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Growth Hormone Replacement Therapy in Adult Growth Hormone Deficiency and Risk of Cancer: A Meta-Analysis

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Abstract

The growth hormone (GH) replacement therapy in adult growth hormone deficiency (AGHD) is now well developed, nevertheless, the safety of GH replacement, especially the incidence of cancer in these patients remains to be further clarified. To summarize the evidence on the safety of using GH in AGHD, we conduct this meta-analysis to assess the relationship between the risk of cancer and GH replacement therapy. Randomized controlled trials and cohort studies involved in GH therapy for AGHD were selected. Meta-analysis was performed and risk ratio (RR) was pooled with 95% confidence interval (CI) to investigate the relationship between GH replacement and the risk of cancer. The result indicated that there was no evidence to draw a conclusion that GH replacement therapy will increase the risk of cancer (P = 0.001, RR = 0.77, 95% CI [0.65, 0.90]). Meanwhile, according to the calculated analysis, the replacement therapy might even reduce the risk of cancer. Furthermore, subgroup analysis demonstrated that there was no correlation between replacement therapy of GH and the risk of cancer both in prospective and retrospective cohort design research, and in prospective group, the risk of cancer even decreased (P = 0.0002, RR = 0.71, 95%CI [0.59, 0.85]). In conclusion, our study corroborates evidence from previous studies showing that GH replacement therapy in AGHD patients would not increase the risk of cancer; instead, it might be even decrease cancer risk. The results suggested that GH replacement therapy in AGHD patients was safe.

#These authors contributed equally to this work.

Keywords

Growth Hormone, Replacement Therapy, Adult Growth Hormone Deficiency, Cancer, Meta-Analysis

1. Introduction

Growth hormone (GH) was originally used to remedy short stature in childhood [1]. As experience with the treatment improved, the range of indications was expanded. The GH replacement therapy for adults with hypopituitarism and GH deficiency is now well established, however, some reports have raised concern about the safety of GH therapy. The biological effect of GH is associated with the GH-GH receptor-insulin-like growth factor 1 (IGF-1) axis, while IGF-1 has significant effects on cell proliferation and differentiation [2]. Epidemiological studies had shown a relationship between elevated circulating levels of IGF-1 and an increased risk of several types of cancers such as prostate, colorectal and breast neoplasms [3] [4] [5]. The association between GH-IGF axis and carcinogenesis was also announced by the study in which patients enrolled suffering from acromegaly, which characterized by hypersecretion of GH and elevated levels of IGF-1. This research showed that the individual with GH replacement therapy has a higher risk of developing thyroid and colorectal carcinoma [6]. A meta-regression analysis conducted by Renehan *et al.* drew a same conclusion [7]. Data from the Pharmacia International Metabolic Surveillance (KIMS) study showed that the overall occurrence of the novo cancer or the rate of recurrence for primary pituitary adenomas were not increased [8]. There is ongoing concern about the potential mitogenic property of GH-IGF-1 axis and the safety of GH replacement in adult because of currently widely used of GH replacement therapy.

To further definitely resolve this cancer-related safety issue in GH replacement therapy, specifically in AGHD patients, we therefore used meta-analysis methodology to assess published studies which examined incidence of cancer in AGHD patients who applied GH replacement therapy.

2. Materials and Methods

2.1. Literature Search Strategy

PUBMED, Web of Science, Ovid, Cochrane library, CBM, CNKI and Wan Fang database were systematically searched for articles published from the beginning of the database to July 2017. Keywords included in the search were "growth hormone deficiency/GHD/AGHD/adult growth hormone deficiency/hypopituitarism" AND "GH therapy/GH treatment/growth hormone treatment/growth hormone therapy/replacement" AND "cancer/tumor/neoplasm" All our work in this systematic review referred to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [9]. All analyses were based on previous published studies, thus no ethical approval and patient consent are re-

quired.

2.2. Study Inclusion Criteria

Two investigators assessed the eligibility of all retrieved papers and disagreement was resolved by a thorough discussion. Studies were preserved if they satisfied the following criteria: 1) case-control or cohort study; 2) participants were aged at least 18 years old or above; 3) reported definitions and measurement of AGHD; 4) reported risk, odds or hazard ratios across different exposure categories of GH; 5) reported morbidity outcomes for cancer; 6) published in English or Chinese language.

2.3. Data Extraction and Quality Assessment

Data pertaining to the study and participant details, intervention measures, follow-up duration as well as research outcomes were extracted independently by two reviewers using a standardized data extraction form and reconciled for accuracy.

Studies reported tumorigenesis outcomes of AGHD patients treated with GH were considered for inclusion in the analysis. For studies that were eligible but without detailed number of tumorigenesis, the investigators would contact with authors in order to get the additional information essential for analysis.

Quality of inclusion studies was assessed by the Newcastle-Ottawa Scale [10]. A "star system" was used to evaluate data quality based on three broad aspects for studies: the selection, the comparability and the outcome. The scores ranged from 0 to 9. Researches with scores of 6 stars to 9 stars were regarded to be of high quality. The quality as well as the bias of included studies was cross-checked by two reviewers independently and disagreements between two reviewers would be settled by open discussion.

2.4. Statistical Analysis

Meta-analysis was performed with extracted data by statistical software Revman 5.0, the interesting outcome of this meta-analysis was the incidence of cancer. Risk ratio values and the corresponding 95% confidence interval were used to estimate the relationship between GH replacement therapy and risk of cancer in AGHD patients.

Statistical analysis was performed as previously described by Tsilid is *et al.* [11]; all analyses were conducted using the fixed effects model. Methods of fixed effect meta-analysis were based on the assumption that a single common (or "fixed") effect underlies every study in the meta-analysis without any heterogeneity between studies. We assessed heterogeneity between studies using the P value of the χ^2 based Cochrane Q test and the I^2 metric of inconsistency; this could reflect either genuine diversity or bias. The Q test is obtained by the weighted sum of the squared differences of the observed effect in each study minus the fixed summary effect. The I^2 metric ranges between 0% and 100% and is the ratio of variance between

studies over the sum of the variances within and between studies. We further conducted subgroup analyses stratified by study characteristics according to prospective study design or retrospective study design. Then, in order to assess the risk of bias, we drew a funnel plot using the software of Revman 5.0. As the funnel plot was symmetrical, it prompted that the literature publication bias was controlled passably. Finally, Sensitivity analysis was performed to quantify the effect proportion of each included studies (through a "leave-one-out" method) on the overall evaluation.

3. Results

3.1. Study Identification

An online database search with the specified terms retrieved 3640 records presented or published. After removing duplicate records, 2993 items were left. Then 64 articles were selected for full-text screening for eligibility through reading the titles and abstracts. After final screening, data from 10 selected studies published from 2002 to 2017 were extracted for inclusion in the current analysis [12]-[21]. A flow diagram of literature search methodologies is provided in **Figure 1**.

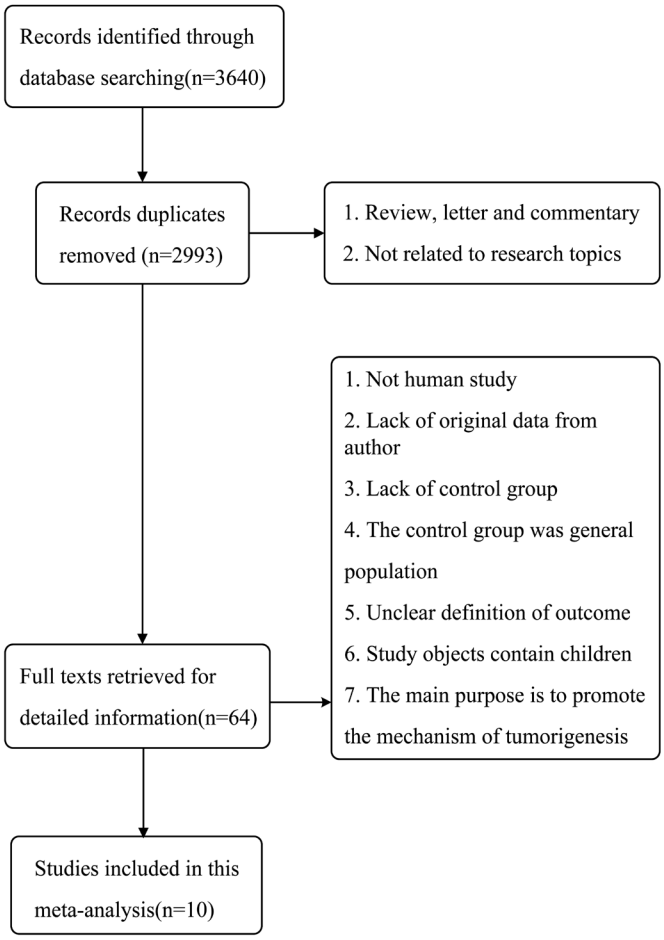


Figure 1. Flow chart of identification process for eligible studies.

3.2. Study Characteristics

No randomized, controlled studies comparing GH replacement therapy versus without GH replacement therapy in AGHD patients were identified. All studies included in this analysis were prospective or retrospective researches. Overall, the current meta-analysis included 13,404 patients and the largest studies which were reported by Child *et al.* (2015) accounted for more than half of these patients. Half of the studies defined pituitary tumors as the outcome. Four studies mentioned second neoplasms. The follow-up duration was no less than 10 years in five studies. The majority of patients were with an average age of around 50 years old, while the study conducted by Brignardello *et al.* did not reveal the age of patients. All studies but one described the proportion of gender distribution. Baseline characteristics for patients included in this analysis are outline in Table 1. The quality assessment showed that all of the selected studies obtained 6 or more scores evaluating by the NOS, which indicated the studies quality were generally high.

3.3. Publication Bias

Symmetrical funnel plot showed in Figure 2 proved little publication bias.

3.4. Quantitative Synthesis

Results of the meta-analysis about risk of cancer in AGHD patients treated with GH compared with untreated group are shown in Figure 3. No significant association was revealed between GH replacement therapy and cancer risk (P = 0.001, RR = 0.77, 95% CI [0.65, 0.90]). As the forest plot shown, the risk of cancer in AGHD patients treated with GH might even decrease compared with the untreated

Table 1. Characteristic of studies included in the meta-analysis.

Study	Year	Study types	Cases/controls	Age, (years)	Gender (male, %)	Follow-up period (years)	Study	Year
Arnold [12]	2009	Retrospective	23/107	53.7 ± 14.6* 56.2 ± 14^	69.6%* 57%^	6.8 ± 4.2	NFPA	6
Buchfelder [14]	2007	Retrospective	55/55	50.6 ± 9.7	NA	5	NFPA	7
Brignardello [13]	2015	Retrospective	26/23	NA	61.2%	11	Second neoplasms	6
Child [20]	2015	Prospective	8418/1268	45.5* 53.8^	52%* 59%^	4.8 3.5	Primary malignancies	7
Hartman [15]	2013	Prospective	1988/442	46 ± 15*	56%*	2.3	Intracranial tumor Second neoplasms	7
Hatrick [16]	2002	Prospective	47/28	49* 52^	46.8%* 64.3%	3.6	Pituitary tumor	7
Mackenzie [17]	2011	Retrospective	69/68	33* 29^	54.5%* 48.2%^	14.5* 15^	Tumor recurrence Second tumor	8
Olsson [18]	2009	Prospective	121/114	66.7 ± 11.2* 66.7 ± 11.0^	66%	13.6 ± 5.0* 13.4 ± 7.8^	Craniopharyngioma	8
Olsson [19]	2012	Prospective	56/70	46.6 ± 16.1* 45.7 ± 16.2^	57%* 49%^	14.5* 15^	Tumor recurrence Second tumor	8
Olsson [21]	2017	Prospective	207/219	56.3* 65.2^	70%* 59%^	12.2* 8.2^	Malignant tumors	8

*. GH treated group; ^. control group; NA: not available; NFPA: non-functioning pituitary adenoma.

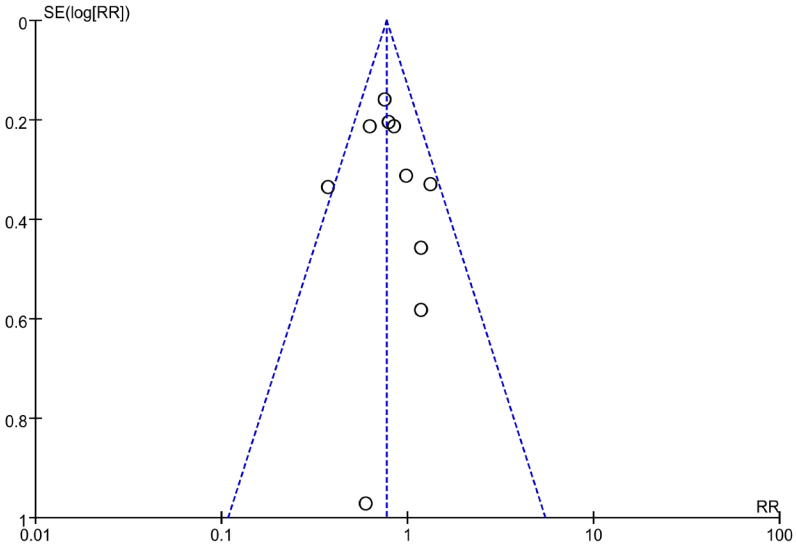
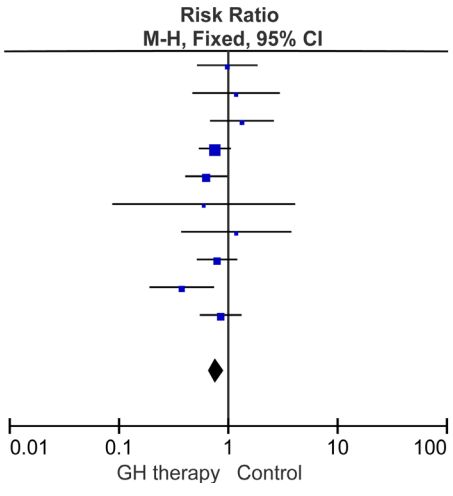


Figure 2. Funnel plot.

Study or Subgroup	GH therapy Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Arnold 2009	8	23	38	107	5.0%	0.98 [0.53, 1.81]
Brignardello 2015	8	26	6	23	2.4%	1.18 [0.48, 2.89]
Buchfelder 2007	16	55	12	55	4.5%	1.33 [0.70, 2.55]
Child 2015	225	8418	45	1268	29.2%	0.75 [0.55, 1.03]
Hartman 2013	79	1988	28	442	17.1%	0.63 [0.41, 0.95]
Hatrick 2002	2	47	2	28	0.9%	0.60 [0.09, 4.00]
Mackenzie 2011	6	69	5	68	1.9%	1.18 [0.38, 3.69]
Olsson 2009	31	121	37	114	14.2%	0.79 [0.53, 1.18]
Olsson 2012	9	56	30	70	10.0%	0.38 [0.19, 0.72]
Olsson 2017	33	207	41	219	14.9%	0.85 [0.56, 1.29]
Total (95% CI)		**11010**		**2394**	**100.0%**	**0.77 [0.65, 0.90]**
Total events	417		244			

Heterogeneity: Chi² = 10.62, df = 9 (P = 0.30); I² = 15%
Test for overall effect: Z = 3.18 (P = 0.001)

(a)



(b)

Figure 3. Forest plot of the risk of cancer in AGHD patients treated with GH compared with the untreated group (Fix-effect model).

group. Heterogeneity (I^2 = 15%, P = 0.30) was low indicating the consistency of a decreased risk among GH treated group in AGHD patients.

3.5. Sensitivity Analyses

For sensitivity analyses, we left out each of the studies in turn, in order to investigate the effect of a single study on the overall risk estimation (Table 2). When we excluded the study "Buchfelder 2007" and "Olsson 2012" that measured at least 5-year tumor progression-free survival rate (PFSR) in pituitary adenomas and craniopharyngioma patients on long-term growth hormone replacement therapy, the pooled risk ratio was 0.74 (P = 0.0005, 95% CI [0.63, 0.88]) and 0.81 (P = 0.02, 95% CI [0.69, 0.96]) respectively (Figure 4 and Figure 5). The I^2 was 0% and P value was 0.45 after the exclusion of "Buchfelder", the I^2 was 0% and P value was 0.70 after the exclusion of "Olsson 2012", suggested that the study "Buchfelder 2007" and "Olsson 2012" caused heterogeneity mainly.

3.6. Subgroup Analysis

Subgroup analysis based on study design demonstrated that the pooled risk ratio was statistically significant in prospective studies (P = 0.0002, RR = 0.71, 95% CI [0.59, 0.85]). Heterogeneity (I^2 = 3%, P = 0.4) was low indicating the consistency of the decreased risk of cancer for GH treated group in prospective studies. In the retrospective subgroup, there was no significant differences between the GH treated group and control group as the pooled statistic shown (P = 0.45, RR = 1.16, 95% CI [0.79, 1.69]) (Figure 6). The pooled risk ratio suggested that the risk of cancer was not increasing in GH treated group. There was no heterogeneity (I^2 = 0%, P = 0.93), indicating the consistency of no increasing risk of cancer for GH treated group in retrospective studies.

Table 2. "Leave-one-out" for sensitivity analyses.

Study leave out	Pooled RR	95% CI	P value	Heterogeneity (P value, I^2)
Arnold 2009 [12]	0.76	[0.64, 0.90]	0.001	(0.26, 20%)
Buchfelder 2007 [14]	0.74	[0.63, 0.88]	0.0005	(0.45, 0%)
Brignardello 2015 [13]	0.76	[0.64, 0.89]	0.001	(0.28, 18%)
Child 2015 [20]	0.77	[0.64, 0.94]	0.008	(0.23, 24%)
Hartman 2013 [15]	0.8	[0.67, 0.95]	0.01	(0.31, 15%)
Hatrick 2002 [16]	0.77	[0.65, 0.91]	0.002	(0.23, 24%)
Mackenzie 2013 [17]	0.76	[0.64, 0.90]	0.001	(0.26, 21%)
Olsson 2009 [18]	0.76	[0.64, 0.91]	0.003	(0.22, 25%)
Olsson 2012 [19]	0.81	[0.69, 0.96]	0.02	(0.70, 0%)
Olsson 2017 [21]	0.75	[0.63, 0.90]	0.002	（0.24, 23%）
None	0.77	[0.65, 0.90]	0.001	（0.3, 15%）

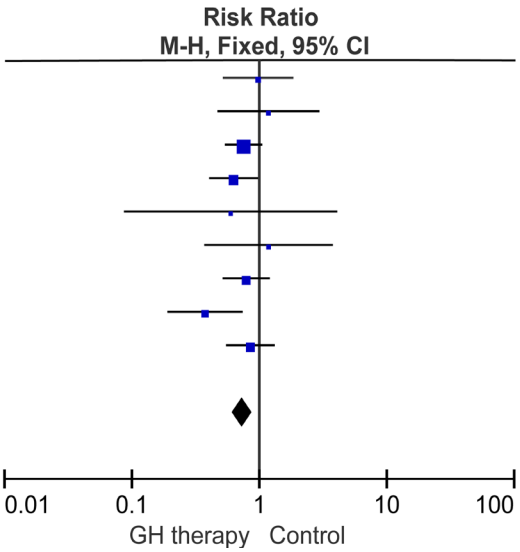
"None" means no study was left out.

Study or Subgroup	GH therapy Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Arnold 2009	8	23	38	107	5.3%	0.98 [0.53, 1.81]
Brignardello 2015	8	26	6	23	2.5%	1.18 [0.48, 2.89]
Child 2015	225	8418	45	1268	30.6%	0.75 [0.55, 1.03]
Hartman 2013	79	1988	28	442	17.9%	0.63 [0.41, 0.95]
Hatrick 2002	2	47	2	28	1.0%	0.60 [0.09, 4.00]
Mackenzie 2011	6	69	5	68	2.0%	1.18 [0.38, 3.69]
Olsson 2009	31	121	37	114	14.9%	0.79 [0.53, 1.18]
Olsson 2012	9	56	30	70	10.4%	0.38 [0.19, 0.72]
Olsson 2017	33	207	41	219	15.6%	0.85 [0.56, 1.29]
Total (95% CI)		**10955**		**2339**	**100.0%**	**0.74 [0.63, 0.88]**
Total events	401		232			

Heterogeneity: Chi² = 7.79, df = 8 (P = 0.45); I² = 0%

Test for overall effect: Z = 3.48 (P = 0.0005)

(a)



(b)

Figure 4. Forest plot of leaving "Buchfelder 2007" out.

4. Discussion

A doubtful association between GH replacement therapy and risk of developing cancer or recurrence of tumor has long been speculated. A number of studies have been undertaken to investigate the safety of GH replacement therapy. More data about the safety of GH treatment are available in children, while the safety problem of GH treatment in adult especially for cancer was not fully established.

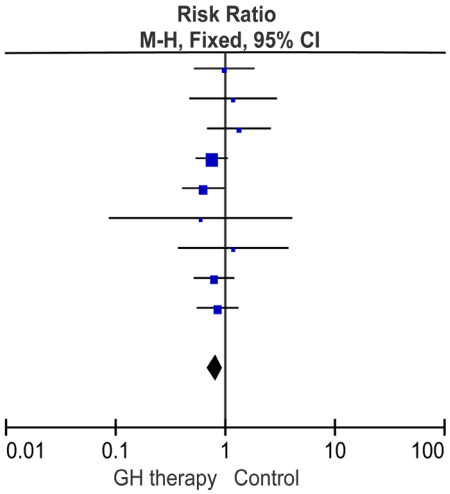
A systematic review and meta-analysis was previously carried out to assess the association between GH therapy and cancer risk in patients treated with GH during childhood and adolescence, the result showed that both the overall cancer standardized incidence ratio (SIR) 2.74 (95%CI 1.18 - 5.42) and risk ratio (RR) 1.99 (95% CI 1.28 - 3.08, P = 0.002) for second neoplasms were significantly increased [22]. And another meta-analysis showed that the risk of recurrence for pediatric brain tumors was not increased in patients treated with GH [23].

Study or Subgroup	GH therapy Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Arnold 2009	8	23	38	107	5.6%	0.98 [0.53, 1.81]
Brignardello 2015	8	26	6	23	2.6%	1.18 [0.48, 2.89]
Buchfelder 2007	16	55	12	55	5.0%	1.33 [0.70, 2.55]
Child 2015	225	8418	45	1268	32.4%	0.75 [0.55, 1.03]
Hartman 2013	79	1988	28	442	19.0%	0.63 [0.41, 0.95]
Hatrick 2002	2	47	2	28	1.0%	0.60 [0.09, 4.00]
Mackenzie 2011	6	69	5	68	2.1%	1.18 [0.38, 3.69]
Olsson 2009	31	121	37	114	15.8%	0.79 [0.53, 1.18]
Olsson 2017	33	207	41	219	16.5%	0.85 [0.56, 1.29]
Total (95% CI)		**10954**		**2324**	**100.0%**	**0.81 [0.69, 0.96]**
Total events	408		214			

Heterogeneity: Chi² = 5.54, df = 8 (P = 0.70); I² = 0%

Test for overall effect: Z = 2.43 (P = 0.02)

(a)



(b)

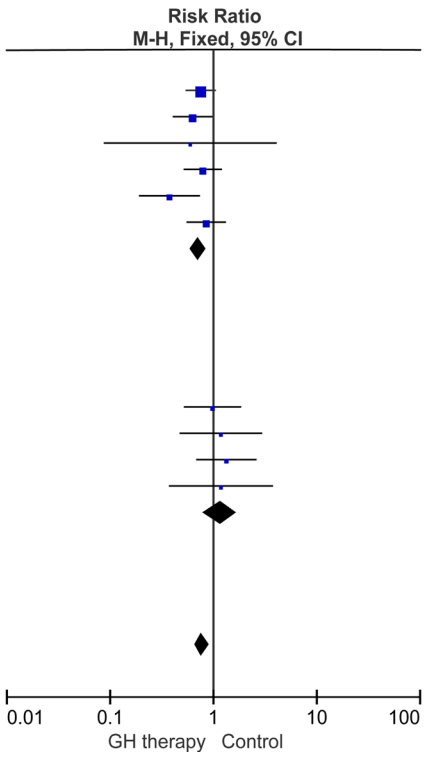
Figure 5. Forest plot of leaving "Olsson 2012" out.

On the contrary, Liang Shen *et al.* indicated that GH replacement therapy decreased the risk of recurrence or progression in children with intracranial tumors, such as craniopharyngioma, medulloblastoma, astrocytoma, or glioma, but not for pituitary adenomas, non-functional pituitary adenomas, and ependymoma. There was no relation between GHRT and pituitary adenomas, non-functional pituitary adenomas [24]. And a study of pediatric GH treatment which conducted by Child C.J *et al.* also showed that if there has no history of malignancy, the risk of primary cancer did not increase. [25]. Study conducted by Rosen observed a decreased rate of malignancies in hypopituitarism men without GH replacement therapy [26], whereas Svensson *et al.* and Stochholm *et al.* found there was an increased rate of malignancies in hypopituitarism adults without GH replacement therapy [27] [28].

Study performed by Chung T.T. *et al.* observed that GH treatment was not associated with increased tumor recurrence or second neoplasms [29]. Child *et al.* demonstrated no increased risk of primary cancers in GH-treated AGHD

Study or Subgroup	GH therapy Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.2.1 Prospective studies						
Child 2015	225	8418	45	1268	29.2%	0.75 [0.55, 1.03]
Hartman 2013	79	1988	28	442	17.1%	0.63 [0.41, 0.95]
Hatrick 2002	2	47	2	28	0.9%	0.60 [0.09, 4.00]
Olsson 2009	31	121	37	114	14.2%	0.79 [0.53, 1.18]
Olsson 2012	9	56	30	70	10.0%	0.38 [0.19, 0.72]
Olsson 2017	33	207	41	219	14.9%	0.85 [0.56, 1.29]
Subtotal (95% CI)		**10837**		**2141**	**86.3%**	**0.71 [0.59, 0.85]**
Total events	379		183			
Heterogeneity: Chi² = 5.13, df = 5 (P = 0.40); I² = 3%						
Test for overall effect: Z = 3.77 (P = 0.0002)						
1.2.2 Retrospective studies						
Arnold 2009	8	23	38	107	5.0%	0.98 [0.53, 1.81]
Brignardello 2015	8	26	6	23	2.4%	1.18 [0.48, 2.89]
Buchfelder 2007	16	55	12	55	4.5%	1.33 [0.70, 2.55]
Mackenzie 2011	6	69	5	68	1.9%	1.18 [0.38, 3.69]
Subtotal (95% CI)		**173**		**253**	**13.7%**	**1.16 [0.79, 1.69]**
Total events	38		61			
Heterogeneity: Chi² = 0.47, df = 3 (P = 0.93); I² = 0%						
Test for overall effect: Z = 0.76 (P = 0.45)						
Total (95% CI)		**11010**		**2394**	**100.0%**	**0.77 [0.65, 0.90]**
Total events	417		244			
Heterogeneity: Chi² = 10.62, df = 9 (P = 0.30); I² = 15%						
Test for overall effect: Z = 3.18 (P = 0.001)						
Test for subgroup differences: Chi² = 5.33, df = 1 (P = 0.02), I² = 81.2%						

(a)



(b)

Figure 6. Forest plot of subgroup analysis based on study design.

patients in hypopituitary control and complications study compared with cancer rates of general population, standardized by country, gender, and age [30]. Bunderen *et al.* played a review to discuss the long-term efficacy and safety of GH treatment in AGHD patients with emphasis on morbidity [31]. In a subgroup of the review, the risk of regrowth and recurrences of pituitary tumors were not increasing in AGHD patients treated with GH compared with untreated AGHD patients, while secondary brain tumors remained more prevalent. Generally, the conclusion showed that fatal and nonfatal malignancies were not more prevalent in GH-treated adults compared to the general population. In our meta-analysis, we compared the risk of cancer between GH-treated AGHD patients with the patients without receiving GH treatment. Furthermore, it differed from Bunderen *et al.* who focused on morbidity; the only outcome of our study was the risk of cancer in AGHD patients treated with GH. And unlike the review previously carried out by Kirstine Stochholm *et al.* showed that the GH replacement did not increase the cancer risk [32], the consequence of our study was more positive, we found the risk of cancer in AGHD patients treated with GH might even decrease.

Our meta-analysis showed that AGHD patients treated with GH demonstrated no increased risk of cancer compared with the untreated group; moreover, the result indicated that GH replacement therapy might even decrease the risk of cancer. The subgroup analysis revealed that GH treatment was associated with decreased risk of cancer in prospective design group, whereas no significant difference of cancer risk was observed between GH treated group and untreated group in retrospective design group.

The above observations led us to hypothesize that the possible mechanism might be related to the improvement of body composition, exercise performance and the individual GH dose adjusted according to the serum IGF-1 level regularly conducted by titration regimen.

It was well recognized that AGHD patients had an abnormal body composition with a decrease in body lean mass, whereas an increase in total and visceral fat mass which was related to insulin resistance [33]. Adipose tissues release a variety of different small protein factors, including chemokines [monocyte chemotactic protein 1 (MCP-1)], IL-6, IL-1, TNF-α, adipokines [haptoglobin, leptin, visfatin, resistin, and vascular endothelial growth factor (VEGF)], on the other hand, the secretion of anti-inflammatory adipokines (adiponectin, IL-10, IL-1) decline [34] [35]. TNF-α appears to contribute to the development of the tissue architecture necessary for tumor growth and metastasis [36] [37], while IL-6 regulates chronic inflammation, which can create a cellular microenvironment beneficial to cancer growth [38]. Releasing of short-range cytokines boosts the local expansion of other immune cells and the regeneration of damaged tissue, these include strong inducers of proliferation, metastasis, and angiogenesis; releasing of long-range cytokines (IL-6, TNF-α) will boost insulin resistance in the liver and other metabolism-controlling organs, thus generating increased levels of insulin that may in turn

promote cancer growth [39]. In contrast, adiponectin with anti-atherogenic, anti-inflammatory, and insulin-sensitivity effects might have the function to inhibit the growth of tumor [40]. In consistent with this hypothesis, several case-control studies have verified that serum adiponectin levels were significantly decreased in breast cancer patients [41]. Studies have reported that GH replacement was associated with a significant reduction in body fat and improvement in insulin resistance [33]. Therefore, we believe that a decrease of total and visceral fat mass result from the replacement therapy of GH may reduce the risk of cancer in AGHD patients.

Aside from being associated with the improvement of body composition, there may be other potential mechanism. Study revealed that physical activity have the effect to protect against colon, breast and endometrial cancers, besides, insufficient physical activity levels were also estimated to cause 9% of breast cancer cases and 10% of colon cancer cases in Europe [42]. Observational studies demonstrated that physical activity was independently related to decreased risk of all-cause mortality in cancer survivors [43]. A great deal of researches has showed that GH replacement was associated with an improvement in exercise tolerance [18], and probably decreased the risk of cancer.

During the period of GH replacement treatment, the dose of GH was adjusted regularly according to serum level of IGF-1. Previously human population studies revealed that higher IGF-1 levels could be associated with increased risk of cancer [44]. The study conducted by Popovic *et al.* concluded that IGF-1 levels targeted to within normal age-related reference ranges during GH replacement were not associated with the occurrence of malignancies [45]. Current guidelines recommended that high inter-individual variability in both GH absorption and sensitivity makes the stepwise, individualized, upward titration method rather than standard weight-based dosing strategies, and individualized-dose titration regimens leads to similar beneficial effects and fewer side effects than weight-based regimens [46]. Consequently, all the cohort studies included in our analysis managed the dose of GH according to the individual titration regimen, which might be the other reason for the outcome.

The "leave-one-out" analysis revealed no substantial changes after exclusion of each study from the pooled analyses except the study "Buchfelder 2007" and "Olsson 2012". When the study "Buchfelder 2007" was left out, the result (RR = 0.74, 95% CI [0.63, 0.88]) and when the study "Olsson 2012" was left out, the result (RR = 0.81, 95% CI [0.67, 1.05]), which showed that the risk of cancer for GH replacement therapy group was not increased compared with the untreated group. However, the indicator I^2 was declined to 0% and P value was 0.45 and 0.70 respectively. This result suggested study "Buchfelder 2007" and "Olsson 2012" were the main source of heterogeneity. None of the cross-sectional studies was of low quality according to the NOS; therefore, we did not perform sensitivity analyses based on study quality.

The result of the detail information about gender and age were unavailable in

study conducted by Buchfelder *et al.* and Brignardello *et al.*, the subgroup analyses stratified by gender and age were unable to implement. Meanwhile, the inconsistent definition of event outcomes covered tumor recurrence and second neoplasms made it difficult to precise classification, so we were unable to perform the subgroup analyses according to classification of tumor. Finally, the doses of GH were individually conducted by titration regimens instead of specific dose, which induced the implementation of dose-response analyses difficulty.

There are some limitations in our study. First of all, available data were limited to non-randomized studies; all studies included were only retrospective or prospective cohort studies. Secondly, the study populations were heterogeneous, and the case number of the non GH-treated group was much smaller than the GH-treated group. Thirdly, for GH replacement therapy, there might have selection bias, untreated patients might be older, sicker, and more likely to have an intracranial tumor than treated patients. Additionally, the optimum duration of tumorigenesis or recurrence was probable beyond the follow-up period; similar analysis with longer follow-up is needed to confirm assurance of no increase, even decrease about the risk of cancer during GH therapy in adults.

5. Conclusion

This meta-analysis suggests that in AGHD patients treated with GH, there are no major safety concerns associated with cancer risk; moreover, GH replacement therapy might even decrease the risk of cancer for AGHD patients. Similar results were also reflected from the analysis conducted by Liang Shen *et al.* in children with intracranial tumors, craniopharyngioma, medulloblastoma, astrocytoma, or glioma [24]. Ideally, this result should be confirmed by a large-scale multicenter prospective randomized study with sufficiently long follow-up duration.

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Author Contributions

Conceived and designed the experiments: XXH and XXS. Database searches: LZ and CHL. Data abstraction: LZ and CHL Analyzed and interpreted the data: LZ, XXS and CHL. Wrote the paper: LZ, XXS and CHL. Revised the manuscript: JKH, PXY and JW

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Declaration of Interest

We guarantee to submit this manuscript without any conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

References

[1] Raben, M.S. (1958) Treatment of a Pituitary Dwarf with Human Growth Hormone. *Journal of Clinical Endocrinology & Metabolism*, **18**, 901-903. https://doi.org/10.1210/jcem-18-8-901

[2] Biernacka, K.M., Perks, C.M. and Holly, J.M. (2012) Role of the IGF Axis in Prostate Cancer. *Minerva Endocrinologica*, **37**, 173-185.

[3] Hankinson, S.E., Willett, W.C., Colditz, G.A., Hunter, D.J., Michaud, D.S., *et al.* (1998) Circulating Concentrations of Insulin-Like Growth Factor-I and Risk of Breast Cancer. *Lancet*, **351**, 1393-1396. https://doi.org/10.1016/S0140-6736(97)10384-1

[4] Stattin, P., Bylund, A., Rinaldi, S., Biessy, C., Dechaud, H., *et al.* (2000) Plasma Insulin-Like Growth Factor-I, Insulin-Like Growth Factor-Binding Proteins, and Prostate Cancer Risk: A Prospective Study. *Journal of the National Cancer Institute* **92**, 1910-1917. https://doi.org/10.1093/jnci/92.23.1910

[5] Ma, J., Pollak, M.N., Giovannucci, E., Chan, J.M., Tao, Y., *et al.* (1999) Prospective Study of Colorectal Cancer Risk in Men and Plasma Levels of Insulin-Like Growth Factor (IGF)-I and IGF-Binding Protein-3. *Journal of the National Cancer Institute*, **91**, 620-625. https://doi.org/10.1093/jnci/91.7.620

[6] Baris, D., Gridley, G., Ron, E., Weiderpass, E., Mellemkjaer, L., *et al.* (2002) Acromegaly and Cancer Risk: A Cohort Study in Sweden and Denmark. *Cancer Causes Control*, **13**, 395-400. https://doi.org/10.1023/A:1015713732717

[7] Renehan, A.G., Zwahlen, M., Minder, C., O'Dwyer, S.T., Shalet, S.M., *et al.* (2004) Insulin-Like Growth Factor (IGF)-I, IGF Binding Protein-3, and Cancer Risk: Systematic Review and Meta-Regression Analysis. *Lancet*, **363**, 1346-1353. https://doi.org/10.1016/S0140-6736(04)16044-3

[8] Monson, J.P. (2003) Long-Term Experience with GH Replacement Therapy: Efficacy and Safety. *European Journal of Endocrinology*, **148**, S9-S14. https://doi.org/10.1530/eje.0.148S009

[9] Moher, D., Liberati, A., Tetzlaff, J. and Altman, D.G. (2010) Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *International Journal of Surgery*, **8**, 336-341. https://doi.org/10.1016/j.ijsu.2010.02.007

[10] Stang, A. (2010) Critical Evaluation of the Newcastle-Ottawa Scale for the Assessment of the Quality of Nonrandomized Studies in Meta-Analyses. *European Journal of Endocrinology*, **25**, 603-605.

[11] Tsilidis, K.K., Kasimis, J.C., Lopez, D.S., Ntzani, E.E. and Ioannidis, J.P. (2015) Type 2 Diabetes and Cancer: Umbrella Review of Meta-Analyses of Observational Studies. *BMJ*, **350**, g7607. https://doi.org/10.1136/bmj.g7607

[12] Arnold, J.R., Arnold, D.F., Marland, A., Karavitaki, N. and Wass, J.A. (2009) GH Replacement in Patients with Non-Functioning Pituitary Adenoma (NFA) Treated Solely by Surgery Is Not Associated with Increased Risk of Tumour Recurrence. *Clinical Endocrinology*, **70**, 435-438.

https://doi.org/10.1111/j.1365-2265.2008.03391.x

[13] Brignardello, E., Felicetti, F., Castiglione, A., Fortunati, N., Matarazzo, P., *et al.* (2015) GH Replacement Therapy and Second Neoplasms in Adult Survivors of Childhood Cancer: A Retrospective Study from a Single Institution. *Journal of Endocrinological Investigation*, **38**, 171-176. https://doi.org/10.1007/s40618-014-0179-1

[14] Buchfelder, M., Kann, P.H., Wuster, C., Tuschy, U., Saller, B., *et al.* (2007) Influence of GH Substitution Therapy in Deficient Adults on the Recurrence Rate of Hormonally Inactive Pituitary Adenomas: A Case Control Study. *European Journal of Endocrinology*, **157**, 149-156. https://doi.org/10.1530/EJE-07-0164

[15] Hartman, M.L., Xu, R., Crowe, B.J., Robison, L.L., Erfurth, E.M., *et al.* (2013) Prospective Safety Surveillance of GH-Deficient Adults: Comparison of GH-Treated vs. Untreated Patients. *The Journal of Clinical Endocrinology & Metabolism*, **98**, 980-988. https://doi.org/10.1210/jc.2012-2684

[16] Hatrick, A.G., Boghalo, P., Bingham, J.B., Ayres, A.B., Sonksen, P.H., *et al.* (2002) Does GH Replacement Therapy in Adult GH-Deficient Patients Result in Recurrence or Increase in Size of Pituitary Tumours? *European Journal of Endocrinology*, **146**, 807-811. https://doi.org/10.1530/eje.0.1460807

[17] Mackenzie, S., Craven, T., Gattamaneni, H.R., Swindell, R., Shalet, S.M., *et al.* (2011) Long-Term Safety of Growth Hormone Replacement after CNS Irradiation. *The Journal of Clinical Endocrinology & Metabolism*, **96**, 2756-2761. https://doi.org/10.1210/jc.2011-0112

[18] Olsson, D.S., Buchfelder, M., Schlaffer, S., Bengtsson, B.A., Jakobsson, K.E., *et al.* (2009) Comparing Progression of Non-Functioning Pituitary Adenomas in Hypopituitarism Patients with and without Long-Term GH Replacement Therapy. *European Journal of Endocrinology*, **161**, 663-669. https://doi.org/10.1530/EJE-09-0572

[19] Olsson, D.S., Buchfelder, M., Wiendieck, K., Kremenevskaja, N., Bengtsson, B.A., *et al.* (2012) Tumour Recurrence and Enlargement in Patients with Craniopharyngioma with and without GH Replacement Therapy during More than 10 Years of Follow-Up. *European Journal of Endocrinology*, **166**, 1061-1068. https://doi.org/10.1530/EJE-12-0077

[20] Child, C.J., Conroy, D., Zimmermann, A.G., Woodmansee, W.W., Erfurth, E.M., *et al.* (2015) Incidence of Primary Cancers and Intracranial Tumour Recurrences in GH-Treated and Untreated Adult Hypopituitary Patients: Analyses from the Hypopituitary Control and Complications Study. *European Journal of Endocrinology*, **172**, 779-790. https://doi.org/10.1530/EJE-14-1123

[21] Olsson, D.S., Trimpou, P., Hallen, T., Bryngelsson, I.L., Andersson, E., *et al.* (2017) Life Expectancy in Patients with Pituitary Adenoma Receiving Growth Hormone Replacement. *European Journal of Endocrinology*, **176**, 67-75. https://doi.org/10.1530/EJE-16-0450

[22] Deodati, A., Ferroli, B.B. and Cianfarani, S. (2014) Association between Growth Hormone Therapy and Mortality, Cancer and Cardiovascular Risk: Systematic Review and Meta-Analysis. *Growth Hormone & IGF Research*, **24**, 105-111. https://doi.org/10.1016/j.ghir.2014.02.001

[23] Wang, Z.F. and Chen, H.L. (2014) Growth Hormone Treatment and Risk of Recurrence or Development of Secondary Neoplasms in Survivors of Pediatric Brain Tumors. *Journal of Clinical Neuroscience*, **21**, 2155-2159. https://doi.org/10.1016/j.jocn.2014.04.016

[24] Shen, L., Sun, C.M., Li, X.T., Liu, C.J. and Zhou, Y.X. (2015) Growth Hormone

Therapy and Risk of Recurrence/Progression in Intracranial Tumors: A Meta-Analysis. *Neurological Sciences*, **36**, 1859-1867. https://doi.org/10.1007/s10072-015-2269-z

[25] Child, C.J., Zimmermann, A.G., Jia, N., Robison, L.L., Bramswig, J.H., *et al.* (2016) Assessment of Primary Cancer Incidence in Growth Hormone-Treated Children: Comparison of a Multinational Prospective Observational Study with Population Databases. *Hormone Research in Paediatrics*, **85**, 198-206. https://doi.org/10.1159/000444124

[26] Rosen, T. and Bengtsson, B.A. (1990) Premature Mortality Due to Cardiovascular Disease in Hypopituitarism. *The Lancet*, **336**, 285-288. https://doi.org/10.1016/0140-6736(90)91812-O

[27] Svensson, J., Bengtsson, B.A., Rosen, T., Oden, A. and Johannsson, G. (2004) Malignant Disease and Cardiovascular Morbidity in Hypopituitary Adults with or without Growth Hormone Replacement Therapy. *The Journal of Clinical Endocrinology & Metabolism*, **89**, 3306-3312. https://doi.org/10.1210/jc.2003-031601

[28] Stochholm, K., Gravholt, C.H., Laursen, T., Laurberg, P., Andersen, M., *et al.* (2007) Mortality and GH Deficiency: A Nationwide Study. *European Journal of Endocrinology*, **157**, 9-18. https://doi.org/10.1530/EJE-07-0013

[29] Chung, T.T., Drake, W.M., Evanson, J., Walker, D., Plowman, P.N., *et al.* (2005) Tumour Surveillance Imaging in Patients with Extrapituitary Tumours Receiving Growth Hormone Replacement. *Clinical Endocrinology*, **63**, 274-279. https://doi.org/10.1111/j.1365-2265.2005.02338.x

[30] Child, C.J., Zimmermann, A.G., Woodmansee, W.W., Green, D.M., Li, J.J., *et al.* (2011) Assessment of Primary Cancers in GH-Treated Adult Hypopituitary Patients: An Analysis from the Hypopituitary Control and Complications Study. *European Journal of Endocrinology*, **165**, 217-223. https://doi.org/10.1530/EJE-11-0286

[31] Van Bunderen, C.C., van Varsseveld, N.C., Erfurth, E.M., Ket, J.C. and Drent, M.L. (2014) Efficacy and Safety of Growth Hormone Treatment in Adults with Growth Hormone Deficiency: A Systematic Review of Studies on Morbidity. *Clinical Endocrinology*, **81**, 1-14. https://doi.org/10.1111/cen.12477

[32] Stochholm, K. and Johannsson, G. (2015) Reviewing the Safety of GH Replacement Therapy in Adults. *Growth Hormone & IGF Research*, **25**, 149-157. https://doi.org/10.1016/j.ghir.2015.06.006

[33] Fukuda, I., Hizuka, N., Muraoka, T. and Ichihara, A. (2014) Adult Growth Hormone Deficiency: Current Concepts. *Neurologia Medico-Chirurgica* (*Tokyo*), **54**, 599-605. https://doi.org/10.2176/nmc.ra.2014-0088

[34] Maccio, A., Madeddu, C. and Mantovani, G. (2009) Adipose Tissue as Target Organ in the Treatment of Hormone-Dependent Breast Cancer: New Therapeutic Perspectives. *Obesity Reviews*, **10**, 660-670. https://doi.org/10.1111/j.1467-789X.2009.00592.x

[35] Kershaw, E.E. and Flier, J.S. (2004) Adipose Tissue as an Endocrine Organ. *The Journal of Clinical Endocrinology & Metabolism*, **89**, 2548-2556. https://doi.org/10.1210/jc.2004-0395

[36] Tomita, Y., Yang, X., Ishida, Y., Nemoto-Sasaki, Y., Kondo, T., *et al.* (2004) Spontaneous Regression of Lung Metastasis in the Absence of Tumor Necrosis Factor Receptor p55. *International Journal of Cancer*, **112**, 927-933. https://doi.org/10.1002/ijc.20493

[37] Balkwill, F. (2009) Tumour Necrosis Factor and Cancer. *Nature Reviews Cancer*, **9**,

361-371. https://doi.org/10.1038/nrc2628

[38] Van Kruijsdijk, R.C., van der Wall, E. and Visseren, F.L. (2009) Obesity and Cancer: The Role of Dysfunctional Adipose Tissue. *Cancer Epidemiology, Biomarkers & Prevention*, **18**, 2569-2578. https://doi.org/10.1158/1055-9965.EPI-09-0372

[39] Mazzarella, L. (2015) Why Does Obesity Promote Cancer? Epidemiology, Biology, and Open Questions. *E Cancer Medical Science*, **9**, 554. https://doi.org/10.3332/ecancer.2015.554

[40] Kadowaki, T. and Yamauchi, T. (2005) Adiponectin and Adiponectin Receptors. *Endocrine Reviews*, **26**, 439-451. https://doi.org/10.1210/er.2005-0005

[41] Schaffler, A., Scholmerich, J. and Buechler, C. (2007) Mechanisms of Disease: Adipokines and Breast Cancer—Endocrine and Paracrine Mechanisms That Connect Adiposity and Breast Cancer. *Nature Clinical Practice. Endocrinology & Metabolism*, **3**, 345-354. https://doi.org/10.1038/ncpendmet0456

[42] Leitzmann, M., Powers, H., Anderson, A.S., Scoccianti, C., Berrino, F., *et al.* (2015) European Code against Cancer 4th Edition: Physical Activity and Cancer. *Cancer Epidemiology*, **39**, S46-S55. https://doi.org/10.1016/j.canep.2015.03.009

[43] Ballard-Barbash, R., Friedenreich, C.M., Courneya, K.S., Siddiqi, S.M., McTiernan, A., *et al.* (2012) Physical Activity, Biomarkers, and Disease Outcomes in Cancer Survivors: A Systematic Review. *Journal of the National Cancer Institute*, **104**, 815-840. https://doi.org/10.1093/jnci/djs207

[44] Samani, A.A., Yakar, S., LeRoith, D. and Brodt, P. (2007) The Role of the IGF System in Cancer Growth and Metastasis: Overview and Recent Insights. *Endocrine Reviews*, **28**, 20-47. https://doi.org/10.1210/er.2006-0001

[45] Popovic, V., Mattsson, A.F., Gaillard, R.C., Wilton, P., Koltowska-Haggstrom, M., *et al.* (2010) Serum Insulin-Like Growth Factor I (IGF-I), IGF-Binding Proteins 2 and 3, and the Risk for Development of Malignancies in Adults with Growth Hormone (GH) Deficiency Treated with GH: Data from KIMS (Pfizer International Metabolic Database). *The Journal of Clinical Endocrinology & Metabolism*, **95**, 4449-4454. https://doi.org/10.1210/jc.2010-0287

[46] Gasco, V., Prodam, F., Grottoli, S., Marzullo, P., Longobardi, S., *et al.* (2013) GH Therapy in Adult GH Deficiency: A Review of Treatment Schedules and the Evidence for Low Starting Doses. *European Journal of Endocrinology*, **168**, R55-R66. https://doi.org/10.1530/EJE-12-0563