



Research Paper

Epidemiology of benign giant cell tumor of bone in the Chinese population

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ABSTRACT

Background: Quantifying the incidence of giant cell tumor (GCT) of bone is challenging because it is a rare, histologically benign bone tumor for which population-level statistics are unavailable in most countries. We estimated the 2017 incidence of GCT in China using a direct (registry-based) approach with available population-based data.

Materials and Methods: The most recent age- and sex-specific incidence rates of GCT recorded in the Bone Tumor Registry in Japan (2015) were applied to 2017 age- and sex-matched populations projected by the United Nations for China in order to estimate 2017 incidence. An adjustment factor calculated using registry data suggesting that GCT may represent a greater proportion of bone tumors in China than in Japan (Guo, 1999) was applied to provide secondary estimates.

Results: Annual GCT incidence was estimated to be 1.49 per million population or 2094 new cases in China for 2017. A comparison of this estimated incidence with Japan (1.25 per million) and the United States (1.38 per million) indicates that the incidence is somewhat higher in China using identical methods. Secondary estimates suggest that GCT incidence in China may be as high as 2.57 per million or 3625 new cases in 2017. The corresponding 3-year limited-duration prevalence of GCT in China using a registry-based approach and general age-specific mortality is 6276 (secondary estimate: 10,876).

Conclusions: Leveraging unique population-based registry data, we estimated that GCT is a rare disease in the Chinese population with an incidence ranging between 1.49 and 2.57 cases per million persons per year. Possible differences in diagnostic classification of GCT, urban-rural demographics, and the younger demographic distribution of the Chinese population may underlie observations that GCT, a condition that primarily affects young individuals (20–40 years of age), accounts for a higher proportion of skeletal tumors in China than in other regions.

1. Introduction

Giant cell tumor (GCT) of bone is a rare, histologically benign but locally aggressive neoplasm of the bone [1]. Active untreated lesions are associated with significant focal bone lysis and skeletal complications, including pathologic fracture, pain, limitation of joint motion, nerve compression, and mechanical destabilization of adjacent joints or the axial spine depending on location [2]. Historically, surgery has been the primary treatment despite the fact that bone loss due to surgical excision may result in substantial morbidity or functional deficits. In

severe cases, amputation of the affected joint or limb may be necessary to achieve local tumor control [3]. Even if the initial tumor is fully removed, GCT may recur locally and result in new tumors that continue to grow and destroy bone. The recurrence rate varies depending on the size, level of invasiveness, and skeletal location of the tumor, as well as the type of surgical intervention employed [3,4].

In June 2013, the first pharmaceutical treatment (denosumab, a fully human monoclonal antibody against RANKL [receptor activator of nuclear factor kappa-B ligand]) became available in the United States (U.S.) for use in adults and skeletally mature adolescents with a GCT

Abbreviations: BMUS, The Burden of Musculoskeletal Diseases in the United States; GCT, giant cell tumor; RANKL, receptor activator of nuclear factor kappa-B ligand; STROBE, Strengthening of Reporting of Observational Studies in Epidemiology; U.N., United Nations; U.S., United States

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Table 1
Giant Cell Tumor (GCT) of bone epidemiology publications from China and Japan.

Data Source	GCT (benign), n	Years	Male: Female	Mean Age, years	GCT: osteosarcoma (%)	GCT: Bone Cancers (%)
Hu et al. 2016 [21]	410	2000–2014	217:193	35.7	–	–
Lin et al. 2016 [24]	334	2000–2014	178:156	35.1	–	–
Li et al. 2016 [23]	179	1998–2010	99:80	32.0	–	–
Jiang et al. 2013 [22]	140	2001–2011	87:53	30.5	–	–
Niu et al. 2015 [10]	1,536	1973–2012	818:718*	–	–	16.7**
Niu et al. 2012 [11]	621	1989–2009	359:262	–	–	13.7
Sung et al. 1982 [12]	194	1957–1979	106:88	–	–	16.1
Guo et al. 1999 [9]	3996	1957–1988	–	–	74.0	16.6***
Guo et al. 1999 [9]	1505 (Japan)	1972–1990	–	–	62.7	9.6***
Bone Tumor Registry in Japan, 2006–2015 [20]	1513 (Japan)	2006–2015	–	–	82.9	8.6

* Estimated based on 1.14 sex ratio **Used in *BMUS-like* method in Table 3: 16.7% *** Benign GCT: benign bone cancers.

that is either not surgically resectable or for which resection would be likely to result in severe morbidity [5]. The RANKL pathway plays a key role in the pathogenesis of GCT, which are rich in osteoclast-like giant cells and contain mononuclear (stromal) cells that express RANKL, a key mediator of osteoclast activation [6]. There is growing interest in more fully defining the incidence and prevalence of GCT to help estimate the number of patients who may benefit from such a pharmaceutical intervention [7,8].

Quantifying the incidence of GCT of bone is challenging. Most countries, including the U.S., do not have national population-based sources for reporting the epidemiology of benign bone tumors. We previously compared the estimation of incidence of benign GCT in ten countries resulting from direct and indirect estimation methods [6]. The direct approach applied age- and sex-specific incidence rates from population-based registries to a target population to calculate GCT incidence while taking age and sex distributions into account. The indirect approach used ratios of expected GCT relative to osteosarcoma (or bone cancers) cases based on surgical case series and has been reported in earlier editions of *The Burden of Musculoskeletal Diseases in the United States (BMUS)* [1,6]. Notable limitations of the indirect approach were the range in the published case series [1,9–11] as well as the absence of a population-based source for the incidence of bone cancers. Ultimately, the preferred method is the direct registry-based approach since it accounts for population demography (e.g., age and sex distribution) unique to each country.

In China, GCT has been reported to account for a higher proportion of skeletal tumors in retrospective clinical case series [9–12] than in other regions. Since GCT predominately affects skeletally mature young individuals [4,13,14] who are usually between 20 and 40 years of age [13,15,16], it is possible that the younger age distribution of the Chinese population, in which 31% of individuals are age 20–39 compared with 27% in the United States and 23% in Japan [17], may help explain the larger proportion of GCT observed among skeletal tumors in China. Even among population-based registries that specifically record benign bone tumors, diagnostic misclassification have been shown to influence estimated incidence in important ways, and it is possible that such misclassification plays a role in the greater prominence of GCT among skeletal tumors in China. In the Swedish Cancer Registry, for example, a higher proportion of malignant versus benign GCT was observed in the earlier period of the registry (1958–1982) than that either expected from clinical case series or observed in the more recent registry data (after 1983). These disparities have been attributed to changes in the standard diagnostic workup and the addition of a mandated multi-disciplinary review for giant-cell containing tumors in Sweden, both of which were introduced around 1982 [18].

The objective of the present study was to estimate the incidence of GCT of bone in 2017 in China by leveraging age- and sex-specific incidence data from a population-based registry that records benign bone tumors. We also used identical methods to explore whether the GCT

incidence rate is higher in China than in the U.S. and Japan.

2. Materials and methods

2.1. Overview and data sources

We used incidence data derived from cases reported as benign GCT of bone in the Bone Tumor Registry in Japan (2015) [19]. Incidence rates (per million person-years) determined from these registry data were then used to estimate the incidence of GCT in China and the U.S., two countries that do not have mandatory or voluntary reporting of benign GCT cases to registries. Estimates of age- and sex-matched populations for China and the U.S. in 2017 were obtained from the United Nations (U.N.) projections [17]. The Population Division of the U.N. is the leading authority on population sizing methods, producing constantly updated census-based demographic estimates and projections for all countries with emphasis on techniques that control for incomplete and deficient census data. Reporting in the present study conforms to the STROBE (Strengthening of Reporting of Observational Studies in Epidemiology) statement [20].

2.2. Calculations

The Bone Tumor Registry in Japan [19] provided age- and sex-specific incidence rates for GCT, osteosarcoma, and all bone cancers that could be used for comparisons. We also used the latest sources of data to determine the incidence rates of GCT, osteosarcoma, and all bone cancers for an indirect estimation approach, similar to the one proposed in *BMUS* [1] (*BMUS-like*) and have noted results based on this approach in the Discussion. To estimate 2017 incidence, the most recent age- and sex-specific incidence rates were applied to projected age- and sex-specific population data for 2017 [17].

3. Results

In Table 1, the summary of recent studies of benign GCT in China (and Japan) feature more males than females diagnosed with GCT and a mean age at diagnosis ranging from 30.5 to 35.7 years [21–24]. Other studies, including a study with 1,536 patients reported by Niu et al. and published in 2015, have reported that benign GCT accounts for 13.7% to 16.7% of bone tumors [9–12]. The proportion of benign bone cancers comprising benign GCT may be lower in Japan than in China according to some reports [9,17].

For estimating incidence of GCT, we applied the most recent annual data from the Bone Tumor Registry in Japan (2015) [19] to U.N.-projected 2017 population estimates for each country [17]. This registry-based method yielded benign GCT age-adjusted incidence rates of 1.49 per million (China), 1.25 (Japan), and 1.38 (U.S.); or incidence of 2,102 new cases in China, 160 in Japan, and 447 in the U.S. in 2017 (Table 2).

Table 2
Registry-based approach used to estimate giant cell tumor (GCT) of bone incidence and incidence rates in 2017.

Country	2017 Population	GCT Incidence	GCT Incidence Rate per Million
China	1,409,517,397	2094*	1.49*
Japan	127,484,451	160	1.25
US	324,459,468	447	1.38

* 3625 new cases in 2017 or 2.57 per million accounting for proportionally higher incidence of GCT in China per Guo et al [9].

Taking into account the report by Guo et al. [9] that GCT represents a greater proportion of benign bone tumors in China (18.4%) among GCT than in Japan (10.6%), the true incidence of GCT in China could be 73% higher than the projected incidence using age- and sex-specific incidence rates from Japan directly (3,625). From Guo et al, the majority of GCT cases were benign (9.7% malignant GCT in China and 5% malignant GCT in Japan) and adjusted values for the proportion of all bone tumors represented by benign GCT are 16.6% in China and 9.6% in Japan [9]. When applying the 73% Guo et al. [9] adjustment factor, the 2017 GCT incidence rate in China is projected to be 2.57 per million population.

Estimation of prevalence is dependent on incidence and survival data. Since both are limited for GCT, the results presented here should be interpreted with caution. If we assume the three-year survival of patients with GCT is high and resembles life expectancy in the general population [25], the three-year limited-duration prevalence using Japan registry data is 6,276 affected individuals (three-year cumulative incidence). Similarly, the five-year limited-duration prevalence is 10,447 (five-year cumulative incidence). The three- and five-year prevalence estimates are 10,867 and 18,091, respectively, after factoring in potential differences in the disease incidence between China and Japan per Guo et al. [9].

4. Discussion

The primary goals of this study were to estimate the incidence of GCT in 2017 in China, and to compare estimated incidence rates with those for Japan and the United States. We determined that GCT is a rare disease with a corresponding annual incidence rate ranging from one to three new cases per million persons in the Chinese population. Although population-based incidence data for benign bone tumors like GCT are not recorded in most countries, incidence of GCT can be derived by applying the available registry data to population projections. The incidence rate of GCT in China (1.49 per million per year) was somewhat higher than for Japan (1.25 per million per year) and the U.S. (1.38 per million per year) using identical estimation methods. These incidence rates correspond to 2,094 new cases in China, 160 in Japan, and 447 in the U.S. in 2017.

Estimates presented here were derived from registry data. The Bone Tumor Registry of Japan used in our study has previously been shown to be consistent with recent GCT incidence trends reported by another population-based registry, the Swedish Cancer Registry [6]. The Swedish registry data indicate that the incidence rates of GCT have been relatively stable over the last few decades [19]. Nonetheless, we recognize that a registry-based incidence estimation model cannot account for underlying differences, other than the sex and age distribution, between the Chinese and Japanese populations. Therefore, we increased our initial registry-derived incidence estimates by 73% to account for differences reported among GCT cases between China and Japan by Guo et al. [9]. These adjusted estimates, however, should be interpreted with caution, and should be considered secondary to the estimates obtained from our primary analysis. We also note that diagnostic misclassification of GCT, inter-country differences in the urban-rural distribution, and the younger age distribution of the Chinese

population are some of the factors that may underlie observations that GCT, a condition that primarily affects young individuals (20–40 years of age) [18], accounts for a higher proportion of skeletal tumors in China than in either Japan or the United States.

Using assumptions that survival among individuals in China with GCT is equivalent to that of age and sex matched individuals in the general Chinese population, the prevalence of GCT is estimated at approximately 6276 individuals diagnosed within the past three years. The three-year limited duration prevalence represents individuals who may be actively seeking medical and/or surgical treatment. However, for defining rare diseases and designing orphan drug policies for China, where an evidence-based prevalence threshold definition is still needed, a prevalence of all individuals living with the condition may be necessary. With 35.7 years as the mean age of GCT diagnosis and assuming life expectancy of 76.1 in 2015, a 40-year limited duration prevalence would represent the total number of patients living with benign GCT [21,26]. Cui and Han proposed a threshold between 300,000 and 500,000 patients as a potential reference threshold for China to define rare diseases [27]. GCT would fall below this threshold with a 40-year prevalence of approximately 80,000 based on cumulative incidence projected using age- and sex-specific incidence rates from Japan and 140,000 after integrating the 73% Guo et al. adjustment factor and assuming the same age- and sex-matched survival as the general population.

The registry-based incidence estimates of GCT we derived were consistent with estimates obtained using alternate strategies such as the indirect *BMUS-like* approach with adaptation to capture published clinical case series from China; data are summarized in Table 3 [1,10,19,28–34]. The study by Niu et al. of 1536 patients published in 2015 [10], which is most recent and features a large sample, provided the most appropriate factor of 16.7% for comparison in a *BMUS-like* indirect estimation approach. The range of incidence rates per million in 2017 was 0.68 in Japan (CI5plus) to 3.14 in China (Chinese Cancer Registry) using the *BMUS-like* approach, whereas estimates from the registry-based approach ranged from 1.25 (Japan) to 2.57 (China). Consistent with our previous report on GCT incidence in 10 countries [6], the registry-derived method presented here is useful and intuitive, likely more precise and is used to estimate the incidence of other rare benign bone cancers across regions.

The limitations of the registry-based approach for GCT incidence estimation are: (1) reliance on the completeness and accuracy of the source registry data; (2) reliance on U.N. population projections; and (3) inability to account for all factors beyond age and sex distributions that may influence incidence rates between countries. The bone tumor registry data in Japan allowed us to compare bone cancer, osteosarcoma, and GCT incidence. The age at diagnosis and sex distribution for individuals with GCT were consistent between the Bone Tumor Registry in Japan [19] and the Swedish Cancer Registry [34], whereby similar incidence estimates for GCT can be calculated (Table 3). Registry data confirm that osteosarcoma peak incidence occurs in adolescence while GCT affects young adults between the ages of 20 and 40 [13,15,16,31]. Age- and sex-specific incidence may differ for GCT, osteosarcoma, and other bone cancers. These are important considerations when applying registry data to countries with differing demographics, and may result in estimates that are not as accurate as age- and sex-specific incidence rates for GCT.

Diagnostic histopathologic misclassification of GCT is another possible source of error when using the registry-based approach. There are challenges in differentiating benign GCT from other rare giant-cell containing bone lesions including primary malignant GCT tumors, giant cell-rich osteosarcomas, aneurysmal bone cysts, and others [4]. The diagnosis of GCT requires integrating histologic features with radiologic, laboratory, and demographic characteristics to exclude other similar osteolytic disease entities and is not made solely on the basis of a distinct set of histologic features. Given the rarity of these lesions, expert evaluation of both pathology and radiology is an important

Table 3Estimated bone and joint cancer and giant cell tumor (GCT) of bone incidence rates per million persons in 2017, registry-based and *BMUS-like* approaches.

		China	Japan	U.S.
Bone and Joint Cancers	Country Registry	18.82 [32]	17.46 [19]	10.05 [33]
	CI5plus [29]	8.39	7.35	11.05
Osteosarcoma	Country Registry		1.55 [19]	3.01 [30]
Giant Cell Tumor	Registry-Based Approach (Japan) [19]	1.49	1.25	1.38
	Registry-Based Approach (Sweden) [34]	1.23	1.07	1.14
	<i>BMUS-like</i> Approach (Registry) [1,10,19, 30,32, 35]	3.14	1.61	1.31
	<i>BMUS-like</i> Approach (CI5plus) [1,10,19, 29,35]	1.4	0.68	1.48

***BMUS-like* Approach Data Sources**

- Method: *BMUS-like* Approach uses a relative index or ratio of GCT:Bone Cancers. The incidence of bone and joint cancers (ICD-10 [International Classification of Diseases, Tenth Edition] codes, C40–41) was from country registry and also determined from age-specific incidence rates derived from registry data reported in Cancer Incidence in Five Continents (CI5plus) [16].
- Japan: Bone Tumor Registry in Japan [19] provided age- and sex-specific incidences for benign GCT, malignant osteosarcoma, and malignant bone tumors that could be used for comparisons (Table 1).
- China: 2009 age- and sex-specific incidence rates for bone cancer [32]. 16.7% relative index used benign GCT:Bone Cancers per Niu et al. 2015 [10] (Table 1).
- U.S.: SEER data [30], and the 2017 incidence of all bone and joint cancers was taken from the American Cancer Society data [33]. Bone cancer incidence rates were estimated with use of SEER*Stat [30] incidence rate data for eighteen registries (2000 to 2014) for the location “bones and joints” and histologic types given by ICD-O-3 (International Classification of Diseases for Oncology, Third Edition) codes 8000–8004, 8812, 9180–9187, 9192–9194, 9200, 9250, 9260–9261, 9270, 9290, 9310, 9312, 9321, and 9330 (excluding C90, multiple myeloma and malignant plasma cell neoplasms). Osteosarcoma incidence rates were estimated with use of SEER*Stat incidence rate data for eighteen registries (2000 to 2014) for the location “bones and joints” and histologic types given by ICD-O-3 codes 9180–9187, 9192–9194, and 9200.
- Sweden: Swedish Cancer Registry [34] provided age- and sex-specific incidences for benign GCT.

contributor to accurate diagnoses. The registries in Japan are subject to such a system of expert pathologic and clinical confirmation, and have been shown to be reliable for GCT classification [19]. To better estimate prevalence, additional research will be required to better understand risk factors that may have an impact on survival.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and material

Data used in this study are publicly available.

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Conflicts of Interest

A Liede, RK Hernandez, ET Tang, C Li, and D Jandial are employees and stockholders of Amgen Inc. B Bennett and SS Wong are employed by Plan A, Inc. which has received consulting fees from Amgen, Inc.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jbo.2018.07.003.

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