Malignancy in Three Medieval Polish Osteological Collections

Thomas J. Siek[1], Carolyn Rando[1], Anna Spinek[2], Agata Cieślik[2] and Tony Waldron[1]

[1]Institute of Archaeology, University College London, London, United Kingdom

[2] Ludwik Hirszfeld Institute of Immunology and Experimental Therapy, Polish Academy of Sciences, Wrocław, Poland

Corresponding Author: Thomas Siek, thomas.siek.14@ucl.ac.uk

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Abstract:

This paper presents the archaeological skeletal remains of four adult females presenting with cranial lesions typical of malignant neoplastic disease. The four cases were sourced from three medieval Polish skeletal assemblages: Milicz (12-13th century), Pawłów Trzebnicki (15-6th century), and Gródek nad Bugiem (13-15th century). The observed pathological skeletal changes were evaluated with a comprehensive macroscopic analysis of the skeleton, and radiography of the affected bones. The observed osteolytic lesions were largely limited to the crania and were multiple and varied in size; further internal lesions were revealed with radiography. Three cases were differentially diagnosed as highly consistent with metastatic carcinoma, and the fourth case was differentially diagnosed as typical of multiple myeloma. This report adds to the scant number of palaeopathological examples of malignant neoplasms in Poland and it discussed the possible impact of cancer on medieval lives, as well as possible factors in the occurrence of malignant neoplasms in medieval Poland.

Declarations of interest: none.

1. Introduction

Neoplasia is a disease process characterised by the proliferative and uncontrolled growth of cells, resulting in the formation of neoplasms or tumours. It encompasses a broad spectrum of pathological processes and is the result of genetic mutations brought on by the complex interaction of age and carcinogenic exposure over the life course (Pierce and Damjanov 2006; Stephens and Aigner 2009; Marques 2019). Malignant neoplasms or cancers, grow uncontrollably and interfere with the function of bodily systems (Waldron 2009). Cancers are broadly classified based on their tissue or organ of origin. The most common solid tumours are carcinoma, cancers that arise from the epithelial tissue that lines external and internal surfaces of the body. Sarcomas are cancers that arise from any connective or supportive tissue, including fat, muscle and bone (Carbone 2020). Other classifications of cancer include non-solid cancers including hematopoietic malignancies, which arise from blood-forming cells, and neuroectodermal tumours, which arise from the central and peripheral nervous systems (Weinberg 2014). Specific tumour typing is further outlined by the WHO Classification of Tumours, a series of reference volumes dedicated to a different organ system, which have been in publication since 1957 and are in their fifth edition (Carbone 2020). Globally, at least 280 cases of malignant disease have been reported in archaeological material since 1900, 57% of which were skeletal metastases (Hunt *et al.* 2018). This report will highlight four new cases of malignant neoplastic disease observed in three Polish archaeological collections.

2. Materials and Methods

The skeletal material for this investigation was 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. From the osteological collection at HIIET-PAS, three medieval assemblages were surveyed for malignant disease (Figure 1). Two cases were from the Milicz cemetery, located approximately 0.5 km northeast of the town of Milicz, which is approximately 60 km north of Wrocław. The cemetery is dated to the 12-13th century and was used as a burial place for nearby settlements that occupied the left bank of the Barycz River (Miszkiewicz and Gronkiewicz 1986). A third case was from the medieval cemetery of Pawłów Trzebnicki located southwest of the village of the same name, approximately 20 km north of Wrocław. It was excavated in 1965 and initially believed to be a modern cemetery from the Second World War but was not mentioned on any maps or in historical literature. After excavation the cemetery was dated to be in use from the 15-16th century based on stratigraphy and associated grave goods, including ceramic fragments, nails and two dated coins (Miszkiewicz 1968). The fourth case comes from Gródek nad Bugiem, a historical cemetery located in the southeastern part of Poland, near the Polish-Ukrainian border. The cemetery is dated to the 13-15th century (Belniak et al. 1961).

Figure 1 The geographic location of the Polish skeletal assemblages (in bold), currently held at the Polish Academy of Sciences.

The palaeopathological investigation used clear inclusion criteria for each assemblage in order to promote standard data collection. This involved the examination of the following skeletal elements from the axial skeleton: the cranium, ribs, and thoracic and lumbar vertebrae; from the appendicular skeleton: the ossa coxae, femora, tibiae, humeri, and scapulae. These elements were selected for their predilection as sites for primary malignant bone tumours, as well as typical sites for skeletal metastases from soft tissue cancers (Coleman 2006; Greenspan *et al.* 2007). Incomplete skeletal remains were also examined if a minimum of three required elements were present, provided there was representation of both the axial and appendicular skeletons. In regard to the vertebrae and ribs, there was a minimum requirement of one lumbar vertebra, six thoracic vertebrae and six ribs, as complete sets of these skeletal elements were not always preserved. Lastly, an individual would also be included in cases where there were no postcranial remains if the skull exhibited noticeable indications of malignant neoplastic lesions. With the applied inclusion criteria, 233 of 469 were selected from the Milicz assemblage, 49 of 75 were selected from the Pawłów Trzebnicki assemblage and 79 of 237were selected from the Gródek nad Bugiem assemblage. Each examined individual was assessed to estimate age-at-death and sex through standard anthropological methods (Buikstra and Ubelaker 1994) (Table 1).

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	Male				Female				Indeterminate Sex					
Assemblage	**Young Adult**	**Middle Adult**	**Mature Adult**	**Indeterminate Adult**	**Young Adult**	**Middle Adult**	**Mature Adult**	**Indeterminate Adult**	**Young Adult**	**Middle Adult**	**Mature Adult**	**Indeterminate Adult**	**Non-Adult**	**Total**
Milicz	3 (1.3%)	34 (14.5%)	22 (9.4%)	55 (23.6%)	6 (2.6%)	16 (6.9%)	11 (4.7%)	72 (30.9%)	1 (0.4%)	4 (1.7%)	0 (0.0%)	5 (2.1%)	4 (1.7%)	233 (100%)
Pawłów Trzebnicki	0 (0.0%)	9 (18.4%)	10 (20.4%)	1 (2.0%)	2 (4.1%)	5 (10.2%)	17 (34.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (4.1%)	3 (6.1%)	49 (100%)
Gródek nad Bugiem	0 (0.0%)	7 (8.9%)	19 (24%)	15 (19.0%)	2 (2.5%)	9 (11.45 %)	14 (17.7%)	6 (7.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (8.9%)	79 (100%)

70 **Table 1** Demographic characteristics of the three skeletal assemblages at the Polish Academy of Sciences.

The skeletal material underwent macroscopic analysis to note osteoblastic and/or osteolytic lesions consistent with a skeletal response to primary or secondary malignancy. This analysis followed established guidelines regarding neoplastic lesions, which included noting lesion shape, size and border definition (Nerlich et al. 1997; Marques 2019). A secondary radiographic analysis was also performed on 11 individuals who had bones that presented with osteolytic lesions suspected of being metastatic (Rothschild and Rothschild 1995). The radiographic analysis followed established palaeoradiological standards concentrating on lesion margin patterns and the periosteal reaction (Chhem et al. 2008; Ragsdale et al. 2018). All radiographs were made using the following settings: 51-56 kV, 150 SMA, 4.1 mAs. The radiographs were viewed and analysed using the open-source software, *OsirX Lite*. Diagnostic operational definitions for commonly reported primary malignant neoplastic and metastatic lesions in palaeopathology were employed to aid in the differential diagnosis (Table 2). For consistency and standardization, the modified Istanbul Terminological Framework (Appleby et al. 2015) was adopted and used in the differential diagnosis. Benign neoplasms were also noted during this survey of the skeletal material, the results of which formed a separate investigation (Siek et al. 2021).

Neoplasm	Diagnostic Operational Definition: Macroscopic	Diagnostic Operational Definition: Radiographic
Osteosarcoma	Bony spicules penetrating outward from the cortex Cortical thickening or destruction Mixture of osteolytic and sclerotic lesions Metaphyseal origin; occasionally diaphyseal	'Sunburst' or 'onion-skin' appearance Formation of Codman's Triangle, where periosteum is lifted by expansion of tumour Osteoid matrix pattern – dense, homogenous, cloudlike
Chondrosarcoma	Intra-medullary, with erosion of the cortex Osteolysis of cortex, causing endosteal cortical scalloping	Chondroid matrix pattern – arcs and circles
Langerhans Cell Histiocytosis	Single or multiple osteolytic lesions Poorly defined circular lesions	Bevelled margins Multiple coalescing lesions Possible sequestrum
Multiple Myeloma	Small, roughly uniformly sized, 'punched out' osteolytic lesions No evidence of healing or periosteal reaction	Numerous osteolytic lesions of roughly uniform size
Metastasis	Osteolytic lesions of varying size Undercut edges without evidence of healing or remodelling Sclerotic lesions	Poorly defined, with irregular defects Faint sclerotic margins Revelation of more lesions within bone

Table 2 Diagnostic operational definitions for commonly reported malignant neoplasms in palaeopathology (Ortner 2003; Chhem et al. 2008; Waldron 2009; Marques 2019; Riccimi et al. 2019)

3. Results

From the three skeletal assemblages, four out of 361 individuals were found with lesions considered to be consistent with malignant neoplastic disease (Figure 2).

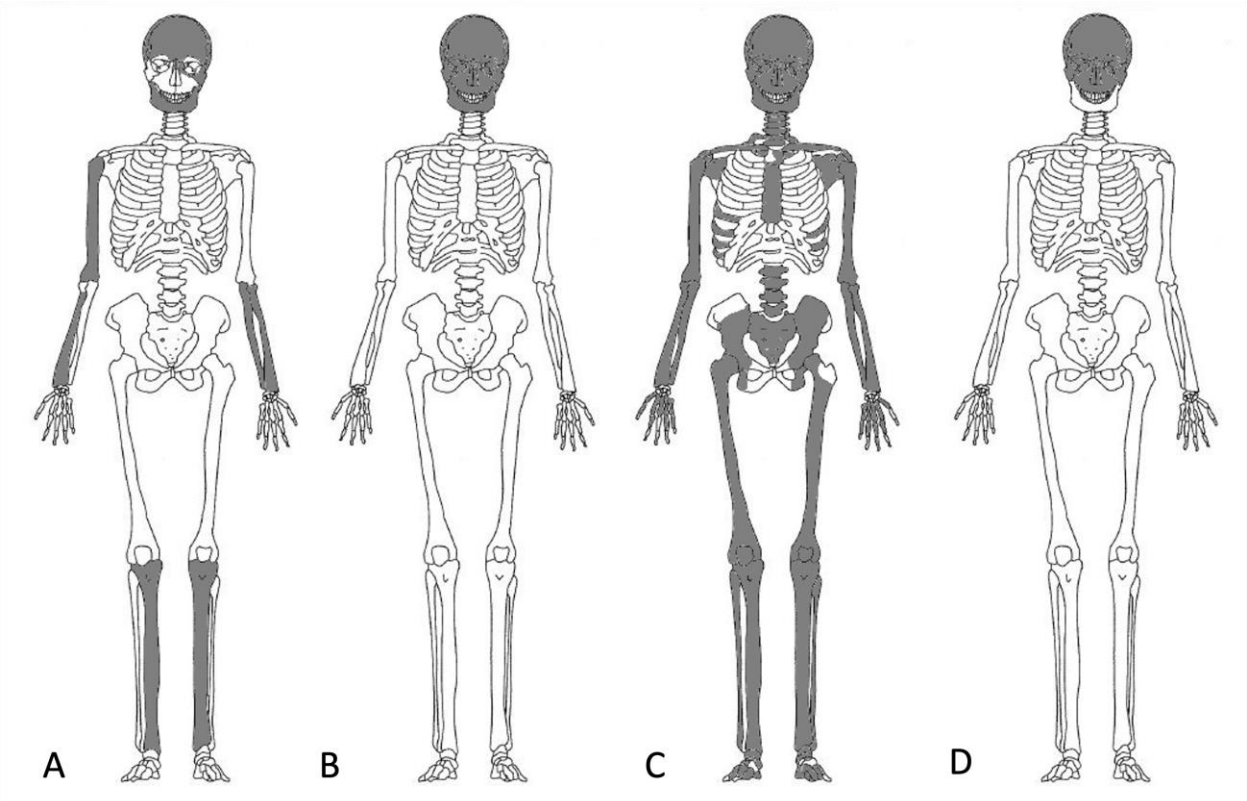

Figure 2 Schematic diagrams of the skeletal remains reported in this study. Preserved skeletal elements are shown in grey. A) Individual M212, an adult female from the Milicz assemblage; B) Individual GB443, an adult female from the Gródek nad Bugiem assemblage; C) Individual PT5, an adult female from the Pawłów Trzebnicki assemblage; D) Individual M167, an adult female from the Milicz assemblage.

3.1. Case 1: M212

The first case, M212, was from the Milicz assemblage. M212 was poorly preserved, with only the skull and upper and lower long bones present (Figure 2a). Taphonomic cortical erosion was observed along the majority of the right parietal bone. The preserved long bones displayed complete epiphyseal fusion with complete obliteration of the epiphyseal lines. In the mandible, there was full dental eruption, along with antemortem tooth loss and visible attrition. The spheno-occiptial synchondrosis was not preserved. Based on the epiphyseal fusion and observed dental eruption, age-at-death was estimated to be an adult >21 years old. Sex was estimated to be female based on the morphology of the cranium and mandible (Buikstra and Ubelaker 1994). Pathological osteolytic lesions were observed on the frontal, parietal, and occipital bones (Figure 3a, 3b). There were no lesions observed on the long bones of the upper or lower limbs. The lesion on the left frontal bone was the largest and measured 15x11 mm. It was of irregular shape, with jagged edges and penetrated both the inner and outer table. There was some porosity on the outer table surrounding the lesion margins. Two other osteolytic lesions were present on the right parietal bone. The first was 8x7 mm with smooth edges and formed a circular crater-like depression. The second lesion was also circular, measured 11x9 mm and had a sclerotic reaction around the margins resulting in a 4 mm-wide raised

border. The lesion on the occipital bone was endocranial and was approximately 10x5 mm. Similar to the lesion on the frontal bone, the occipital lesion was irregular in shape and surrounded by a porosity. Radiographs were taken of the crania (Figure 3c) which revealed small, osteolytic defects ranging in size from 3-7 mm.

Figure 3 The cranium of M212, an adult female from the Milicz assemblage. A) An osteolytic lesion is observed on the left portion of the frontal bone, as well as a small osteoma; B) osteolytic defects are present on the right parietal and temporal bones; C) A radiograph of M212 revealing smaller lytic lesions within the diploë.

3.2. Case 2: GB443

The second case was the skull of GB443 from the Gródek nad Bugiem assemblage. GB443 (Figure 2b). The skull was in a good state of preservation, but the postcranial elements of the skeleton were absent. The spheno-occipital synchondrosis was completely fused, indicating the individual was >26 years old. Sex was estimated to be female based on the morphology of the cranium (Buikstra and Ubelaker 1994). An extensive osteolytic lesion was observed on the left parietal bone, with sharp, irregular margins. Both, inner and outer tables as well as the diploë were affected, and the outer table showed signs of porotic reaction. The lesion size was 35x40 mm and was more extensive at the endocranial surface, indicating the ectocranial direction of the pathological process (Figure 4). Upon radiograph, two small translucencies were observed adjacent to the lesion indicating further internal osteolytic lesions (Figure 5).

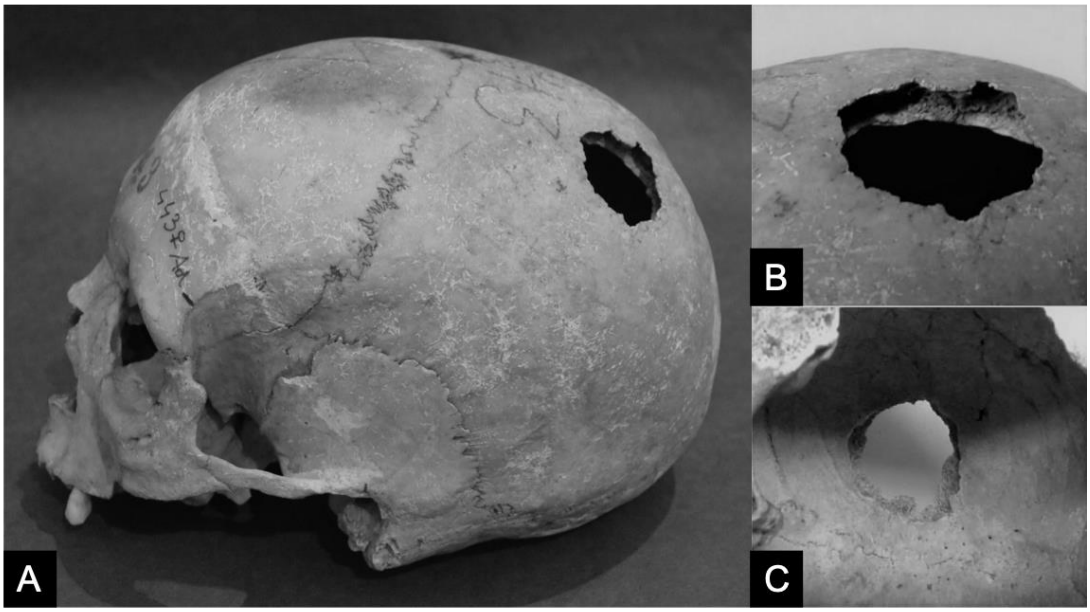

Figure 4 The cranium of GB 443 an adult female from the Gródek nad Bugiem assemblage. A) A large osteolytic lesion is visible on the left parietal bone; B) A close-up image of the osteolytic lesion with some observable porosity surrounding the lesion margins; C) an endocranial view of the lesion – the internal diameter of the lesion is bigger than the external opening indicating an ectocranial direction of pathological spread.

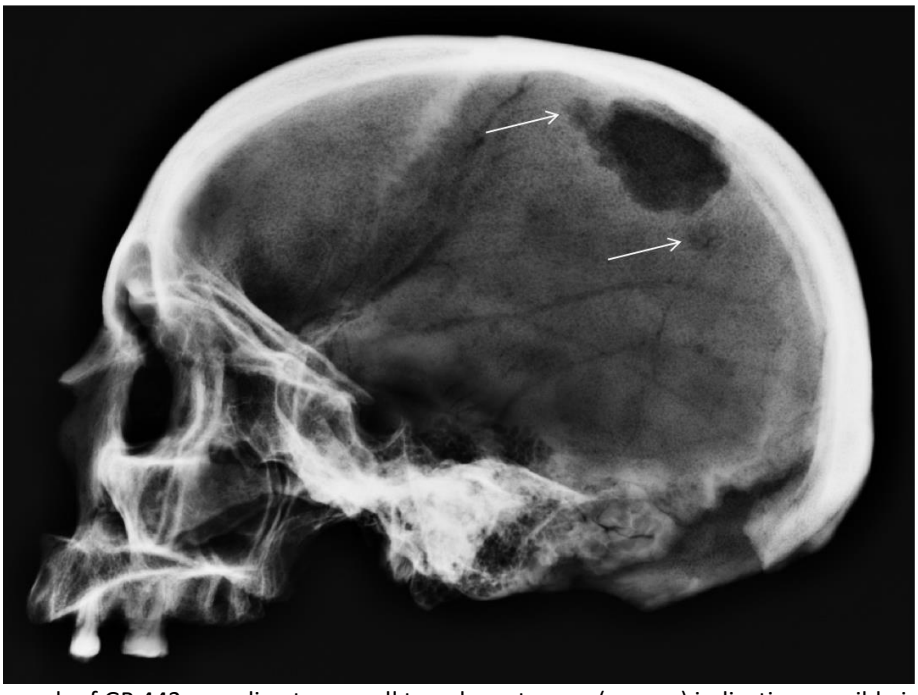

Figure 5 A radiograph of GB 443 revealing two small translucent areas (arrows) indicating possible internal osteolytic lesions.

3.3. Case 3: PT5

The third case was, PT5 from the Pawłów Trzebnicki assemblage. The skeleton was represented by the skull, both clavicles and scapulae, the complete upper and lower limbs, the sacrum, the ossa coxae, the sternum, and the lumbar vertebrae (Figure 2c). Sex was estimated to be female based on the morphology of the cranium and ossa coxae (Buikstra and Ubelaker 1994). The epiphyses of the long bones and the spheno-occipital synchondrosis was fused, giving a lower bound age estimate of 26 years. The pubic symphyses were not preserved. The left and right auricular surfaces were scored as stage 4, giving and upper bound age estimate of 39 years (Lovejoy et al. 1985). Osteolytic lesions were observed on the cranium and ossa coxae (Figure 6). The largest cranial lesion was on the left frontal and parietal bones, along the coronal suture and measured 33x31 mm, with sharp, scalloped edges. The diploë was destroyed leaving a bevelled appearance between the inner and outer tables; there was no porotic or sclerotic reaction at the lesion margins. The second cranial lesion was on the right parietal bone. This lesion was also round, with scalloped edges and bevelled between the inner and outer tables. On the ossa coxae, numerous osteolytic lesions were present on both ilia and the left ischium (Figure 7a). On the ilia, the lesions were circular with sharp, sometimes scalloped edges; the largest was 17x13 mm and the smallest was 10x6 mm. A similar osteolytic lesion was also present on the retroauricular area of the right ossa coxae, creating a circular hole 16x13 mm in diameter. On the left ossa coxae, the retroauricular area was more extensively destroyed. The remaining trabecular bone had been absorbed and the edges of the cortical bone appeared jagged in places. Radiographs were taken of the cranium and ossa coxae. No internal lesions were revealed in the cranium, however, in the ossa coxae, more extensive osteolytic lesions were observed in the ischium around the acetabulum, extending down towards the ischial tuberosity (Figure 7b).

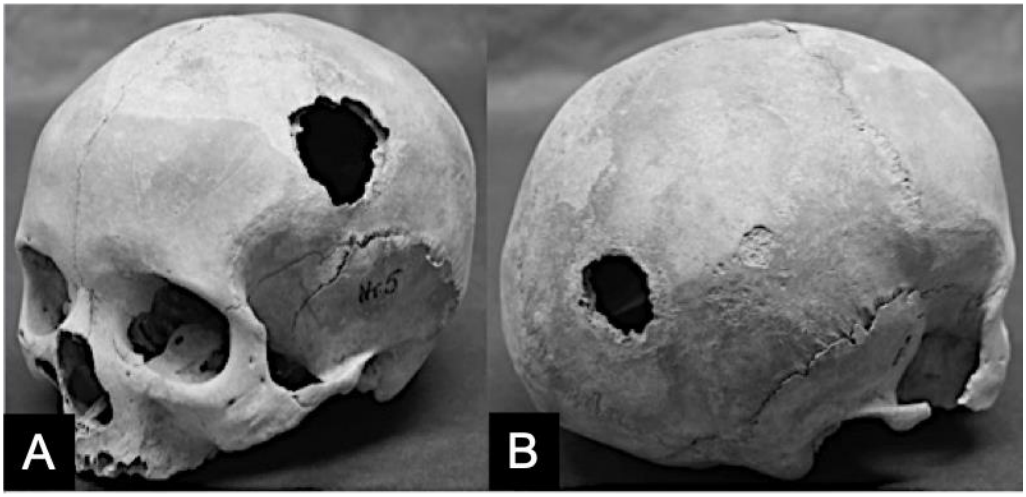

Figure 6 The cranium of PT5, an adult female from the Pawłów Trzebnicki assemblage, with observable osteolytic lesions on both parietal bones (A, B).

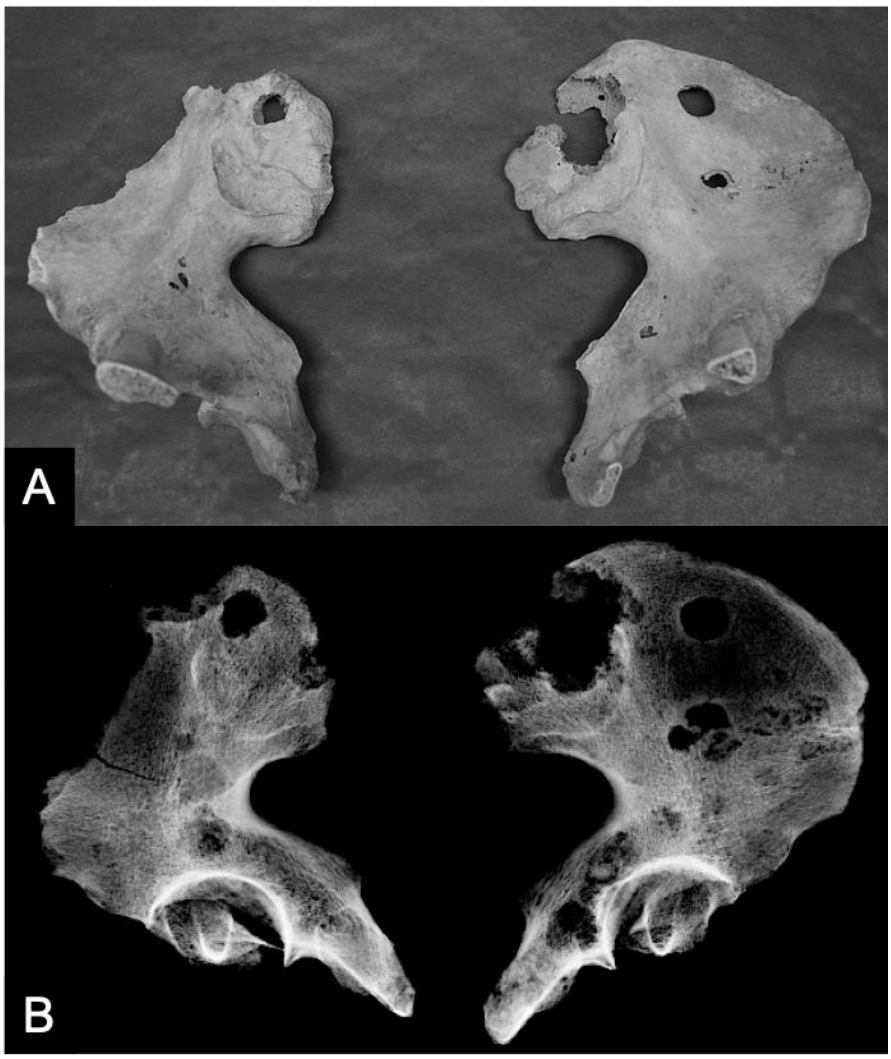

Figure 7 The ossa coxae of PT5, from the Pawłów Trzebnicki assemblage. A) A macroscopic view with osteolytic lesions along the ilia and ischium; B) a radiograph of the ossa coxae revealing more internal osteolytic lesions.

3.4. Case 4: M167

The fourth case was M167 from the Milicz assemblage, which consisted of well-preserved cranium without postcranial remains. Sex was estimated to be female based on the cranial morphology (Buikstra and Ubelaker 1994). Although the spheno-occipital synchondrosis was not preserved, the individual was designated as an indeterminate adult. M167 was noted for displaying many osteolytic lesions (Figure 8). Approximately 90 osteolytic lesions were observed ectocranially and an additional 60 lesions were observed endocranially, encompassing the frontal, parietal, occipital, temporal and sphenoid bones. The majority of the lesions ranged between 5-10 mm, with some coalescing into larger ones. All the lesions were osteolytic, with sharply defined margins and no bony reaction or sclerotic margins. The lesions on the endocranial surface were similar to those on the ectocranial surface in their shape and dimensions. In the larger lesions of M167, the diploë was destroyed and only small portions of the inner and outer tables remained, creating a bevelled appearance.

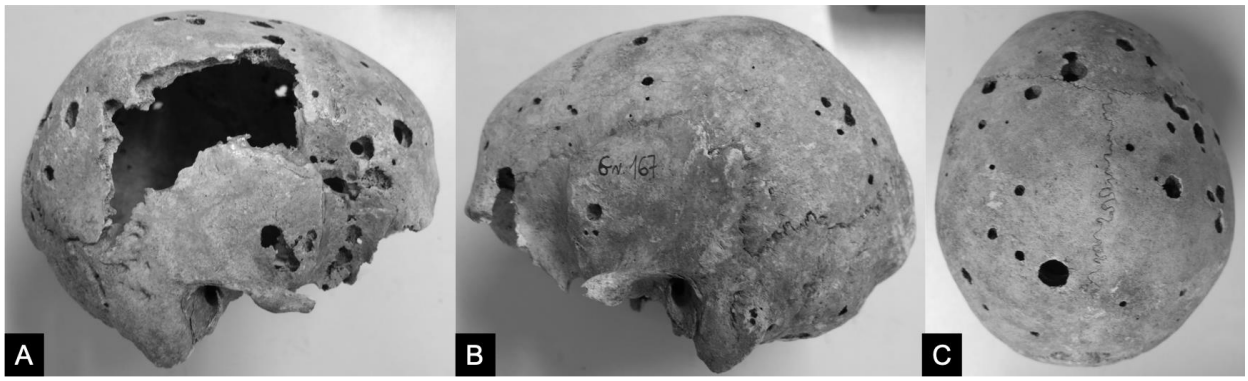

Figure 8 The cranium of M167, an adult female from the Milicz assemblage, displaying numerous lytic lesions on the lateral (A, B) and superior (C) aspects of the calvaria.

4. Discussion

4.1 Differential Diagnosis

Individual M212 displayed macroscopic cranial osteolytic lesions of various sizes which penetrated both the inner and outer tables. The lesions were mostly irregularly shaped, with jagged edges and were surrounded by either porosity or sclerotic activity. A radiograph revealed radiolucent lesions as well. Individual GB443 was noted for having a macroscopic, cranial osteolytic lesion that had penetrated the inner and outer tables. The lesion was irregular shaped, with sharp margins and porosity was observed on the outer table. Small radiolucent lesions were also observed. Individual PT5 exhibited macroscopic osteolytic cranial and pelvis lesions. The cranial lesions had sharp, scalloped edges and no porotic or sclerotic activity. The pelvic lesions were circular with sharp, sometimes scalloped edges, without porotic or sclerotic activity. A radiograph revealed further radiolucent pelvic lesions. Individual M167 presented with numerous, macroscopic osteolytic cranial lesions that either completely or nearly penetrated both the inner and outer tables. The lesions were all small and similar in size, with sharply defined margins and no porosity or sclerotic reaction. The osteolytic character and pattern of the observed lesions in Individuals M212, GB443, PT5 and M167 are typical of a neoplastic process. The differential diagnosis for the skeletal lesions in all four cases includes Langerhans cell histiocytosis, multiple myeloma and metastatic carcinoma.

Langerhans cell histiocytosis (LCH) is a proliferative disorder involving the Langerhans cells, which are found in the bone marrow and are responsible for the removal of abnormal and dead cells (Abla et al. 2010; Grauer 2019). Clinically, there is an ongoing debate regarding LCH's status as a reactive or neoplastic disorder (Abla et al. 2010). In general, skeletal lesions resultant of LCH are osteolytic, with or without sclerotic margins or reactive bone formation (Grauer 2019). LCH has three clinical manifestations that are relevant in palaeopathology: Letterer-Siwe disease, Hand-Schüller-Christian disease, and eosinophilic granuloma. These three conditions are distinguished by their distribution. Letterer-Siwe disease or disseminated multifocal multisystem LCH, involves multiple lesions of the cranial vault and base (Grauer 2019), which is consistent with Individuals M212, PT5 and M167. Hand-Schüller-Christian disease or multifocal unisystem LCH is characterised by large, multiple coalescing cranial lesions that are without periosteal reactive bone (Grauer 2019), which is not consistent with any of the four cases. Eosinophilic granuloma or unifocal LCH consists of a round or oval solitary, osteolytic lesion in the cranium with beveled edges and occasional central sequestrum (Grauer 2019; Riccomi et al. 2019); this is consistent with Individual GB443, however a central sequestrum was not observed.

Multiple myeloma is a haematological malignancy of the plasma cells in the bone marrow. The most common clinical symptoms of multiple myeloma are fatigue and bone pain, and osteolytic lesions are present in 80% of patients (Rajkumar and Kumar 2016). In palaeopathology this malignancy is characterised by numerous purely osteolytic lesions, relatively similar in size (usually 5mm to 2cm in diameter), that are distributed across the cranium, vertebrae, ribs, pelvis and proximal femur (Rothschild et al. 1998; Riccomi et al. 2019; Grauer 2019). These "punched-out" lesions are sharply demarcated without periosteal or osteoblastic reaction (Riccomi et al. 2019). The lesions observed in Individual M167 were typical of multiple myeloma, as they were all small, circular, similar in size with sharp margins and no boney reaction. Multiple myeloma is consistent with the lesions observed in Individuals M212, GB443 and PT5, however those lesions were irregularly shaped, ranged in size, and some demonstrated scalloped or jagged edges.

Metastasis is the process in which cancer cells detach from a primary tumour and spread to other tissues and bodily regions via the lymphatic system and/or the bloodstream or by direct spread (McKinnell 2006). The skeleton is one of the most common sites for metastasis, most often originating from carcinomata of the breast, lung, and prostate (Macedo et al. 2017; Maurizi and Rucci 2018). This is due to the favourable microenvironment of bone, which holds a large reservoir of minerals and hormonal growth factors (Fornetti et al 2018). Skeletal metastases may be osteolytic, osteoblastic, or a mix of the two and normally occur in the axial skeleton, especially the cranium, ribs, sternum, and vertebrae (Marques 2019). In the appendicular skeleton, metastases occur in the ossa coxae and the extremities of the femur and humerus. Metastatic lesions may vary in their pattern, and this is influenced by multiple factors including, but not limited to, the molecular and cellular characteristics of the tumour cells, vascular pathways, blood flow and capillary structure (Coleman 2001; Fornetti et al. 2018). In general, metastatic lesions can be multiple and are distributed across the cranium; these lesions have a marked size difference and display osteolytic, osteoblastic, or mixed reactions (Marques 2019). In reference to the skeleton of a modern 62-year-old female with untreated breast cancer, Marks and Hamilton (2007) observed lesions on the skull, vertebrae, pelvis, ribs and scapulae. They described the lesions to be of varying size and shape with possible coalescence and consisted of osteoblastic, osteolytic or mixed activity. In the cranium, noted characteristics included the retention of the contour of the inner table, the partial or complete destruction of the diploë, uplifted borders of the outer table and osteoblastic remodelling. Biehler-Gomez et al. (2019) examined 14 female skeletons from a modern, identified collection, all of which had breast cancer noted in their medical records. Their results also showed that metastatic lesions were commonly observed on the ribs, pelvis, vertebrae and skull. The lesions were predominantly osteolytic, followed by mixed activity. The osteolytic lesions appeared as irregular, ovular, perforating lesions with serrated margins, surrounded by pitting (Biehler-Gomez et al. 2019). The observed lesions in Individual M167 are consistent with skeletal metastases and highly consistent for Individuals M212, GB443 and PT5. Most skeletal metastases arise from carcinomata of the breast, lung, prostate, kidney and thyroid (Waldron 2009). The probability of carcinomata of the breast, prostate and lung as the site of origin for skeletal metastases is 75%; thyroid and kidney cancers have a 30-40% chance of bone metastasis and there is a 10% chance for bone metastasis from cancers of the gastrointestinal tract (Coleman 2006). Breast and lung cancer are possible primary sources for the lesions observed in Individuals M212, GB443 and PT5, although this is speculative as the lesions were mainly limited to the cranium and postcranial remains were not well preserved in each case.

4.2 Previously Reported Cases of Malignancy in Polish Palaeopathology

The results of this investigation add to the scant reports of palaeopathological cases of malignancy from Poland. Gładykowska-Rzeczycka (1982) described malignant lesions in the skull and left ossa coxae of an adult female from 12-13th century Czersk in northern Poland. The cranium exhibited numerous circular and elliptical osteolytic lesions, measuring 3-10mm in diameter. The lesions had sharp margins and most penetrated the bone, while others were confined to the diploë or the outer table. Similar lesions were present on the ossa coxae, but were not

as macroscopically visible. A radiograph of both boney structures revealed more internal lesions that had not yet penetrated the outer table of the cortex. This case was later listed as a metastasis (Gładykowska-Rzeczycka 1991) and then revised to multiple myeloma (Gładykowska-Rzeczycka 1997), in which no differential diagnosis or reasoning was provided. In her seminal survey of neoplasms in east and central Europe, Gładykowska-Rzeczycka (1991) listed two further cases from the 10-12th century site, Ostrów Lednicki in western Poland. These individuals were both mature adult females and were listed as cases of metastasis and multiple myeloma, respectively. No further details were given for these cases regarding the lesions observed or their diagnoses. Gładykowska-Rzeczycka (1997) later described a case of parosteal osteosarcoma from Skrwilno in north-central Poland, dated to the 13-16th century. This individual was a poorly preserved, mature adult female who exhibited a noticeable tumour at the distal metaphysis of the right humerus. The tumour appeared porotic, rugged and irregular; sagittal sectioning of the bone revealed a narrow medullary cavity and thickened trabeculae. A radiograph revealed irregular densities, spiculae and a detached and raised periosteum. Another report by Kornafel et al. (2000) described a large, osteolytic lesion in the cranium of an adult female from a 15-16th century ossuary in Wrocław. The circular lesion was located at the posterior aspect of the right parietal bone and was noted as having wavy edges which widened at the outer edge; there was also some porosity and cortical thickening. The differential diagnosis for this lesion included angioma, an unidentifiable brain tumour and meningioma. Lastly, Jeneczek et al. (2019) reported a dog cranium with pathological neoplastic lesions, recovered from Poliwca-Skrypnik, a 1-5th century site, in southwest Poland. The dog cranium was part of a zooarchaeological assemblage and porous, osteolytic lesions were noted on the body of the left maxilla and in the infraorbital region. The lesion was diagnosed as a telangiectatic osteosarcoma, based on radiography, computed tomography, and histopathology.

To date there have been only two published palaeoepidemiological studies of neoplasms from Poland, the most recent of which was focused solely on osteomata, a benign skeletal tumour (Siek et al. 2020). In that study 67 of 590 individuals were found with at least one osteoma, resulting in a crude prevalence of 11.4% with a 95% confidence interval of 8.9-14.2. The other investigation included both benign and malignant neoplasms and was based on previously reported neoplastic cases from two Neolithic and eight medieval Polish cemetery assemblages (Gładykowska-Rzeczycka 1991). Their results consisted of three reported malignant tumours from 2,653 individuals, resulting in a crude prevalence of 0.0011%. This reported prevalence was not accompanied by a 95% confidence interval, there was no reference to sex- or age-specific prevalence, nor was any demographic data provided. Due to their omission of a full demographic breakdown for each assemblage, the unknown inclusion criteria, the wide difference in temporal context, as well as the large difference between the total number of individuals in both datasets, these two investigations were deemed to be incomparable.

4.3 The Possible Impact of Cancer on Medieval Lives

In the modern clinic, patients with skeletal metastases suffer from numerous associated complications, clinically referred to as skeletal related events (Brook et al 2018). These include pathological fractures, spinal cord compression, bone marrow aplasia, bone pain and hypercalcemia (Macedo et al. 2017). Large osteolytic lesions erode the cortex and reduce the load-bearing ability of bones, leading to pathological fractures. Initially, these present as painful micro-fractures, which then lead to macro-fractures, most commonly in the ribs and vertebrae (Coleman 2006; Macedo et al. 2017). Diffused bone pain is common and can be of inflammatory or mechanical origin; it is typically worse at night and cannot be relieved with sleep (Macedo et al. 2017). Hypercalcaemia, an excess of calcium in the blood, is the most common complication of metastases and results from metastatic osteolytic activity. If left untreated, hypercalcaemia will lead to impairment of the gastrointestinal tract, kidneys and the central nervous system; the final stages result in cardiac arrhythmias and acute renal failure (Macedo et al. 2017). Hypercalcaemia and bone pain are also complications associated with multiple myeloma (Michels and Petersen 2017). Other non-specific symptoms of multiple myeloma include nausea, vomiting, malaise, weakness,

297 recurrent infections, and weight loss (Michels and Petersen 2017). For both metastatic bone disease and multiple
298 myeloma, these skeletal related events non-specific symptoms can impact a patient's mobility, daily routine,
299 overall quality of life and mental health (Brook et al. 2018). These cancers likely followed a similar course in
300 medieval Poland and thus those who suffered from these diseases, experienced the same related complications,
301 symptoms and impact on daily life.

302 Prior to the 10th century, medical treatment among the Polish was based in magic and it was believed that diseases
303 were the result of demons, thus treatments included charms, incantations and symbolic cutting (Matczak and
304 Chudziak 2018). In 966 CE Poland converted to Christianity and medical tradition became more influenced by
305 western Europe, where medicine was largely shaped by ancient Greek and Roman medical treatises, the
306 translations of which were brought to Poland in the 11th century by Benedictine monks (Teiten et al. 2013; Matczak
307 and Chudziak 2018). The most impactful was the work of the 1st century CE physician Galen, whose theories and
308 teachings became the foundation of medicine in Europe until the 16th century (Hajdu 2011). According to Galen,
309 cancers were understood to be the result of an excess of black bile, one of the four bodily humours, which had
310 become corrupted, thick, stagnant and solidified into a tumour (Demaitre 1998). The dominant belief was that
311 people with malignant cancers had no hope of survival or cure, but nevertheless various treatments were
312 prescribed, including surgery, cautery, caustic pastes, blood-letting and the application of mineral and herbal
313 medicines (Morrison 2010).

314 Herbal medicine was widely practiced in medieval Europe as well as in Poland, and like medical theory, it was also
315 rooted in antiquity. Galen prescribed the application of juices derived from several plants including winter cherry
316 (*Physalis alkekengi*), hound's berry (*Soplanum nigrun*), thorn apple (*Datura stramonium*) and sleepy nightshade
317 (*Witharia somnifera*). He also advised using zinc oxide or a remedy made from rock-alum (Karpozilos and Pavlidis
318 2004). Another 1st century CE physician, Dioscorides, prescribed autumn crocus (*Colchicum autumnale*), which in
319 the modern clinic has been shown to be effective at slowing tumour development due to its high chemical
320 concentration of colchicine, although it cannot stop malignant growth (Elgsti and Dustin 1955; Riddle 1985).
321 Dioscorides also recommended plants of the genus *Vinca*, which modern chemotherapy drugs, such as vincristine
322 and vinblastine, are derived from (Morrison 2010). However, these herbal medications for cancers were likely not
323 curative due to the low concentration of chemical compounds that could be derived from medieval processing and
324 inconsistent dosage. Instead, it is possible that herbal medications were better suited to alleviating a patient's
325 symptoms. For instance, some plants used by medieval herbalists, including chamomile (*Matricaria chamomilla*)
326 and St John's wort (*Hypericum perforatum*), contain compounds that can help alleviate non-specific cancer
327 symptoms, such as pain and inflammation (Teiten et al. 2013).

328 Regardless of these various attempts at treatment, cancers were considered by medieval physicians to be fatal.
329 There was no standard diagnostic method for cancers until the 20th century and deep-seated, internal cancers
330 would have likely progressed unchecked. In the modern clinic, metastasis to the skeleton is an incurable, chronic
331 condition and a major cause of morbidity among cancer patients (Macedeo et al. 2017; Maurizi and Rucci 2018).
332 The median survival of patients with skeletal metastases from prostate cancer is 53 months; for breast cancer, 20
333 months; and for lung cancer, 6 months (Maurizi and Rucci 2018). For those in medieval Poland, cancer was surely a
334 fatal disease preceded by numerous complications and symptoms that would have greatly, negatively impacted
335 and limited an individual's life.

336 4.4 Possible Factors in the Occurrence of Cancer in Medieval Poland

337 All forms of neoplastic disease arise as a result of an accumulation of genetic damage and mutations over time. In
338 conjunction with age and possible familial genetic predisposition, carcinogens are a main factor in neoplastic

development (Carlberg and Velleuer 2021). Carcinogens are external, environmental factors that, through constant exposure over time, will damage DNA and alter the genetic coding for cellular mechanisms. This is why some occupations and lifestyle habits are at a higher risk for neoplastic development (Carlberg and Velleuer 2021).

Heavy metals have been used by humans for millennia to varying extents, although the carcinogenic risks they bring were only fully realized in the modern era (Järup 2003). Heavy metals may enter the environment through the air (e.g., combustion and processing), water (via runoff) or soil, which could then enter the groundwater or surrounding crops (Järup 2003). Notable carcinogenic heavy metals include lead, arsenic, and cadmium. These elements can be found in the environment through either natural or anthropogenic origins, and most were known of and used in the Middle Ages. As such, a possible source of medieval carcinogenic risk from heavy metals may have been metallurgical production. When metallic ores are processed, their crushing and washing releases trace elements into the water and soil, and heavy metal particulates accumulate in the surrounding environment over time (Hoffman 2014). The emissions from ancient and medieval metalworking would be the result of roasting, smelting, oxidizing and refining metal ores in crude open furnaces, the emissions of which would have remained relatively uncontrolled until the 19th century with the development of heavy industrialization (Tylecote 1992; Hong et al. 1996). Lead is one of the earliest metals to be used by humans and its exposure to the environment is mainly through anthropogenic means (Hunter 1978). It is classified by WHO as a Group 2A carcinogen – probably carcinogenic to humans (IARC 2006). Arsenic and cadmium enter the environment as by-products from the mining and smelting of non-ferrous metals including lead, copper, and zinc. They are both classified by WHO as a Group 1 carcinogen – carcinogenic to humans, and increase the risk of cancers of the lung, bladder, skin, kidney, and prostate (IARC 2012a). In medieval Poland, the Silesia-Kraków region became an important centre of lead, silver and iron mining in the 12th century, and the Rudawy Janowickie Mountains were the largest centre for copper, silver and arsenic mining and smelting in south-west medieval Poland, as early as 1310 CE (Dziekoński 1972; Kierczak and Pietranik 2011; Cabała et al. 2020). To reconstruct historical levels of pollution, core samples were taken from the Słowińskie Błoto bog in northern Poland. In the core sections corresponding with the Middle Ages, the lead isotope ratios showed stable values and confirmed the main source of lead in the bog was anthropogenic. Furthermore, the core samples showed a lead enrichment period between the 9–11th centuries, a period associated with medieval lead smelting (De Vleeschouwer et al. 2009). With the intense lead and silver mining in southwest Poland, it is likely that trace amounts of cadmium and arsenic were released into the surrounding environment throughout the centuries. As time progressed, these mining and smelting activities may have increased the overall risk for various cancers.

Indoor pollution has been a potential health risk for humans since the transition from a mobile to a sedentary way of life. A notable component of indoor pollution that would likely have been present in medieval Poland are polycyclic aromatic hydrocarbons (PAHs), a mixed group of chemically related organic compounds. Of the PAHs one, benzo(a)pyrene, has been classified as a Group 1 carcinogen, three other PAHs have been classified as Group 2A carcinogens, and 11 more PAHs were classified as Group 2B carcinogens – possible carcinogenic to humans; these compounds have been linked to an increased risk in lung cancer (IARC 2010; 2012b; Moorthy et al. 2015). Modern PAHs enter the environment primarily from the incomplete combustion of organic materials, such as wood, coal, biomass and dung, for light, heat, and cooking (Rangarajan et al. 2015; Jameson 2019). Christensen and Ryhl-Svendsen (2015) demonstrated the potential health risks of indoor pollution in the past by living in reconstructed, Iron Age Danish houses during the winter months, mimicking a period when the majority of time and activities would take place indoors. The investigation measured carbon monoxide, nitrous dioxide, and particulate matter levels at varying distances from the open hearth. Their results suggested a high level of personal exposure due to smoke from the open hearth, which would be hazardous to human health over long periods of time throughout one's life. In the Middle Ages, there was little knowledge regarding indoor air pollution beyond

avoiding overly nauseous odours or miasmas (Sundell 2004). In medieval Poland, houses were poorly ventilated due to their lack of chimneys and small windows (Miśkiewicz 2010; Krenz-Niedbała and Łukasik 2016). The constant inhalation of emissions from an open hearth would likely have involved a constant exposure to various PAHs, which in turn may have increased an individual's carcinogenic risk for cancers of the lung and respiratory tract.

Natural sources of radiation can also be carcinogenic to humans and would also likely have been present in the Middle Ages. A recent investigation assessed the potential risk of ancient naturally occurring ionizing radiation after observing malignancy in pre-Columbian burials from Ancestral Puebloan communities in New Mexico, dated 1050–1320 CE (Whitley and Boyer 2018). Radon, a Class 1 carcinogen, was selected as the source of naturally occurring, non-ionizing radiation to be tested due to the high levels present in the region (IARC 2012c). Since radon is found in the soil and concentrates in modern basements and small rooms with little to no ventilation, it was suspected the earthen pit structures of the Ancestral Puebloans would be at higher risk than typical ground level dwellings. Short-term and long-term radon-detector kits were placed in a previously excavated pit structure and the results showed high concentrations of radon that possibly impacted the risk of neoplasms in the Ancestral Puebloans (Whitley and Boyer 2018). In Poland, the modern average annual effective dose of radiation from natural sources is 2.48 millisieverts (mSv), half of which is from radon (Fornalski and Dobrzyński 2012); the recommended yearly dose is 1mSv as per the International Commission on Radiological Protection (Ojovan et al. 2019). In recent Polish history, the annual effective dose has remained relatively the same and further to this, the south and south-west regions of Poland have been identified as having higher background radiation and higher cancer mortality (Janik and Tokonami 2009; Fornalski and Dobrzyński 2012). Although there are no data regarding estimated radiation levels in medieval Poland, from the modern data it is a reasonable assumption that natural radiation background levels may not have greatly fluctuated. Thus, people may have been exposed to radon further increasing their carcinogenic burden.

Recently, Marques et al. (2021) noted the possibility that infection-related cancers, such as that of the liver, gastrointestinal tract, rectum, bladder, cervix, and oropharynx, may have been at a higher risk in the past than in modern populations. For example, the Epstein-Barr virus and human papillomavirus, both Class 1 carcinogenic viruses, have been present for most of human history (Epstein 2001; IARC 2012d; Pimenoff et al. 2018). Hepatitis B, another Class 1 carcinogenic virus, has circulated in Europe for at least 7,000 years and its genotype's geographical distribution does not coincide with modern data; for instance, the genotypes that are typical of modern Africa and Asia were shown to have an early Eurasian presence (IARC 2012d; Krause-Kyora et al. 2018; Mühlemann et al. 2018). It is possible that in a medieval context, these diseases could have easily been spread within a population and one's carcinogenic burden may have increased through repeated infections.

Poland was not free of carcinogenic risk in the medieval period, as both natural and anthropogenic sources did exist. However, it is difficult to estimate the magnitude of these carcinogens based solely on bioarchaeological or archaeological data. As with modern cancer occurrence, an individual's carcinogenic burden is a unique multifactorial process dependent on routine exposure to various carcinogens over time, genetic mutation, and biological processes. Thus, it is difficult to identify a primary carcinogen as a main factor in cancer occurrence in medieval Poland. Rather, it is more likely that cancers occurred as a result of multiple carcinogens over time. Moreover, some sources of carcinogenic risk may not lead to cancers that produce skeletal lesions, thus obscuring them from bioarchaeology. Nevertheless, it is plausible that the risk of these malignancies existed in medieval Poland and four cases of malignancy observed in the skeletal assemblages from HIIET-PAS support this conclusion.

5. Conclusion

Four cases of malignant neoplasms were identified in three medieval Polish skeletal assemblages. Three of these cases were differentially diagnosed as highly consistent with metastatic carcinoma and a fourth displayed morphological and radiographic features typical of multiple myeloma. These cases add to the scant palaeopathological literature of malignant neoplastic disease in Poland. They also add to the global number of reported neoplasms in palaeopathology, which in turn contribute to a temporal and spatial framework that further facilitates the study of cancers in the past. It is clear that neoplastic disease is not unique to the modern age and in addition to being fatal, malignancies likely brought on numerous complications and symptoms. It is suggested that future research be directed toward investigating the impact of possible carcinogenic factors in ancient environments. Doing so may shed further insight on to the types of cancers that may have been experienced, including those that do not often leave traces on bone.

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