International Journal of Paleopathology xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

International Journal of Paleopathology

journal homepage: www.elsevier.com/locate/ijpp

Paleo-oncology: Taking stock and moving forward

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ARTICLE INFO

Keywords:
Cancer
Neoplastic disease
Past prevalence
7 "S-es"
Vertebrates
Invertebrates
Special issue

ABSTRACT

This article serves as an introduction to the International Journal of Paleopathology's special issue, *Paleo-oncology: Taking Stock and Moving Forward*. Reflecting the goals of the special issue, this paper has been designed to provide an overview of the current state of paleo-oncology, to introduce new and innovative paleo-oncological research and ideas, and to serve as a catalyst for future discussions and progress. This paper begins with an overview of the paleo-oncological evidence that can be found in ancient remains, followed by a summary of significant paleo-oncological findings and methodological advances to date. Thereafter, challenges in estimating past prevalence of cancer are highlighted and recommendations are made for future advancements in paleo-oncological research. The ground-breaking studies included in the special issue and referenced throughout this introduction embody the many ways in which progress can be made in the field of paleo-oncology.

1. Introduction

This special issue of the International Journal of Paleopathology (IJPP), *Paleo-oncology: Taking Stock and Moving Forward,* has been designed to provide an overview of the current state of paleo-oncology, to introduce new and innovative paleo-oncological research and ideas, and to serve as a catalyst for future discussions and progress. It is also meant to provide supporting evidence for the antiquity of cancer while discussing the challenges associated with estimating the past prevalence of cancer. Additionally, we hope that this issue will spread awareness of cancer's antiquity to professionals and the public alike, dispelling popular views that all cancers are caused by modern diets and lifestyles alone.

This introductory article has similar goals, beginning with an overview of the paleo-oncological evidence that can be found in ancient remains, followed by a summary of significant paleo-oncological findings and methodological advances to date. Thereafter, challenges in estimating past prevalence of cancer are highlighted and recommendations are made for future advancements in paleo-oncological research. The ground-breaking studies included in the special issue and referenced throughout this introduction embody the many ways in which progress can be made in the field of paleo-oncology.

2. Paleo-oncology: the paleopathological study of neoplastic disease

This introduction begins with the definition of paleo-oncology and associated terms, along with a brief discussion of the evidence for neoplastic disease that can be seen in ancient remains. Paleo-oncology (or "palaeo-oncology", as coined by Spyros Retsas, 1986) is the study of the global history of malignant and benign neoplastic diseases. This growing field of study uses a multidisciplinary perspective that harnesses methods and insights from archaeology, history, medicine, paleopathology, radiology, histology, bio-molecular science, and other relevant disciplines, to collect data that are used to consider the origin, evolution and history of benign and malignant neoplastic diseases.

A neoplasm [Greek: *neo* = new, *plasm* = formation] is a proliferation of new and abnormal tissue that can grow unchecked by the normal mechanisms of cellular proliferation (Segen, 2012). If a neoplasm grows to form a mass, it can be described as a tumor; however, not all tumors are neoplasms and vice versa (Zaydfudim et al., 2013). Benign neoplasms are usually slow-growing and remain confined to one bodily area or tissue. Some benign neoplasms may remain asymptomatic and unnoticed by the affected person and medical professionals alike (Kumar et al., 2009). However, some benign neoplasms may have a grave health impact by obstructing normal functions or pressing against vital organs and structures such as nerves and blood vessels; in some cases, they may even leave skeletal evidence resembling

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https://doi.org/10.1016/j.ijpp.2018.02.001
Received 2 August 2017; Received in revised form 2 February 2018; Accepted 3 February 2018

malignant growths. Benign neoplasms may also become malignant (*e.g.* giant-cell tumors, ovarian teratomas, meningiomas, or osteochondromas) (Moscow and Cowan, 2011).

Malignant neoplasms generally show rapid growth and division of abnormal cells that are capable of destroying surrounding normal tissues, do not obey normal growth-regulating mechanisms, are generally made up of poorly differentiated tissue, and are defined by the ability to establish new foci in other regions of the body; that is to produce metastases (Kumar et al., 2009). Although it has been demonstrated that some primary soft tissue tumors are detectable in mummified remains through radiographic analysis (Willoughby et al., 2016), neoplastic diseases affecting bone make up the vast majority of paleo-oncological evidence, due to the fact that bone is more likely to be preserved than soft tissue (Steinbock, 1976: 316–397; Ortner, 2003: 503; Brothwell, 2011). The two categories of primary malignant bone neoplasms are sarcomas and carcinomas. Carcinomas occur in epithelial tissues, whereas sarcomas manifest in connective tissues (*e.g.* bone, cartilage, muscle, fat, *etc.*). Sarcomas may spread to other tissues and sites within the body; however, this occurs more commonly with carcinomas (Ortner 2003: 532).

The spread of cancer from a *primary* site in the body to bone may occur hematogenously, lymphatically, through spinal fluid, or from soft tissue spread to adjacent bone, and is often referred to as *secondary* or *metastatic cancer, or metastatic bone disease* (Resnick and Niwayama, 1995: 3992–3996). In paleopathology, metastases can either mask or present clues to the identity of the primary cancer (the first malignant neoplasm to form and the tissue it affects). Despite the difficulties presented in the analysis of metastases, lesion distribution patterns and bio-molecular analysis can help narrow the differential diagnosis.

Although sarcomas and carcinomas make up the majority of primary cancers that are detectable in the human skeleton, other malignant conditions may also leave skeletal evidence. For example, multiple myeloma, the malignant proliferation of plasma cells in bone marrow (Steinbock 1976), produces skeletal lesions similar to metastatic cancers (cf. Marks and Hamilton 2007; Rothschild et al., 1998; Strouhal, 1991, 1993; Steinbock 1976: 374–384; Ortner 2003: 376–382; Brothwell 2008: 275–276; Aufderheide et al., 1998: 371–392; Marques et al., 2013a; Abegg and Desideri, this issue). The acute forms of other blood cancers such as leukemia and lymphoma can also generate widely scattered, destructive bone lesions that can be detected in the archaeological record (Rothschild et al., 1997; Stathopoulos, 1975). Additionally, melanoma, cancer of melanocytes in the skin, is less common than basal or squamous cell carcinomas, but it is more likely to metastasize, resulting in the production of bone lesions (Marks, 1995).

In addition to the neoplastic diseases that affect bone, benign or malignant soft tissue tumors may also leave skeletal evidence as pressure defects from sustained contact with bone in a confined space, *e.g.* meningioma (Waldron, 2009: 228). Some soft tissue neoplasms (*e.g.* urinary bladder tumors, chondrosarcomas, enchondromas) may also result in the formation of calcifications, which are more easily preserved than soft tissues; however, some of these calcifications are so small that they are easily overlooked during excavation (Ferris and O'Connor, 1965; Brothwell, 2011). Soft tissue pituitary tumors can also have an impact on skeletal morphology, as these tumors may induce hypopituitary dwarfism, or hyperpituitary acromegaly or gigantism (Ortner, 2003: 419–425; Waldron, 2009: 196–197, 207–208; *e.g.* Molto and Kirkpatrick, 2017).

Apart from pressure defects, calcifications and pituitary disturbances, neoplastic disease presents itself as osteoblastic and/or osteoclastic lesions in bone (for more detail see Ragsdale et al., this issue). Given the limitations of these bony reactions, there are abundant opportunities for misdiagnosis, particularly in fragmentary or incomplete remains (Miller et al., 1996; Capasso, 2005; Brothwell, 2011; Marques et al., 2013a; Ragsdale et al., this issue). Paleopathologists must also consider non-neoplastic conditions that produce similar bone lesions; developmental abnormalities, rheumatic diseases, cysts, and infectious diseases can produce lesions similar to those created by neoplastic disease (Ragsdale et al., this issue). Even normal skeletal variation can be confused with evidence of neoplastic disease. Trauma (including culturally or medically prescribed trauma, such as trephination) and its subsequent healing can also resemble osteolytic lesions from certain cancers, and tight wrappings may cause mummified tissue to bulge, resembling subcutaneous tumors (Aufderheide et al., 1998: 12–13, 17). Further complicating differential diagnosis is pseudopathology; a taphonomic change that may mimic neoplastic lesions (Wells, 1967). For example, skeletal remains may be affected by algal or fungal growths, and post-mortem rodent, insect or carnivore activity; all of which alter the bone in a manner resembling neoplastic disease (Aufderheide et al., 1998: 15–16). Supplementary diagnostic methods, such as plain radiography (Ragsdale et al., this issue), computed tomography (Micciche, this issue), microCT (Odes et al., this issue), 3D imaging (Micciche, this issue), histology (deBoer and Maat, this issue; Fornaciari, this issue), and biomolecular analysis (Nerlich, this issue), are thus strongly recommended along with visual analysis to better differentiate pseudopathologies from true pathological conditions. Even when multiple diagnostic methods are used, researchers must remain aware of the limitations of each method when applied to archaeological material (*e.g.* misinterpretation of foreign matter in radiographs, limited standards for histopathological dry bone analysis, contamination and degradation of biomolecular material), and be cautious in their differential diagnoses.

Diagnosis of neoplastic disease can be difficult even in living patients today, and these difficulties are compounded when trying to assess ancient, often fragmentary, remains. As such, a categorical diagnosis of 'neoplastic disease' is often the most specific one can be without sacrificing accuracy (Brothwell, 2011; Marques et al., 2013a; Ragsdale et al., this issue).

3. Taking stock

3.1. Non-hominin vertebrates and invertebrates

Despite the many challenges associated with the diagnosis of neoplastic disease in ancient remains, significant physical evidence supports an argument for the antiquity of benign and malignant neoplastic disease (for more details, see Capasso, 2005). The earliest possible evidence for a benign tumor has been reported in an Upper Devonian armored fish dating to approximately 350 million years ago (mya) (Scheele, 1954; Capasso, 2005). The earliest undisputed case of benign neoplastic disease is an osteoma identified in a fossilized fish, *Phaneroosteon mirabile*, dating to approximately 300 mya during the Lower Carboniferous Period (Moodie, 1927; Capasso, 2005). Benign tumors have been found in many later species and deserve further attention in their own right; however, we will focus here on the less common malignancies seen in the archaeological record.

The earliest unequivocal malignancy is a chondrosarcoma in a Jurassic Period dinosaur, allosaurus fragilis (Stadtman, 1992; Capasso, 2005). In addition to this case, Jurassic Period dinosaurs have also been observed with possible evidence of metastatic cancer (Reasoner, 1929; Rothschild et al., 1999; Weiss, 2000), osteochondroma (Capasso, 2005), and hemangioma (Moodie, 1921; Rothschild et al., 1998). The subsequent Cretaceous Period dinosaurs have similarly preserved evidence of metastatic disease, desmoplastic fibroma, osteoblastoma (Rothschild et al., 2003), hemangioma (Moodie, 1918, 1921; Rothschild et al., 2003; de Souza Barbosa et al., 2016), multiple myeloma (Lull, 1933; Norman, 1985; Tanke, 1999), and ameloblastoma (Dumbravă et al., 2016). Dozens of neoplasms, mostly benign, have also been diagnosed in remains from the tertiary and quaternary eras (Capasso, 2005). Examples of malignant neoplastic disease from these eras include possible osteosarcomas in a Pleistocene buffalo (Conkling, as cited by Capasso, 2005) and a Holocene Capra (Capasso and Di Tota, 1996).

Given the amount of neoplastic evidence that has been discovered