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Absence of evidence or evidence of absence? A discussion on paleoepidemiology of neoplasms with contributions from two Portuguese human skeletal reference collections (19th–20th century)

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ABSTRACT

Biological, sociocultural, demographic and environmental factors are major contributors to the contemporary burden of oncological diseases. Although cancer's current epidemiological landscape is fairly well known, its past occurrence and history seem more obscure. In order to test the hypothesis that paleopathological diagnosis is an adequate measure of the prevalence of malignant neoplasms in human remains, 131 skeletons (78 females, 53 males, age-at-death range: 15–93 years) from Coimbra and Lisbon Identified Skeletal Collections, 19th/20th century (Portugal), were examined. The cause of death for all of the selected skeletons was a malignant neoplasm, as recorded in the collection's documental files. Through the application of standard paleopathological protocols, it was determined that 17.6% (n = 23) of the skeletons had unequivocal osseous signs of metastatic and/or neoplastic lesions. Forty-five percent (n = 59) had manifest osseous lesions, however the lesional patterns were not clearly pathognomonic. Although all of the analyzed individuals were documented as having succumbed to malignant neoplastic disease, a total of 37.4% (n = 49) of the individuals did not exhibit osseous abnormalities. Individuals with breast cancer often exhibited lesions. This study presents a quantitative estimate of the accuracy of paleopathological diagnosis; as well as a theoretical reflection on the burden of cancer in the past. We emphasize the need for a paradigm shift while thinking about the future of paleo-oncology.

1. Introduction

Oncological conditions became the epitome of modern diseases, with malignant neoplasms figuring among the leading causes of death worldwide, ranking second in high-income countries and third in low and middle income ones (Ferlay et al., 2013; World Health Organization, 2015). As contributor to 15% of total deaths globally—with an estimation of 8.8 million for 2015—, cancer becomes a global scale problem, and ubiquitous in human societies (Forman and Ferlay, 2014; Kumar et al., 2015; World Health Organization, 2015). The growing burden of cancer attained recognition by the turn of the 20th century, as it became the "new scourge" of mankind (Hoffman, 1915; Hayter, 2003; Pinell, 2004). As Hayter (2003: 258) writes, this period brought a "new view of an old illness"; an antiquity testified through the non-human and human paleopathological record (Capasso, 2005). Malignant neoplasms affected human populations from the Neolithic Period to modern times (Capasso, 2005; Strouhal and Němečková, 2009; Hunt, 2013), with sporadic evidence noted in the paleoanthropological record (Odes et al., 2016). Although the historiography of cancer provides written depictions of these conditions from antiquity to the early Middle Ages, the documentary information for these periods remains fairly incomplete and often raises interpretative doubts (Retief and Cilliers, 2006; Strouhal and Němečková, 2009; Olszewski, 2010). Nevertheless, the impact, fear, and social stigma of cancer was already appreciable in early periods of our history, as illustrated by Pinell (2004: x) describing how "at the end of the fourteenth century, Catherine of Sienna herself tested her charitable heroism by collecting in a bowl the pus from the breast of a cancerous women to drink it like Christ's blood". Postmortem examination reports from 15th century anatomists also clearly depict the presence of cancer (Hajdu, 2011). Still, the question of how ubiquitous and prevalent it was in past populations remains unanswered. Paleopathology is exceptionally positioned

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to assist in such a quest for knowledge (Waldron, 1996; Brothwell, 2012; Zuckerman et al., 2015).

In the last decade, paleopathological reports of malignant neoplasms have become more frequent, with recent evidence recovered from diverse geographic and chronological settings (e.g. Prates et al., 2011; Binder et al., 2014; Lieverse et al., 2014; Luna et al., 2015). Strouhal and Němečková (2009) listed 250 cancer cases published up to 2007, and Hunt's (2013) survey points to similar values (n = 263). The majority of these publications are case-reports, whereas paleoepidemiological approaches are less frequent. Some population-based archaeological approaches suggest that the prevalence of cancer in the past ranged from ca. 0.5% to ca. 3.1% (Nerlich et al., 2006; Baxarías et al., 2009). Waldron (1996) and Nerlich et al. (2006) provided estimates of cancer burden in archaeological samples. In these works, the obtained prevalence in the skeletal samples was not very different from the expected values based on a reference model from the 1900–1905 period in England, provided by Waldron (1996). Despite these figures, malignant neoplasms are still traditionally deemed rare in paleopathology, leading to the assumption that cancer burden was negligible in past populations (Capasso, 2005; David and Zimmerman, 2010). Advocates of this viewpoint argue that shorter life expectancy, low exposure to carcinogens, different lifestyle and dietary habits, or higher mortality due to infectious diseases, trauma or famine were responsible for a low prevalence of cancer in the past. In addition, several scholars have also argued that small sample sizes, an expected low prevalence, taphonomic effects, or methodological and diagnostic limits can bias the interpretation of past cancer rates (Waldron, 1996; Capasso, 2005; Nerlich et al., 2006; Strouhal and Němečková, 2009; Brothwell, 2012; Zuckerman et al., 2015).

It is well known that the limits in paleopathological diagnostic accuracy preclude reliable estimations of disease prevalence in the past (Wood et al., 1992; Armelagos and van Gerven, 2003; Ortner, 2003; Waldron, 2007). Quantifying these limits for the case of malignant neoplasms is germane to the debate on its antiquity. Non-systematic use of radiological survey (neoplasms located in the medullary cavity without cortical breakthrough will be undetected by gross examination), presence of unspecific bony lesions in primary or secondary malignant neoplasms (especially in early stages of disease), difficulties in differential diagnosis (particularly with infectious diseases), absence of standardized diagnostic criteria, or the small proportion of soft tissue neoplasms that produce osseous metastases, are well-known problems in the recognition of neoplasms in archaeological settings. Thus, a key question is whether the diagnostic difficulties can justify the scarce paleopathological evidence, or if, as David and Zimmerman (2010: 731) argue, "the minimal diagnostic evidence for cancer in ancient remains indicates the rarity of the disease in antiquity". It seems reasonable to emphasize the need to conduct paleopathological research that quantifies the diagnostic accuracy of cancer in skeletal remains, before reaching conclusions on their rarity in the past (Brothwell, 2012).

Analysis of identified human skeletal collections with documented and known cause of death has the potential to clarify the aforementioned question, as demonstrated by several studies concerning other diseases (e.g. Matos and Santos, 2006). In the present paper we selected two Portuguese identified human skeletal collections (Coimbra and *Museu Bocage* Identified Skeletal Collections), from the 19th/20th century, as the starting point to address this problem.

Since this paper heavily relies on the biographic data contained within the collection records that exist for each individual of the Coimbra and *Museu Bocage* Identified Skeletal Collections, some brief considerations on the accuracy of the cause of death on these records are needed. The cause of death that is registered for each individual in the collection was transcribed from the respective cemetery records that are based on the certified cause of death. The transcription of the cause of death was carried out by the researchers that amassed the collections (Santos, 2000; Cardoso, 2006). One should expect some inaccuracies in death certification for this period, and caution on interpretations is necessary. This constraint is not unique to paleopathological research in identified collections, but is common in historical demographic research (Alter and Carmichael, 1996; Morais, 2002), retrospective epidemiological studies, and contemporary epidemiological health research that is also based on data obtained from death certificates (Alter and Carmichael, 1996). In Portugal, by the late 19th century, certification of the cause of death was a legal obligation of the attending physician, the municipal doctor, public health medical examiner, or administrative authority (Nunes, 1923; Bicho, 1926). As such, some degree of accuracy is expected. For the particular case of cancer, Nunes (1923) noted that malignant neoplasms were underrepresented in death certificates and in the overall Portuguese mortality statistics of that period. Raposo (1950: 621) also claims that "when the word cancer is registered as cause of death it is because there is confidence in the diagnosis. On the other hand, other diagnoses are frequently obscuring the true oncological cause of death. Many internal cancers are undetected by the physician [. . .], and from the innumerous ignored causes of death a significant portion must belong to cancer". Through these testimonies we can infer that, in the majority of cases, when cancer was registered in the death certificates of this period there was a fairly high degree of certainty of diagnosis. Cancer diagnosis in clinical contexts was also significantly improving during the first decades of the 20th century, with improvement in complementary diagnostic techniques, such as histology, biochemical analysis, and radiology (Costa, 2010). Autopsies were also a common practice within hospital contexts, to validate diagnosis of doubtful cancer cases (e.g. Morais and Melo, 1943). Hence, we have no reasons to consider that a great majority of the records of neoplasms in the reference collections herein analyzed were misdiagnosed. Conversely, more cases may exist without documentation of the true malignant cause of death, as described by Santos (2000) and Marques et al. (2013a).

1.1. Objectives

This study aims to present new data on the paleopathology and paleo-epidemiology of neoplasms, based on the analysis of human remains and their associated documentary records from Coimbra and *Museu Bocage* Identified Skeletal Collections.

Using paleopathological approaches, we quantified the frequency of detectable neoplasms as determined through visual inspection, in a cohort of individuals that died due to a neoplastic disease (as recorded in the collection's cause of death registries). Subsequently, we explored the role of various demographic and biological factors, namely: sex, age-at-death, degree of skeletal completeness/preservation, year of death, and the primary site of the neoplasm (primary organ). Comparison of lesion frequencies obtained in our sample with coeval biomedical data was performed, in order to test our hypothesis: paleopathological diagnosis is an adequate measure of the prevalence of neoplasms in human skeletal remains. In doing this, we attempted to answer the question: how feasible and accurate is the diagnosis of neoplastic disease, based solely on the visual inspection of human skeletal remains?

2. Materials and methods

2.1. Sample

Two Portuguese skeletal reference collections, from the 19th/20th century, were surveyed: Coimbra Identified Skeletal

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