Association between height and malignancy among children in the north of Iran
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Abstract
Background
This study aim to determine the association between height and cancer in the children aged 14 years at the time of diagnosis in Rasht, Iran.

Materials and Methods
In this cross-sectional study, height of patients with a malignancy (≤14) at the time of diagnosis measured in the standard charts of United States National Center for the Health Statistics (NCHS). Data were reported by descriptive statistics and analyzed by Regression tests in SPSS version 19.

Results
Overall, 78 male (38.6%) and 124 female (61.4%) patients with various kinds of malignancies were evaluated for their heights. Leukemia was the most common type of cancer. The median height of the patients was more than 20th percentile and under 50th percentile of the NCHS. No significant association was found between height and leukemia.

Conclusion
Previously, the median height of Iranian girls and boys (≤15) reported under 20th percentile of the NCHS. In this study, the median height of the patients at the time of diagnosis was more than 20th percentile of the NCHS. There was a correlation between height and cancer among our patients, although, this correlation can be assessed by further cohort study.

Keywords
Height, Malignancy, NCHS, Pediatric, Percentile

Introduction
Height alteration is an anthropometric index which could induce and affect different diseases such as heart disease and respiratory disorders (1). According to previous prospective investigations in adults, there is significant association between height and risk of cancer (1). Recent studies demonstrated a significant relation between raised body mass index (BMI) and height with Hodgkin Lymphoma (HL) (2,3). In addition, increased incidence of the osteosarcoma was seen in taller individuals and those with earlier pubertal growth spurs (2, 3). It is hypothesized that this may be correlated with growth-related genes which were associated with vitamin D receptor polymorphisms (4). Furthermore, height was indicated as a main feature for increased rate of shared site cancers in males. It was mentioned that height related issues such as rate of susceptible cells and childhood growth-influencing exposures lead to this increased rate (5). The most reliable relations were noted for adulthood breast cancer in adults (6). In addition to adulthood assessments, there were few studies which investigated association between height and childhood malignancies. They presented controversial results in which at primordial diagnosis, ALL in children and adults was noted in taller patients (7, 8). However, some investigators didn’t find significant relation between elevated height and childhood malignancy. They showed that patients with solid tumors had lower weight (for height) index versus leukemic patients (9). According to the few childhood studies and controversial results, we aimed to investigate association between height and...
malignancy in the patients referred to 17 Shahrivar pediatrics hospital in north of Iran.

**Materials and Methods**

This was an analytic cross-sectional study which included newly diagnosed children aged 14 years or less with a malignancy who admitted to pediatric oncology ward in 17 Shahrivar Children Hospital between 2000 and 2013 in Rasht, Iran. For the children less than 2 years of age recumbent height was assessed. Patients laid down on their back on a firm table and one person hold the head against the headboard with both hands. The second person gently flattened the knees and flexed the ankles of the patients to 90 degrees and brought the footboard up to the flat soles of the flexed feet. The length measurement was then read off the scale to the nearest 1/2 cm. For the patients aged over 2 years, height was measured in standing upright position with bare feet, while closed heels, buttocks, shoulders and occiput touched the stadiometer. Their heights were measured up to 200 centimeters. According to the lack of growth charts which specifically created and standardized for Iranian children and adolescents, the authors applied US NCHS charts for growth monitoring and assessed height status in pediatric population (12).

According to the previous studies, the median height and weight of the Iranian healthy children aged less than 15 years were under 20th percentile of the NCHS (13,14).

They recommended that for boys and girls up to 14 years, the comparison must be evaluated based on 25th and 50th percentile heights (13, 14). Therefore, in this study, investigators applied their recommendation.

**Statistical Analysis**

In this study, data were reported by descriptive statistics and analyzed by Regression tests in SPSS version 19.

**Results**

Two hundred and two patients including 78(38.6%) boys and 124(61.4%) girls were evaluated. Results showed that leukemia was the most common cause of malignancy. The frequencies of malignancies were summarized in Table 1.

Mean heights in children with malignancies were more than 25th percentile, but less than 50th percentile of the US NCHS charts, except for lymphoma, fibrosarcoma and retinoblastoma which were even less than 25th. However, there was no significant difference between mean heights of children with malignancies in comparisons with 25th and 50th percentile of US NCHS charts except for patients with Hodgkin lymphoma. The comparison of heights with normal values of 25th and 50th percentile heights, based on age had been summarized in Tables 2 and 3. Mean heights of children with malignancies according to their sex in comparison with 25th and 50th percentiles of US NCHS charts had been noted respectively in Table 4 and 5. Comparison of height median of children with malignancies with 25th and 50th percentile of US NCHS chart had been summarized in Table 6.

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**Table 1. Frequency of different malignancies among newly diagnosed children**

| Variable           | Frequency | %     | Total |
|--------------------|-----------|-------|-------|
| **Leukemia**       |           |       |       |
| ALL                | 102       | 50.5  | 62.4  |
| AML                | 24        | 11.9  |       |
| **Lymphoma**       |           |       |       |
| HL                 | 7         | 3.5   | 11.4  |
| NHL                | 16        | 7.9   |       |
| **Brain tumor**    |           |       |       |
| Brain tumor        | 12        | 6.0   | 6.0   |
| **Neuroblastoma**  |           |       |       |
| Neuroblastoma      | 11        | 5.4   | 5.4   |
| RMS                | 9         | 4.5   | 4.5   |
| **Wilms’ Tumor**   |           |       |       |
| Wilms’ Tumor       | 4         | 2.0   | 2.0   |
| **Ewing**          |           |       |       |
| Ewing              | 8         | 4.0   | 4.0   |
| **Fibrosarcoma**   |           |       |       |
| Fibrosarcoma       | 3         | 1.5   | 1.5   |
| **Retinoblastoma** |           |       |       |
| Retinoblastoma     | 3         | 1.5   | 1.5   |
| **Germ cell tumor**|           |       |       |
| Germ cell tumor    | 2         | 1.0   | 1.0   |
| **Hepatoblastoma** |           |       |       |
| Hepatoblastoma     | 1         | 0.5   | 0.5   |
| **Total**          | 202       | 100   | 100   |
| Variable            | Mean of Height | N | Mean of SD score | Mean of SE score | p-value |
|---------------------|----------------|---|-----------------|-----------------|---------|
| **Leukemia**        |                |   |                 |                 |         |
| ALL                 | 112.9450       | 100 | 21.42168        | 2.14217         | 0.239   |
| NCHS 50             | 113.9690       | 100 | 20.69071        | 2.06907         |         |
| AML                 | 111.2292       | 24  | 26.77360        | 5.46514         | 0.274   |
| NCHS 50             | 113.3167       | 24  | 26.34722        | 5.37810         |         |
| **Neuroblastoma**   |                |   |                 |                 |         |
| Neuroblastoma       | 105.9000       | 10  | 24.65067        | 7.79523         | 0.520   |
| NCHS 50             | 104.8200       | 10  | 25.01199        | 7.90949         |         |
| **Lymphoma**        |                |   |                 |                 |         |
| HL                  | 119.5714       | 7   | 9.51940         | 3.59800         | 0.013   |
| NCHS 50             | 129.1286       | 7   | 11.90640        | 4.50020         |         |
| **RMS**             |                |   |                 |                 |         |
| RMS                 | 118.0556       | 9   | 34.82316        | 11.60772        | 0.644   |
| NCHS 50             | 119.3444       | 9   | 35.62657        | 11.87552        |         |
| **Wilms’ Tumor**    |                |   |                 |                 |         |
| Wilms’ Tumor        | 124.5000       | 4   | 8.96289         | 4.48144         | 0.566   |
| NCHS 50             | 126.6750       | 4   | 14.35627        | 7.17814         |         |
| **Brain tumor**     |                |   |                 |                 |         |
| Brain tumor         | 111.4545       | 11  | 23.52600        | 7.09336         | 0.271   |
| NCHS 50             | 113.5545       | 11  | 22.33797        | 6.73515         |         |
| **EWING**           |                |   |                 |                 |         |
| Ewing               | 123.0000       | 8   | 23.76672        | 8.40281         | 0.215   |
| NCHS 50             | 125.7625       | 8   | 21.14203        | 7.47484         |         |
| **Fibrosarcoma**    |                |   |                 |                 |         |
| Fibrosarcoma        | 105.6667       | 3   | 37.42103        | 21.60504        | 0.429   |
| NCHS 50             | 118.0333       | 3   | 44.85558        | 25.89738        |         |
| **Retinoblastoma**  |                |   |                 |                 |         |
| Retinoblastoma      | 85.6667        | 3   | 9.60902         | 5.54777         | 0.410   |
| NCHS 50             | 98.6333        | 3   | 12.22675        | 7.05912         |         |
| **Germ cell tumor** |                |   |                 |                 |         |
| Germ cell tumor     | 113.5000       | 2   | 33.23402        | 23.50000        | 0.493   |
| NCHS 50             | 94.3000        | 2   | 6.64680         | 4.70000         |         |
| Variable          | Mean of Height | N  | Mean of SD score | Mean of SE score | p-value |
|-------------------|----------------|----|------------------|------------------|---------|
| **Leukemia**      |                |    |                  |                  |         |
| ALL               | 112.9450       | 100| 21.42168         | 2.14217          | 0.01    |
| NCHS 25           | 110.6830       | 100| 19.83860         | 1.98366          |         |
| AML               | 111.2292       | 24 | 26.77360         | 5.46514          | 0.541   |
| NCHS 25           | 110.0833       | 24 | 25.25275         | 5.15470          |         |
| **Neuroblastoma** |                |    |                  |                  |         |
| Neuroblastoma     | 105.9000       | 10 | 24.65067         | 7.79523          | 0.034   |
| NCHS 25           | 101.9200       | 10 | 24.08083         | 7.61503          |         |
| **Lymphoma**      |                |    |                  |                  |         |
| HL                | 119.5714       | 7  | 9.51940          | 3.59800          | 0.074   |
| NCHS 25           | 125.2429       | 7  | 11.46761         | 4.33435          |         |
| NHL               | 131.3750       | 16 | 18.86399         | 4.71600          | 0.018   |
| NCHS 25           | 126.5000       | 16 | 20.07821         | 5.01955          |         |
| **RMS**           |                |    |                  |                  |         |
| RMS               | 118.0556       | 9  | 34.82316         | 11.60772         | 0.415   |
| NCHS 25           | 115.8000       | 9  | 34.27751         | 11.42584         |         |
| **Wilms’ Tumor**  |                |    |                  |                  |         |
| Wilms’ Tumor      | 124.5000       | 4  | 8.96289          | 4.48144          | 0.646   |
| NCHS 25           | 122.9000       | 4  | 13.80652         | 6.90326          |         |
| **Brain tumor**   |                |    |                  |                  |         |
| Brain tumor       | 114.9098       | 122| 23.06987         | 2.08865          | 0.02    |
| NCHS 25           | 113.5545       | 11 | 22.33797         | 6.73515          |         |
| **Ewing**         |                |    |                  |                  |         |
| Ewing             | 123.0000       | 8  | 23.76672         | 8.40281          | 0.661   |
| NCHS 25           | 122.0250       | 8  | 20.30241         | 7.17799          |         |
| **Fibrosarcoma**  |                |    |                  |                  |         |
| Fibrosarcoma      | 105.6667       | 3  | 37.42103         | 21.60504         | 0.532   |
| NCHS 25           | 114.6667       | 3  | 43.19842         | 24.94062         |         |
| **Retinoblastoma**|                |    |                  |                  |         |
| Retinoblastoma    | 85.6667        | 3  | 9.60902          | 5.54777          | 0.484   |
| NCHS 25           | 96.0667        | 3  | 11.68004         | 6.74347          |         |
| **Germ cell tumor**|               |    |                  |                  |         |
| Germ cell tumor   | 113.5000       | 2  | 33.23402         | 23.50000         | 0.459   |
| NCHS              | 91.8500        | 2  | 6.29325          | 4.45000          |         |

Table 4. Comparison between mean and standard deviation of 25th percentile height in malignancies based on sex

| Sex            | Mean of Height(CM) | N   | Mean of SD score | Mean of SE score | p-value |
|----------------|--------------------|-----|------------------|------------------|---------|
| Female         | 112.9671           | 76  | 24.21602         | 2.77777          | 0.122   |
| NCHS 25        | 111.3263           | 76  | 23.81339         | 2.73158          |         |
| Male           | 114.9098           | 122 | 23.06978         | 2.08865          | 0.02    |
| NCHS 25        | 112.9664           | 122 | 21.30008         | 1.92842          |         |
| Total          | 114.1641           | 198 | 23.47441         | 1.66825          | 0.005   |
| NCHS           | 112.3369           | 198 | 22.5301          | 1.58145          |         |

Table 5. Comparison between mean and standard deviation of 50th percentile height in malignancies based on sex

| Sex            | Mean of Height(CM) | N   | Mean of SD score | Mean of SE score | p-value |
|----------------|--------------------|-----|------------------|------------------|---------|
| Female         | 112.9671           | 76  | 24.21602         | 2.77777          | 0.119   |
| NCHS 50        | 114.6566           | 76  | 24.74739         | 2.83872          |         |
| Male           | 114.9098           | 122 | 23.06978         | 2.08865          | 0.09    |
| NCHS 50        | 116.3246           | 122 | 22.23636         | 2.01319          |         |
| Total          | 114.1641           | 198 | 23.47441         | 1.66825          | 0.022   |
| NCHS 50        | 115.6843           | 198 | 23.18453         | 1.64765          |         |
Table 6. Comparison of height median of children with malignancies with 25th and 50th percentile of US NCHS chart.

| Variable              | Median of Height | SD score |
|-----------------------|------------------|----------|
| Leukemia              |                  |          |
| ALL                   | 110.0000         | 21.31518 |
| NCHS 25               | 109.2000         | 19.94018 |
| NCHS 50               | 112.4000         | 20.79901 |
| AML                   | 100.0000         | 26.77360 |
| NCHS 25               | 105.2500         | 25.25275 |
| NCHS 50               | 108.3500         | 26.34722 |
| Neuroblastoma         |                  |          |
| Neuroblastoma         | 100.5000         | 24.65067 |
| NCHS 25               | 98.9500          | 24.08083 |
| NCHS 50               | 101.8000         | 25.01199 |
| Lymphoma              |                  |          |
| HL                    | 115.0000         | 9.51940  |
| NCHS 25               | 127.3000         | 11.46761 |
| NCHS 50               | 131.3000         | 11.90640 |
| NHL                   | 133.0000         | 17.88641 |
| NCHS 25               | 133.1000         | 19.27019 |
| NCHS 50               | 137.3000         | 20.01986 |
| RMS                   |                  |          |
| RMS                   | 129.000          | 34.82316 |
| NCHS 25               | 127.4000         | 34.27751 |
| NCHS 50               | 131.5000         | 35.62657 |
| Wilms’ Tumor          |                  |          |
| Wilms’ Tumor          | 121.5000         | 8.96289  |
| NCHS 25               | 116.3000         | 13.80652 |
| NCHS 50               | 119.8000         | 14.35627 |
| Brain tumor           |                  |          |
| Brain tumor           | 112.5000         | 24.47311 |
| NCHS 25               | 104.7000         | 22.59800 |
| NCHS 50               | 107.8000         | 23.55402 |
| EWING                 |                  |          |
| EWING                 | 122.000          | 23.76    |
| NCHS 25               | 124.7000         | 20.30241 |
| NCHS 50               | 128.6000         | 21.14203 |
| Fibrosarcoma          |                  |          |
| Fibrosarcoma          | 92.0000          | 37.42103 |
| NCHS 25               | 123.6000         | 43.19842 |
| NCHS 50               | 127.5000         | 44.85558 |
| Retinoblastoma        |                  |          |
| Retinoblastoma        | 84.0000          | 9.60902  |
| NCHS 25               | 95.1000          | 11.68004 |
| NCHS 50               | 97.7000          | 12.22675 |
| Germ cell tumor       |                  |          |
| Germ cell tumor       | 113.5000         | 33.23402 |
| NCHS 25               | 91.8500          | 6.29325  |
| NCHS 50               | 94.3000          | 6.64680  |

Discussion
Childhood cancer occurred due to the aberrations in early developmental process. The genetic processes which can lead to childhood cancer are likely different from adulthood. At least, the carcinogenic process in children has so much shorter time (2, 3, 10). Some of the pediatric malignancies are clearly related to genetic aberrations involving insulin like growth factors such as Ewing sarcoma, Rhabdomyosarcoma, and osteosarcoma (11, 12). On the other hand, insulin like growth factors involve in many aspects of normal physiology (13, 14), which among them, growth is the most investigated (15). Height as an important parameter of growth is a product of many factors such as genetic, environmental, and nutritional factors. Previous studies have found a significant reduction in height of children with acute lymphoblastic leukemia (16, 17). But, according to our results, there was no significant relation between leukemia and height.
Based on previous studies, the median height and weight of the Iranian girls and boys aged less than 15 years were under 20th percentile of the US NCHS charts (18, 19). In order to reduce this gap, cultural education along with the economic development is needed. (18, 19). Furthermore, Mohammad et al mentioned that median heights and weights of Iranian children up to 15 years of age were both below the 20th percentiles of NCHS standards; however, median heights and weights of 15-18 years participants laid on the 20th and 25th percentiles of NCHS, respectively. These results may suggested that the gap could be filled by nutritional and health services improvements along with the socio-economic developments (19). With the best of our knowledge, this is the first study about the correlation between height and pediatric malignancy in Iran. In this study we evaluated the height of 202 patients with different type of pediatric malignancies. We found that mean heights of children with malignancies were less than 50th percentile NCHS but without significant difference (p>0.05) except for Hodgkin lymphoma. On the other hand, mean heights of this patients were significantly (p<0.05) more than 25th percentile NCHS. In a study by Abtahi M and Mohammad K et al. they used median values of height to compare Iranian children with NCHS charts (15). With consideration that in a normally distributed population median and mean values are the same, they found that 50th percentile of healthy Iranian children less than 15 years of age laid on 20th percentiles of NCHS charts; so we can conclude that the mean height of our patients were significantly more than 50 percentile of the Iranian children.

There are few studies performed worldwide that evaluated correlation between height and pediatric malignancies. Our findings were inconsistent with Pui et al. who found no significant deviation from population norms in any of the 10 malignancies’ categories after proper adjustment for multiple significance testing(20). But our findings were consistent with Fraumeni JF et al who mentioned that tall stature and an earlier pubertal growth spurt might be noted as important factors in the etiology of both osteosarcoma and Ewing sarcoma (21). Furthermore, IGF-1 is a responsible factor for enhancing tumor development in certain types of human cancer and non-malignant diseases like benign prostatic hyperplasia(22).

It can increase cancer risk, cell proliferation and suppression of apoptosis (23). Furthermore, Insulin-like growth factor 1 (IGF1) motivates mitosis and hinders apoptosis and can be modified by IGF binding protein 3 (IGFBP)(24). Therefore, decreased IGF-1 can indicate new strategies for cancer prevention. On the other hand, the IGFBP-3/IGFBP-3R axis may present therapeutic and prognostic values for cancer therapy (25, 26). Therefore, it seems that assessing these factors could be beneficial. Our study has three major limitations. The relatively small sample size and unexpected cancer type distribution of our patients can be noted as two major limitations. As it was mentioned, brain tumors are in the second place of the most frequent pediatric malignancies, worldwide (about 20% of total) but it consist only six percent of our patients. In addition, the third limitation comes from the absence of a standardized nationwide growth chart for the Iranian children. Since this study is a clue, further, larger, and preferentially multicenter studies are mandatory which assess control group from the same geographical zone and with matched groups for age and sex.

**Conclusion**

In this study, the median height of the patients at the time of diagnosis was more than 20th percentile of the NCHS. There was a correlation between height and cancer among our patients, although, this correlation can be assessed by further cohort study.

**Conflict of interest**

All authors declare that they have no conflict of interest.

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