in children with brain tumors. Among them, six studies provided the number of patients who suffered a recurrence and the total number of patients in the GH-treated group and non-GH-treated group. The recurrence rate in the GH-treated group ranged from 11.6% to 33.3%, and 23.8% to 48.0% in the non-GH-treated group. The pooled recurrence rates were 21.0% and 44.3% in the GH-treated group and non-GH-treated group, respectively. No significant heterogeneity was found between the studies ($I^2 = 32.8\%$, $p = 0.190$). The pooled RR was 0.470 (95% CI 0.372–0.593; z = 6.33, $p = 0.000$) by fixed-effects model (Fig. 2A). Begg's test (z = 1.88, $p = 0.060$) and Egger's test (t = 2.24, $p = 0.089$) suggested there was no significant publication bias. Figure 2B shows the funnel plot of publication bias.

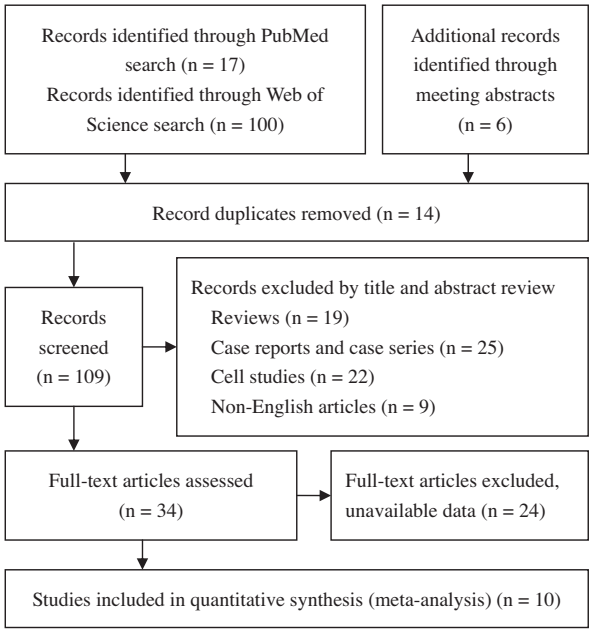

Fig. 1. Flow diagram showing selection of studies.