A Palaeoepidemiological Investigation of Osteomata, with Reference to Medieval Poland

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Abstract: The osteoma, among other forms of benign neoplastic disease, has received little palaeopathological or palaeoepidemiological interest largely due to its asymptomatic nature. This is problematic because these tumours are regarded as common occurrences in bioarchaeological contexts, despite there being scant data to support these claims. This investigation presents a palaeoepidemiological enquiry into osteomata. Five hundred ninety individuals from six skeletal assemblages from Poland, dating from the 9th to 17th century, were macroscopically surveyed for osteomata. This was followed by a palaeoepidemiological analysis, looking at sex and age-specific prevalence. Ninety-three osteomata were observed in 67 individuals. The sex-specific prevalence was 13.5% (95%CI 9.7 to 18.1) for males and 11.6% (95%CI 7.9 to 16.2) for females. The age-specific prevalence for middle adults was 2.1% (95%CI 0.6–5.2) and 5.3% (95%CI 2.5–9.8) for mature adults. The results indicated the prevalence of benign tumours was similar between sex and seemed to increase with age. This case study adds to a sparse area of palaeo-oncological research and calls for further future investigation.

Declarations of interest: none.

Introduction

Benign tumours are non-invasive neoplasms, which typically arise during childhood or adolescence and continue to slowly grow throughout life (Dorfman *et al.* 2002; Vlychou and Athanasou 2008; Hakim *et al.* 2015). In palaeopathology, benign neoplasms have received little attention, unlike their malignant counterparts, and of the vast array of benign skeletal neoplasms, the osteoma has seemed to receive the least amount of enquiry. For example, while the osteoma has been described as a common occurrence in archaeological skeletal remains (Ortner 2003; Roberts and Manchester 2010**;** Giuffra *et al.* 2019), there has been scant research regarding the prevalence of this lesion, confirming the above assertion. The lack of palaeopathological and palaeoepidemiological investigation into osteomata and other forms of benign neoplasms is problematic to an overall understanding of neoplastic disease in bioarchaeological contexts (Siek 2019).

Clinically, the osteoma is a round-shaped, slow-growing osteoblastic lesion (Campillo 1998). It is comprised of compact bone with well-defined borders and no surface irregularities (Hakim *et al.* 2015). Osteomata typically arise from bone (homoplastic) or can arise in other tissues (heteroplastic), such as a choroidal osteoma of the eye (Shields *et al.* 1988; Hakim *et al.* 2015). In the skeleton, osteomata most commonly occur on the outer table of the cranium, particularly on the frontal and parietal bones, and in the frontal and paranasal sinuses (Greenspan *et al.* 2007). They may also occur on the mandible and seldomly on the long and short tubular bones but such cases are rare, representing <0.03% of biopsied primary bone lesions (Peyser *et al.* 1996). Osteomata affect males and females equally and are most often reported between the ages of 30 and 50 years (Greenspan *et al.* 2007)

Osteomata are typically asymptomatic and incidental findings however, they may have adverse secondary effects, depending on their size and location. For instance, in the paranasal sinuses, osteomata may block nasal ducts, leading to headaches, pain and the possible loss of sense of smell (Greenspan 1993). An osteoma may also develop and encroach in the orbit, resulting in possible exophthalmos and vision loss, if it presses against the optic nerve (Greenspan 1993). If it is an endocranial lesion, it may press against the brain causing neurological problems (Greenspan 1993). In cases such as these, surgical intervention may be required to alleviate swelling, nerve compression, and cosmetic issues (Eyesan *et al.* 2011).

The occurrence of multiple osteomata has been linked to the autosomal disorder Gardner's Syndrome, which is a phenotypic variant of familial adenomatous polyposis (Greenspan 1993; Hakim *et al.* 2015; Koh *et al.* 2016). Clinically, Gardner's Syndrome is marked by multiple osteomata, commonly occurring on the mandible and long bones (Bilkay *et al.* 2004; Chimenos-Küstner *et al.* 2005; Panjwani *et al.* 2011; Koh *et al.* 2016). Of patients with Gardner's Syndrome, 68-82% present with multiple, osteomata (Chimenos-Küstner *et al.* 2005; Giuffra *et al.* 2019).

There is some debate in the clinical and palaeopathological literature if osteomata can be considered true neoplasms (Eshed *et al. 2002;* Gundewar *et al.* 2013). For the purpose of this investigation, we consider the osteoma to be a benign neoplasm. Considering that benign neoplasms are composed of differentiated and mature tissues and their structure does not differ significantly from surrounding normal tissues, osteomata meet these criteria (Pierce and Damjanov 2006). Although the mechanisms of osteomata formation are not clear, whichever factor (eg. trauma or genetic predispositions) induces the process of their growth, it leads to a local overgrowth of bony tissue (Hakim *et al.* 2015). Osteomata are therefore benign neoplasms which take the form of a tumor. It should be also noted that there are many neoplasms that do not form soft-tissue tumors, such as leukemia. In contrast, there are also tumors and tumour-like lesions that are often included in clinical and palaeopathological surveys, such as giant-cell tumours and simple bone cysts (Greenspan *et al.* 2007; Marques 2019).

Materials and Methods

The skeletal assemblages examined in this investigation were sourced from the osteological collection of the Department of Anthropology, Hirszfeld Institute of Immunology and Experimental Therapy, Polish Academy of Sciences, (HIIET-PAS) in Wrocław, Poland (Figure 1). For this investigation six human skeletal assemblages were examined. These assemablges were from medieval Polish cemeteries dating from the 9–17th century (Table 1).

Clearly defined inclusion criteria were established for the HIIET-PAS assemblage data collection to ensure standardization and to form the final denominators for the palaeoepidemiological analyses. The skeletal material included in this investigation incorporated individuals regardless of sex or age. The skeletal elements examined in each individual included the cranium and mandible as these are the regions where osteomata are most likely to develop (Greenspan *et al.* 2007). Although osteomata occurring on the long bones are rare, the femora, tibiae and humeri were also examined.

The examination of the skeletal material began with assessing the sex of each individual through standard anthropological methods, using the morphology of the *ossa coxae* and cranium (Phenice 1969; Buikstra and Ubelaker 1994). The age-at-death of the individuals was determined by assessing the morphology of the pubic and auricular surfaces (Todd 1921; Lovejoy *et al.* 1985; Brooks and Suchey 1990; Buikstra and Ubelaker 1994). The individuals were sorted into standard age categories: subadult (≤ 19 years), young adult (20–34 years), middle adult (35–49 years), and mature adult (≥ 50 years) (Buikstra and Ubelaker 1994).

The skeletal material was then analysed macroscopically based on the established palaeopathological guidelines for neoplasms. This included identifying if the lesion was osteoblastic or osteolytic; if it had clear or ill-defined borders; and if it was solitary or multiple. (Nerlich *et al.* 1997; Ragsdale *et al.* 2018). The operative diagnostic definition for an osteoma

was a round-shaped lesion that consisted of well-differentiated mature bone tissue with a predominantly lamellar surface (Greenspan *et al.* 2007).

The identified osteomata were then recorded and photographed. All the lesions were measured using standard, 0.1 cm spreading callipers. In cases where the lesions were located in areas that were deemed too fragile or difficult to access with callipers, a soft, plastic measuring tape was used. A hand-held, endoscopic light was used to examine the interior of complete crania, cranial sinuses and bones where post-mortem damage allowed access.

The typology developed by Eshed *et al.* (2002) was applied to any osteomata that were observed. This included three size categories and four distribution patterns. The size categories were: *small* (1–2 mm), *medium* (3–5 mm), and *large* (≥6 mm). The first distribution pattern is the most common and known as *Button Osteoma* consisting of a solitary, circular ivory-like exostosis with sharply defined margins. The next pattern was *Satellite Osteoma* where flat, small, ivory-like roundels are located in close proximity to a large lesion. This was followed by *Nested Osteoma* where two or more small osteomata are uniform in size and in close proximity with each other. The fourth pattern was *Disseminated Osteoma* characterized by three or more lesions distributed over a large area of the cranium (Eshed *et al.* 2002).

Since all palaeoepidemiological investigations are cross-sectional in nature the only measure of disease frequency that can be calculated is prevalence, which is the proportion of a defined group having a disease condition at a single point in time (Waldron 2007). An odds ratio was calculated to assess the odds of benign neoplasm development for sex and age. The guidelines set forth by Sahai and Khurshid (1996) were used for further clarification regarding the interpretation of the odds ratio. Ninety-five percent confidence intervals were calculated to indicate the precision or imprecision of the prevalence proportions and odds ratios (Gardner and Altman 2000). All calculations were performed using the open-source statistics software, *MedCalc.* The software calculates the 'exact' Clopper-Pearson confidence interval for prevalence (Clopper and Pearson 1934; Fleiss *et al.* 2003) and calculated the odds ratio and its confidence interval according to (Altman 1991).

Results

From the six skeletal assemblages at HIIET-PAS, a total of 590 individuals were examined (Table 2). The largest age category was middle adult (*n*=195); the sex ratio was almost even with 282 males and 251 females. Osteoma was present in at least one individual from each of the six cemetery assemblages (Figures 2–4), and in total 93 osteomata were observed in 67 individuals. All the osteomata presented as round, almost circular, growths of smooth, cortical bone. They were limited to the cranium, with the frontal bone being the most frequent location, but some were also found on the parietal and occipital bones. Half of the observed osteomata were in

the *medium* size group and the average size was 5.9 x 5.1 mm. The majority were classified to the *Button Osteoma* distribution pattern (Table 3).

Among the assemblages at the HIIET-PAS, 67 of 590 individuals exhibited at least one osteoma, therefore the crude prevalence for the entire HIIET PAS assemblage (Table 4) was 11.4% with a 95% confidence interval (95%CI) of 8.9 to 14.2. The sex-specific prevalence for males was 13.5% (95%CI 9.7–18.1) and 11.6% (95%CI 7.9–16.2) for females. The age-specific prevalence for the middle adult group was 2.1% (95%CI 0.6–5.2) and 5.3% (95%CI 2.5–9.8) for the mature adult group (Table 5). The confidence intervals have the expected inverse relationship with the numbers in the assemblage, that is, the larger the assemblage, the narrower the confidence intervals tend to be. Where the confidence interval is narrow (for example the mature adults in Table 5) this suggests that the precision of the estimate of the prevalence is high (Szumilas, 2010). The odds ratio comparing males versus females was 0.9 (95%CI 0.5–1.4) suggesting that females were slightly, but not significantly, less likely to have a benign neoplasm than males. With regard to age, the odds ratio comparing middle and mature adults was 2.6 (95%CI 0.8–8.5) which suggests that mature adults were more likely to have a benign neoplasm than the younger age group.

Discussion

In palaeopathology, research regarding osteomata has typically been approached on a case-by-case basis (Smith 2010; Bartelink and Wright 2011; Premužić *et al.* 2013; Castro *et al.* 2019; Giuffra *et al.* 2019; Galassi *et al*. 2020). In regard to palaeoepidemiology, the prevalence of osteomata is typically reported in general terms. For instance, in Greece, a large number of osteomata were observed in several skeletons from Thasos (Agelarakis 2002), as well as Thrace and other Aegean islands (Bourbou 2003), but no other details, such as an exact number, anatomical location or size were given by the researchers. In the investigation of a 5th century CE skeletal assemblage from the Czech Republic, the prevalence of osteoma was reported to be 3.9% but there was no further discussion regarding these tumours (Vargová *et al*. 2016). Pálfi (1989) reported osteoma in six individuals from a Hungarian skeletal assemblage, but focused his discussion on the prevalence of the observed malignant tumours. The prevalence of osteomata has also been alluded to when reviewing the palaeoepidemiology of neoplastic disease as a whole. For example, Gładykowska-Rzeczyska (1991) and Farkas *et al.* (2007) noted osteomata in their palaeopathological surveys but prevalence was only reported for benign tumours as a single group, rather than individual tumour types, and there was no consideration of age or sex-specific prevalence. Only two studies directly related to the palaeoepidemiology of osteomata were found in the palaeopathological literature. The first investigated the anatomical location of osteomata in regard to age and sex (Antona Montoro *et al*.). The study showed that the majority of osteomata were observed among the young adult age group (20-34 years). Males had a higher frequency of osteomata on the frontal and parietal bones and

females were observed to have a higher frequency of osteomata on the occipital bone (Antona Montoro *et al.*). The second investigation compared the frequency of osteomata in modern and archaeological samples (Eshed *et al.* 2002). The results showed a prevalence of 41% in the archaeological sample and 37.6% in the modern sample, with no difference between sex or ancestry (Eshed *et al.* 2002).

The results of this palaeoepidemiological investigation indicate that the prevalence of osteomata was similar between males and females but seemed to increase with age. This trend is similar to that reported by Eshed *et al.* (2002) in their study on modern osteomata in the Hamann-Todd collection. Similar to Antona Montoro *et al.* the majority of the observed osteomata were on the frontal and parietal bones. The lack of observable osteomata in sub-adults and young adults is possibly due to their characteristic slow growth. While these neoplasms tend to begin developing during childhood and adolescence, their slow growth may result in the tumours not becoming macroscopically visible until adulthood (Greenspan *et al* 2007). As these tumours may occur in any region of the skull and sinuses, searching for them microscopically would be highly difficult and impractical. Another possibility is that an individual died from other causes before the tumour had yet reached a macroscopically visible size. The large number of osteomata is notable as this form of tumour is thought to be underrepresented in modern clinical literature due to its asymptomatic nature and incidental detection (Giuffra *et al.* 2019).

While most clinical sources include osteoma in their overviews of osteogenic, benign tumours (Greenspan *et al*. 2007; El-Mofty 2009; Wei and Stevens 2014; Hogendoorn and de Andrea 2019) there has been some debate whether this lesion can be considered a true neoplasm and no definite conclusion has been reached either clinically or palaeopathologically (Gundewar *et al.* 2013; Odes *et al.* 2018). Kaplan *et al.* (1994) argued against mandibular osteoma as neoplastic because the lesion's growth potential and growth rate are limited, recurrence after surgical excision is rare, and there have been no clinical reports of malignant transformation. Instead, it is possible that mandibular osteoma may be a response to trauma. The proposed mechanism was that trauma caused subperiosteal bleeding that would elevate the periosteum and initiate an ostegenic response (Kaplan *et al.* 1994). Capasso (1997) classified osteoma as a form of circumscribed idiopathic hyperostosis. These forms of hyperostosis are of unknown aetiology and are similar to neoplasms, such as having a slow unlimited growth, but are not pathological. While the rational of Kaplan *et al.* (1994) can also be applied to cranial osteomata, Eshed *et al.* (2002) suggested that, based on their histological features, these lesions be reclassified as hamartoma, a malformation that resembles a neoplasm but results from faulty development. In palaeopathological case reports of osteomata, these lesions are referred to as tumours and the debate regarding their status as a neoplasm is either not mentioned or not discussed (Blau 2006; Zias 2006; Smith 2010; Premužić *et al.* 2013; Dąbrowski *et al*. 2015; Licata

et al. 2016; Piombino-Mascali *et al.* 2017; Odes *et al.* 2018; Castro *et al.* 2019; Giuffra *et al.* 2019; Galassi *et al*. 2020). Bartelink and Wright (2011) seem to be the only researchers who did note this debate in their report of a mandibular tumour from Guatemala, dated to the 6-9th century CE. The lesion was described as a dense, solitary outgrowth of bone on the mandibular corpus with clear demarcations from the surrounding bone. It was classified as a benign lesion due to its localised growth, its well-defined borders, its density suggesting slow growth and its lack of spicules or osteolysis. In their differential diagnosis, Bartelink and Wright (2011) included neoplastic lesions, such as osteoma, and hyperplastic lesions, such as hamartoma.

The present investigation adds to the almost non-existent palaeoepidemiology of benign tumours which certainly existed in antiquity, with numerous cases having been found in prehistoric animals. The earliest fossil evidence of an osteoma was found in a *Phanerosteon mirabile*, a fish from the Lower Carboniferous period, approximately 300 million years ago (Moodie 1927; Capasso 2005). Osteoma was exhibited by hominins such as *Homo naledi*, one of which displayed a mandibular osteoma (Odes *et al.* 2018). Despite these examples, along with numerous palaeopathological case reports, there has never been an in-depth investigation into the prevalence of benign tumours. They are considered to be a common occurrence in palaeopathology, but this has never been empirically confirmed (Giuffra *et al.* 2019; Siek 2019). This parallels modern clinical literature where the frequency of benign tumours is debated and unclear (Hakim *et al.* 2015). The apparent apathy towards benign tumours has also created a circular argument within palaeopathology. This argument is as follows: the supposedly common and asymptomatic nature of benign tumours, which precludes them from meaningful investigation has resulted in a lack of data, however as these tumours are largely asymptomatic and common there is no great need to research their aetiology or palaeoepidemiology.

Conclusion

Utilizing Polish human skeletal material from medieval assemblages, age and sex-specific prevalence was calculated for observed osteomata. The results indicated that while females were slightly less likely to have a neoplasm than males, sex was not a significant factor. In contrast, mature adults were much more likely to have an osteoma. The lack of osteomata among young adults may be due to their slow growth and the inability to detect them on a macroscopic level, similar to modern clinical contexts. This investigation adds to the sparse literature in palaeopathology regarding benign osteomata. Despite being regarded as common, they remain enigmatic and warrant further future investigation.

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Skeletal Assemblage	Polish Region/Province	Chronological Date	Number of Individuals	Reference
Tomice	Lower Silesia	9–12th century	22	Miszkiewicz 1968a; Romanow *et al*. 1973
Sandomierz	Holy Cross	10–12th century	25	Sarama 1957; Zoll-Adamikowa 1966
Wrocław (Ołbin, pl. Dominikański, św. Elżbieta, św.Jakub)	Lower Silesia	12–15th century	188	Kwiatkowska and Gronkiewicz 2003; Kwiatkowska 2005
Milicz	Lower Silesia	12–13th century	233	Miszkiewicz and Gronkiewicz 1986
Gródek nad Bugiem	Masovian	13–17th century	73	Belniak *et al.* 1961
Pawłów Trzebnicki	Lower Silesia	15–16th century	49	Miszkiewicz 1968b

Table 1 The skeletal assemblages from the Polish Academy of Sciences, which were selected for investigation.

	Male				Female				Undefined					
Assemblage	**Young Adult**	**Middle Adult**	**Mature Adult**	**Undefined**	**Young Adult**	**Middle Adult**	**Mature Adult**	**Undefined**	**Young Adult**	**Middle Adult**	**Mature Adult**	**Undefined**	**Sub-adult**	**Total**
Tomice	1	5	2	0	1	6	5	1	0	0	0	0	1	22
Sandomierz	0	5	10	0	0	2	2	2	0	1	1	1	1	25
Wrocław	0	41	33	10	1	42	23	6	3	9	1	15	4	188
Milicz	3	34	22	55	6	16	11	72	1	4	0	5	4	233
Gródek nad Bugiem	0	7	19	15	2	9	14	6	0	0	0	0	1	73
Pawłów Trzebnicki	0	9	10	1	2	5	17	0	0	0	0	2	3	49
Total	4	101	96	81	12	80	72	87	4	14	2	23	14	590

Table 2 Demographic characteristics of the skeletal assemblages at the Polish Academy of Sciences.

Position	
Cranial Position	**Number of Osteomata**
Frontal	57
Parietal	32
Occipital	3
Bregma	1
Size	
Size Category	**Number of Osteomata**
Small	15
Medium	47
Large	31
Distribution	
Distribution Pattern	**Number of Individuals**
Button Osteoma	57
Satellite Osteoma	5
Nested Osteoma	1
Disseminated Osteoma	4

Table 3 The cranial positions, size category and distribution pattern of the osteomata from the Polish Academy of Sciences skeletal assemblages.

Assemblage	Cases	Assemblage Total	Prevalence	95%CI Range
Tomice	1	22	4.5%	0.8–21.8
Sandomierz	2	25	8.0%	2.2–25
Wrocław	6	188	3.2%	1.5–6.8
Milicz	44	233	18.9%	14.1–24.5
Gródek nad Bugiem	10	73	13.7%	7.6–23.4
Pawłów Trzebnicki	4	49	8.2%	3.2–19.2
Total	67	590	11.4%	8.9–14.2

Table 4 The crude prevalence of osteomata from the Polish Academy of Sciences skeletal assemblages.

	Cases	Assemblage Total	Prevalence	95% CI Range
Male	38	282	13.5%	9.7–18.1
Female	29	251	11.6%	7.9–16.2
Sub-adult	0	14	0.0%	-
Young Adult	0	21	0.0%	-
Middle Adult	4	195	2.1%	0.6–5.2
Mature Adult	9	170	5.3%	2.5–9.8

Table 5 The sex and age-specific prevalence of osteomata from the the Polish Academy of Sciences skeletal assemblages.