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Cancers as rare diseases: Terminological, theoretical, and methodological biases

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ABSTRACT

Objective: Was cancer a rare disease in the past? Our objective is to consider the various terminological, theoretical, and methodological biases that may affect perceptions of the rarity of cancer in the past.
Materials and methods: We discuss relevant malignant neoplastic biomedical and paleopathological literature and evaluate skeletal data. We selected 108 archaeological sites (n = 151 cancer cases) with published malignant neoplasms and that were amenable to calculating cancer crude prevalence. Furthermore, datasets from four medieval/postmedieval Portuguese and 12 postmedieval UK sites were used to compare age-adjusted rates for metastatic bone disease and tuberculosis.
Results: In the literature review, mean cancer crude prevalence (1.2 %; 95 % CI = 0.96–1.4) exceeded the threshold for a rare disease (RD). Age-standardized rates of MBD and TB were not markedly different in the sites surveyed.
Conclusions: Methodological, theoretical and historical factors contribute to assumptions that cancers were rare diseases. The assumption that cancers are extremely rare in the paleopathological literature was not fully supported. Cancer is a heterogeneous concept, and it is important to view it as such. If a disease is considered rare, we may fail to recognize it or dismiss it as unimportant in the past.
Significance: We present a re-evaluation of the idea that cancer is a rare disease. We present a more nuanced way of comparing rates of pathological conditions in archaeological contexts.
Limitations: Variation in the amount of useable information in published literature on malignant neoplasms.
Suggestions for further research: More large-scale studies of cancer in the past alongside comparative studies of cancer prevalence with other assumed rare diseases.

1. Introduction

Over the last century, biomedical research has produced an extraordinary body of knowledge regarding oncological disorders. We understand the mechanisms that lead to carcinogenesis and the biological, ecological, and sociocultural factors that underpin the occurrence of malignant neoplasms (i.e., abnormal new cellular growth with altered mechanisms of cellular replication and invasion), as well as therapeutic approaches to cancer prevention and early detection (Weinberg, 2014; Markham et al., 2020; Schilsky et al., 2020). Despite these advances, the growing burden of cancer is evident worldwide as it becomes today a paradigmatic disease of our postmodern world. Research in the field of evolutionary medicine prompts us to look at cancers in a different way, not as conditions that must be fully eradicated "at all costs, but rather as something that must be controlled and shaped into a companion that we can live with" (Aktipis, 2020: 1). Evolutionary perspectives on cancers help us to understand the shifting dynamics of these diseases, ones that have a long evolutionary history.

Cancer has been a disease that has accompanied organisms since the origin of multicellularity, affecting almost all multicellular species, extant and extinct, across the tree of life. Even so, the burden of cancer is remarkably high in our species today. This is particularly evident when compared with the lower cancer rate seen in most modern mammals, including non-human primates (McClure, 1973; Aktipis et al., 2015).

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Various fields of research, including biology, oncology, evolutionary medicine, and paleopathology, have attempted to understand what in our evolutionary history made us so vulnerable to cancer, why the co-evolution of cancer protection mechanisms is not fully efficient, and what the drivers (intrinsic or extrinsic, i.e. environmental) are for our species to experience a high life-time cancer risk. The prevailing concept is that cancer is a result of a relatively recent environmental mismatch (Gluckman et al., 2016; Greaves and Aktipis, 2016; Hochberg and Noble, 2017)

The paleopathological record has unveiled the presence of neoplasms in non-human fossils (Capasso, 2005; Rothschild et al., 1999) and extinct hominins (Odes et al., 2016). Students of ancient disease have also attempted to answer questions related to the antiquity of the different forms of neoplasm: whether neoplasms are distinctive from what is known clinically today; if "Given the context and age composition of the sample, do they display an unusual prevalence?" (Brothwell, 2008: 257); how the history of cancer in humans has been shaped by shifts in environmental risks; and was cancer a rare disease in the past?

Discussions on cancer's antiquity and prevalence by paleopathologists have extended across the decades (e.g., Cockburn, 1974; Retsas, 1986; Cockburn, 1994; Waldron, 1996; Strouhal et al., 2000; Nerlich et al., 2006; Strouhal and Němečková, 2009; David and Zimmerman, 2010; Hunt et al., 2018; Marques, 2018), "with proponents and opponents marshalling their arguments over whether cancer did or did not exist before the modern era" (Cockburn, 1994: 1). In 2010, as a result of media interest in a *Nature* publication (David and Zimmerman, 2010), this discussion was introduced to the public (Grauer, 2010). At one end of the extreme of the discussion, some scholars claim that the past frequency of neoplasms must have been much higher than recorded in archaeological human remains or historical documents, arguing that these sources do not accurately portray the actual frequency of neoplastic disease in the past (Strouhal et al., 2000; Strouhal and Němečková, 2009; Nerlich et al., 2006; Gaeta et al., 2017; Hunt et al., 2018; Marques et al., 2018, 2020). Others assert that malignant neoplasms were rare diseases in the past (Micozzi, 2007; David and Zimmerman, 2010).

Given the emergence of new biomedical knowledge about cancers, the ongoing debate within the paleopathological community, and renewed public interest, we explore the antiquity of cancer (or cancers) from the perspective of them as a rare disease. We first consider possible bias in the history of the paleopathological study of cancers in comparison with other conditions. We then consider whether or not we should be discussing "cancer" or "cancers" as rare diseases, which leads us to focus upon cancer heterogeneity at multiple levels. We also briefly explore existing paleopathological publications on cancer to address certain assumptions made in past studies and propose ways to address some pitfalls noted. The goal of this approach is to evaluate if, according to the current published literature, cancers can be considered rare diseases, or whether this is an "ingrained idea" that cannot be supported by data. We close with a case study that illustrates the importance of age-at-death adjustments. We compared the rarity of reported cases of cancers with those of disseminated tuberculosis to provide a perspective on cancer as a rare disease in the past.

2. Rarely studied: cancer in the history of paleopathology

The diagnosis of cancer in human skeletal remains accompanied the emergence of paleopathology. Jules Le Baron in 1881 published one of the earliest reports on malignant neoplasms from several French sites (Le Baron, 1881), and during his visit to Rome in 1884, Rudolph Virchow identified possible cancer in a human femur unearthed from Tarquinia, Italy (Ciranni and Tempestini, 2008). However, much of this early work was more anecdotal than systematic (Marques, 2018).

Between the early 20th century and the 1940s, several compilations of literary evidence for cancer in paleopathology emerged, including that of Pales (1929). After World War II, with the publication of *Diseases in Antiquity* (Brothwell and Sandison, 1967), Don Brothwell provided a detailed review of published evidence, with reappraisal of older evidence. Brothwell and Sandison (1967) asserted that the apparent scarcity of neoplasms in paleopathology was the result of the intrinsic limits of the discipline and not necessarily proof of low frequencies in the past. By this time, the focus also started to be on the development of diagnostic approaches and systematic classifications of lesions related to cancer (see for example, Grmek, 1975), a goal much developed by Eugen Strouhal, who made significant contributions to the study of ancient cancers in general (Zink, 2012). Strouhal attempted to place paleo-oncology into a paleoepidemiological framework by analysing cancer prevalence alongside paleodemographic profiles across time (e.g., Strouhal and Němečková, 2009). Strouhal is undoubtedly the author with the most extensive research legacy on paleo-oncology, having more than fifty papers published on this topic (listed in Strouhal, 2010). He argued that cancers were not rare in the past. To exemplify his stance, we refer to Cockburn's (1991:6) quote from Strouhal's report on a symposium on cancer in the past held in 1991: "The meeting demonstrated very well that tumours, and more specifically the malignant ones, were (in spite of much lower life expectancy in the past) not rarities, but occurred in many populations. Much more attention should be directed at their detection, including what kind they were, an assessment of their frequency in relation to the age profile of a given human group, and an analysis of the group's living conditions. Such a study would not only enrich the history of diseases, but revealing their time dimension may help in better understanding their recent manifestations."

Domingo Campillo Valéro has also contributed, particularly on issues of cancer diagnosis and terminology (Campillo, 1984; 2005). Further, diagnostic and terminological topics motivated the many papers published by Bruce Ragsdale, which bridged clinical and paleopathological knowledge and data (e.g. Ragsdale, 1995, 1996; Ragsdale et al., 2018). Waldron (1996) and Nerlich et al. (2006) addressed the fundamental idea that the frequency of cancers in past populations cannot be effectively understood without proper paleodemographic contextualization. Rothschild and collaborators (Rothschild and Rothschild, 1995; Rothschild et al., 1998, 2002), and Marques et al. (2018) have contributed evidence-based research on cancer patterns according to different primary sites in the body in documented skeletal collections (skeletal remains with associated documentary causes of death). Only recently has a paper addressed direct measurement of environmental risk factors for cancer at one archaeological site in North America (Whitley and Boyer, 2018). Finally, in a recent study, Western and Bekvalac (2020) used a large sample of skeletal remains (n = 2241) from London and non-urban sites across England to analyze shifts in metastatic bone disease and multiple myeloma prevalence between pre-Industrial and Industrial periods. Macroscopic analysis and radiography were systematically applied in their study. The authors noted an increase of cancer prevalence in the Industrial period, notably within London. The most recent literature review of evidence of cancers was produced by Hunt et al. (2018). Papers focusing on theoretical aspects and the antiquity of cancer have also been published in recent years (e.g., Waldron, 1996; Strouhal and Němečková, 2009; David and Zimmerman, 2010; Zuckerman et al., 2016; Gaeta et al., 2017; Hunt et al., 2018; Marques et al., 2018, 2020). This brief overview demonstrates that despite the long history of cancer studies, large-scale studies, evidence-based-research, broad paleoepidemiological approaches, meta-analyses and theoretical reflections are relatively scarce compared to case studies of individual skeletons or preserved bodies (mummies).

Our review of all the scientific activities of the Paleopathology Association (PPA) also illustrates this pattern, with relatively few sessions and workshops on neoplastic conditions. These include sessions held at the 11th and 13th North American meetings (1984 and 1986, respectively - D. Ortner). These continued in 1994 and 1995 (21st and 22nd meetings, respectively -B. Ragsdale and D. Ortner, and B. Rothschild), in 2005 (32nd meeting - D. Ortner and B. Ragsdale), in 2014 (41st meeting

- K. Hunt, J. L. Willoughby, C. Kirkpatrick, and R. Campbell), and finally in 2018 (45th meeting - C. Kirkpatrick, B. Ragsdale, R. Campbell).

Cancer studies are also disproportionately few when compared to other conditions. For example, our analysis of the PPA Newsletter online archives (see https://paleopathology-association.wildapricot.org/page-18185#Nos.69-108) between 1998 and 2011 indicates that infectious conditions, trauma, joint diseases, and even paleoparasitology have been discussed more than neoplastic diseases. To date, there is no book devoted exclusively to the paleopathology of neoplastic diseases, contrary to the existence of books on other skeletal conditions, such as trauma and violence (e.g., Knüsel and Smith, 2013; Redfern, 2018), joint diseases (e.g. Rogers and Waldron, 1995), tuberculosis (e.g. Roberts and Buikstra, 2003), syphilis (e.g. Powell and Cook, 2005), leprosy (e.g. Roberts, 2020), and metabolic diseases (Brickley et al., 2020), to name a few. As another example, a review of the topical distribution of 184 papers within the *International Journal of Osteoarchaeology* between 1996 and 2005 shows only 8 % reporting neoplastic conditions (benign and malignant), compared to 28 % for trauma, 13 % for infectious diseases, and 12 % for joint diseases as the predominant categories studied (Stodder et al., 2006). Park et al. (2010) analysis of publication trends in Britain for 1997–2006 shows that neoplasms accounted for 5% of the 103 publications examined. Edited volumes that are thematically driven do not usually include neoplastic disease (e.g., Cohen and Armelagos, 1984; Steckel et al., 2019). Only in 2018 was a special issue devoted to paleo-oncology published by the *International Journal of Paleopathology (IJPP)*, which revealed a wide range of different approaches, including paleoepidemiological, paleoenvironmental, and methodologically focused papers, and literature-based reviews. We hope the 2018 *IJPP* special issue will serve to energize the study of cancer in the past beyond case studies. We look forward to additional case studies with explicit differential diagnoses, along with large scale syntheses and evidence-based research.

This discussion shows that there has been an interest in neoplastic conditions since the emergence of paleopathology, but research was (and still is) mostly oriented towards infectious and joint diseases, trauma, dental disease, and in more recent years, paleoparasitology (Ortner, 2011). Because of "historical, clinical, epidemiological, and cultural reasons, the past of diseases like leprosy, syphilis and tuberculosis have been the target of paleopathological focus" (Matos, 2009: 16). Neoplastic conditions are most often a component of differential diagnoses and are rarely considered the most likely diagnosis; often this can be based on the theoretical assumption of their rarity. This tendency biases the recognition of these entities, particularly in the context of primary malignant neoplasms of bone that pose diagnostic problems when there is a unifocal manifestation of the disease.

3. Assumptions requiring scrutiny

3.1. Cancers as rare diseases today?

One pitfall of the question, "*Was cancer a rare disease in the past?*" is that it conceptualizes cancer as a single entity. Cancer is not a single disease but a highly complex and heterogenous entity (Gluckman et al., 2016; Maley and Greaves, 2016). It encompasses hundreds of diseases with their distinct subtypes (see for example the *International Classification of Diseases for Oncology* - ICD-O-3) that have different etiology, epidemiology, clinical features and outcomes. The problem with the question "*Are cancers rare diseases*?" can be answered both "yes" and "no" because the heterogeneity of cancer can be seen at different levels.

The current definition of a rare disease (RD) in the United States specifies conditions that affect fewer than 200,000 people, whereas in the European Union a RD is defined as affecting 1 in 2000 people (Genetic and Rare Diseases Information Center (GARD)., 2020). As such, if we consider cancer as a single entity, then cancer cannot be considered a RD today, as illustrated by current estimates for 2018 that point to 43.8 million people living with cancer (diagnosed within the last 5 years), 18.1 million new cancer cases, and 9.6 million cancer-related deaths worldwide. This corresponds to one in four men (21 % lifetime risk) and one in five women (18 % lifetime risk) having the risk of developing cancer, with 1 in 6 deaths due to this disease (Bray and Soerjomataram, 2019a). In high-income countries like the U.S. one in two men (40 % lifetime risk), and one in three women (39 % lifetime risk) will be affected. Thus, these values markedly differ from the threshold stated for a RD. However, even if some malignant neoplasms, such as lung, colorectal, stomach, liver, prostate and female breast cancers are frequently diagnosed in contemporary societies (Fig. 1) (Bray and Soerjomataram, 2019a), there are more than 400 cancer types and subtypes that are listed by the GARD (2020) as rare diseases. These include several forms of cancers of the central nervous system (e.g., neuroblastoma), malignant neoplasms of the lymphoid and hematopoietic tissues (e.g., multiple myeloma), germ cell neoplasms, as well as multiple primary bone cancers. However, primary bone malignancies are rare, with an estimated annual incidence of 0.8–2 per 100 000 individuals in North America, Europe, and Asia. Even one of the most common primary malignant neoplasms of bone, osteosarcoma, meets the threshold definition of a rare disease having an average annual incidence of 4–5 people per 1 million population. This value is, for example, 1.1 per 1 million for Ewing sarcoma and 0.8 per 1 million for chordoma (Hauben and Hogendoorn, 2015; WHO, 2020).

Furthermore, there is another level of variability, as different populations experience the burden of oncological disorders according to geography and socioeconomic conditions (Bray and Soerjomataram, 2019b). For example, infectious-related cancers (e.g., cervical cancer) still predominate in sub-Saharan Africa (30–50 % of all cancer cases), whereas they are rarer in Europe and North America (3–5 % of all cancer cases). Other examples include the current preponderance of cancers of the lips and the oral cavity in Southern Asian males and Kaposi sarcoma in Eastern African males. These are extremely uncommon in other regions, and vary according to the prevalence of certain infectious diseases and cultural practices (Bray and Soerjomataram, 2019b). Other examples include the high occurrence of Epstein-Barr virus (EBV) - associated carcinomas, namely in the nasopharynx and the salivary glands, but also a high frequency of oesophageal, cervical, bladder, and liver cancers in indigenous populations of the Arctic region (Friborg and Melbye, 2008). Traditionally living groups in the Brazilian Amazon rainforest have been reported as having a high Human Papillomavirus infection (45.9 % of the women surveyed) and a correspondingly high risk of cervical cancers (Fonseca et al., 2015). Indigenous Australian groups of the Northern Territory show a higher incidence of liver (366 % higher), head and neck (325 % higher), cervical (120 % higher), and lung (84 % higher) cancers than other non-indigenous people of this region (Condon et al., 2016). On the other hand, in extant traditional forager societies hormonally-driven cancers tend to occur less frequently. Late menarche and menopause, fewer menstrual cycles, high fertility and multiparity, early births, prolonged lactation, particular dietary patterns and levels of physical activity are factors that have been suggested to relate to a lower risk of breast, endometrial, and ovarian cancers (Eaton et al., 1994; Brinton, 2014; Greaves and Aktipis, 2016), which clearly differs from the pattern observed in modern and postmodern industrial societies.

These differences are also seen across time and in relation to epidemiological transitions in a given country. For example, apart from breast and skin cancers, infection-related cancers (e.g., stomach, cervix, liver) led mortality statistics in the Western world until the mid-20th century (Hoffman, 1915). After this period, a downward trend occurred for uterine/cervical and stomach cancers, with a rise in prostate, colorectal, and lung cancers. These temporal and geographic trends are a product of biological, environmental, and demographic risk-factors, along with

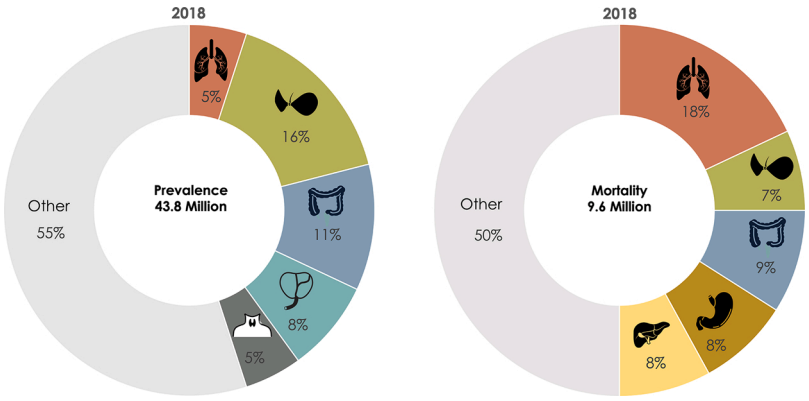

Fig. 1. Global data (sexes combined) for the top cancer sites in 2018. Prevalence (percent) by cancer site among the 43.8 million persons living with cancer who were diagnosed within the last 5 years, indicates that female breast cancer, lung, colorectal, prostate, and thyroid cancers are the most commonly diagnosed. Mortality (percent) according to cancer site among the 9.6 million deaths from cancer, shows that lung, breast, colorectal, stomach and liver cancers are leading mortality statistics from cancer worldwide. Data: The Cancer Atlas (URL: https://canceratlas.cancer.org/the-burden/the-burden-of-cancer/).

cultural practices.

Considering these examples, we must acknowledge that the burden of infectious diseases, particularly those of low pathogenicity, was also important in shaping the cancer landscape in the past (Ewald, 2018; Marques, 2018). The burden of infectious diseases in ancient environments is well known from multiple sources of evidence (Roberts and Buikstra, 2003; Dutour, 2013; Mitchell, 2015). The relevance of infectious diseases in promoting oncogenesis is related both to their carcinogenic potential as well as the promotion of a persistent inflammatory status, factors that are key in cancer development (Weinberg, 2014; Greaves and Aktipis, 2016; Ewald, 2018).

Risk-factors in past environments that induced chronic inflammation (e.g., indoor air pollution) must be also considered when thinking about cancer types in the past (Finch, 2012). For example, we know that smoky environments posed risks for upper respiratory tract (sinus) infections in the past (Lewis et al., 1995; Roberts, 2007). Did they also predispose to nasopharyngeal and lung cancer?

There are two important points to highlight here. Firstly, ancient populations were likely exposed to a highly infectious and inflammatory environment (Finch, 2012; Ewald, 2018), and they were also not experiencing a fully carcinogenic-free (endogenous and exogenous factors) environment (see for example, Lanzirotti et al. (2014); Monge et al. (2015); Álvarez-Fernández et al. (2020) on studies in paleo-pollution; Whitley and Boyer (2018) on radon exposure in an ancestral population; Christensen and Ryhl-Svendsen's (2014) experimental study on the health risks of exposure to indoor woodsmoke; Friborg and Melbye's (2008) discussion of carcinogenic compounds associated with practices for preserving foods using smoking and salting; and Ames' (1983) study of foods with naturally occurring carcinogens). Secondly, it is likely that the types of cancers that affected pre-industrial and pre-modern populations differed markedly from those prevalent today (Fig. 1), with a higher burden of infection-related cancers, including liver, gastrointestinal, rectal, bladder, oropharyngeal, and cervical (Ewald, 2018; Marques et al., 2018), and a lower burden of breast and ovarian cancers due to shifts in reproductive patterns (Eaton et al., 1994). It is incumbent upon the paleopathologist, therefore, to carefully assess the variety of possible environmental and socio-economic risk factors in specific ancient contexts that might have predisposed people to cancer, rather than assuming that relevant risk factors in the past were universally fewer.

Thus, we underscore the multiscale nature of cancers today and in the past. Certain forms of cancer would clearly fit the definition of "rare disease," and thus the inclusion of cancers within this volume is appropriate. In aggregate, of course, we see a persistent, widespread pathological condition that we believe is understudied within paleopathology. We also argue that to fully understand this persistent scourge, we need to step well beyond individual lesions seen in human remains and interrogate the full environmental context of people affected in the past, including cultural factors and the presence of other diseases linked to cancer.

3.2. *Cancers are expressed identically today and in the past*

Another assumption commonly made is that cancers affected individuals the same in the past as they do today, including their propensity to metastasize. To evaluate this assumption, we must first briefly review the nature of cancer(s) and understand another level of heterogeneity.

Cancer, or malignant neoplasm, refers to abnormal new cellular growth with altered mechanisms of cellular replication and invasion due to both genetic and epigenetic mutations. Cancers share a set of commonalities i.e., a set of capabilities acquired by malignant cells that

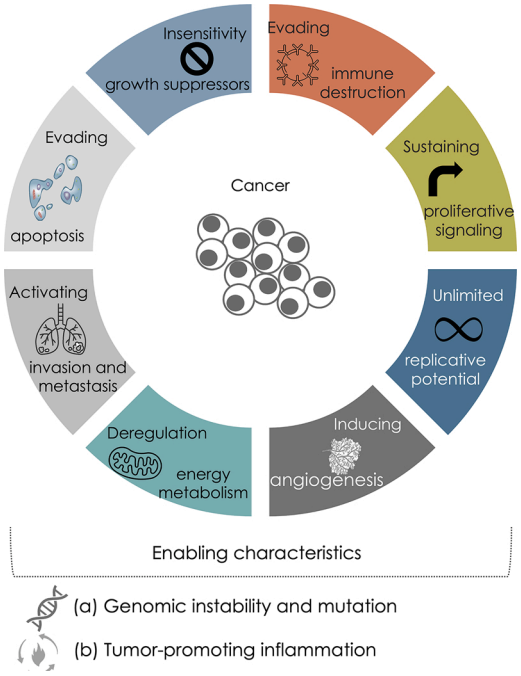

Fig. 2. Illustration of the *hallmarks of cancer* defined by Hanahan and Weinberg (2011, 2014). These are acquired capabilities of the neoplastic cell that enable its survival, proliferation, and dissemination. These capabilities are acquired via distinct mechanisms in different cancer types and at different stages in the course of the multistep tumorigenesis. Two factors facilitate the acquisition of the hallmarks: (a) genomic instability and mutability which bestow cancer cells with genetic alterations that drive cancer progression; and (b) inflammation by immune cells that unintentionally promote several of these hallmarks (Hanahan and Weinberg, 2014).

enable their survival, proliferation, and dissemination through the body, termed the *hallmarks of cancer* by Hanahan and Weinberg (2011, 2014) (Fig. 2). These properties are the result of the impact of an evolutionary process (evolutionary model) on the somatic cells. This involves the accumulation of genetic/epigenetic mutations that foster genomic and phenotypic heterogeneity of the cells upon which selective pressures act (e.g., tissue microenvironments, the immune system, therapeutic measures, etc.), leading to the growth and survival of subpopulations of cells that exhibit the greatest fitness advantage (Hanahan and Weinberg, 2011, 2014; Gluckman et al., 2016; Maley and Greaves, 2016; Caswell and Swanton, 2017). The understanding of cancer as an evolutionary process contributes to its conceptualization as a highly heterogenous disease at many levels (Fig. 3). Not only is there variation among different types of cancer, but variation occurs across patients with the same type of neoplasm, and, ultimately, heterogeneity is also marked within a given cancer at the level of the cell population (intratumor heterogeneity - ITH) (Fig. 3). This heterogeneity in subclones within a neoplasm is "arguably the major force behind tumour progression, evolution and metastasis" development (Caswell and Swanton, 2017:6). Overall, cancers are diseases with different expressions, progression, genomic and molecular characteristics, outcomes and metastatic potential (Gluckman et al., 2016; Maley and Greaves, 2016). These different levels of heterogeneity impact how we must think of cancer in the past and its prevalence.

For example, even if it is well known that breast and prostate cancers exhibit high osteotropism (i.e., propensity to metastasize to the bone), which leads to their excessive and often unwarranted diagnosis in paleopathology, the fact is that breast or prostate cancers, like many other cancers, are highly complex diseases, which include very distinct entities that vary in degrees of osteotropism and their skeletal manifestations. Therefore, the identification of the primary organ affected based on only using dry bone is not advisable (Marques, 2018, 2019). To support this view, we refer to recent studies that have indicated that demographic (e.g., age) or clinicopathological features (e.g., histological grade or size of the tumor) alone do not explain the variable metastatic propensity seen in different neoplasms. The immunohistochemical tumor signature is widely accepted as a major risk factor for bone metastasis development (Pulido et al., 2017). Furthermore, as shown in several studies of different cancers, high intratumor heterogeneity can be more efficient at metastasizing and resisting chemotherapeutics (Pulido et al., 2017; Nguyen et al., 2016; Mishima et al., 2014; Joung et al., 2017). This "heterogeneity may fuel metastasis through the selection of rare, aggressive, somatically altered cells" (Caswell and Swanton, 2017: 6). Of note is that the use of chemotherapy today to treat cancer is a major selective pressure that contributes to changes in the genomic signature of cell populations within a tumor, in some cases contributing to increased resilience and more aggressive phenotypes (Caswell and Swanton, 2017).

However, at this point we have no way of knowing if the aggressive phenotypes that exist today in some of the most osteotropic cancers parallel those of the past, since one important selective pressure, chemotherapy, was unavailable. It is possible that some cancer types metastasize more frequently to the skeletal system today than they did in the past due to a person surviving longer with the disease. It is therefore no surprise that we may be diagnosing a very small proportion of cancers that affected past populations.

As emphasized in this section and mentioned in the previous one, cancer cannot be considered a single disease. The nuances of its expression in the past require further exploration using a multidisciplinary approach.

3.3. *Cancers were rare due to shorter life spans in earlier times*

One frequent explanation for cancers being rare in past populations involves the assumption that life spans were significantly shorter in premodern times. With the exception of certain malignant neoplasms (e.g., Ewing sarcoma), where risk is greatest in adolescents and young adults, the risk of developing cancer increases with age and more rapidly in midlife. Thus, age is indeed a key risk factor for both oncogenesis of, and mortality due to, most soft tissue malignant neoplasms. An ageing population is one key driver to cancer's epidemiological landscape today due to multifactorial processes (Weinberg, 2014; Aunan et al., 2017). Longer life spans increase exposure to exogenous and endogenous mutagens and allows time for accumulation of genetic and epigenetic changes that lead to malignant transformation. Simultaneously, age is associated with increased cancer susceptibility due to several other genomic and cellular factors (e.g., genomic instability, age-related telomere attrition, loss of proteostasis, dysregulation of DNA methylation, reduced immune competence, and diminished effectiveness of DNA repair and cell growth regulation systems) (Weinberg, 2014; Aunan et al., 2017). A commonly expressed assumption, therefore, is that with a well-known lower life expectancy at birth, earlier humans did not live sufficiently long enough for many cancers to develop. However, there are four important considerations that weaken this argument. These include the difference between life expectancy at birth and longevity, the patterning of mortality due to cancers in historical contexts, limitations in osteological age-at-death estimations, and the need for nuanced epidemiological analysis that focuses upon age-specific and sex-specific patterning.

i) mortality statistics and data from documented collections of skeletal remains from the early 20th century indicate that most cancers affected individuals in middle adulthood (roughly between 50 and 69 years) and not exclusively in the elderly (e.g., Marques, 2018). Age range increments towards the older age classes (70–79 years and older) was a later phenomenon, occurring after the mid-20th century (Hoffman, 1915; Marques, 2018). This suggests that in archaeological contexts, we should still find a reasonable number of individuals with cancer who lived until the pre-contemporary "age of cancer"; i.e., middle-age, if demographic arguments are the only consideration.

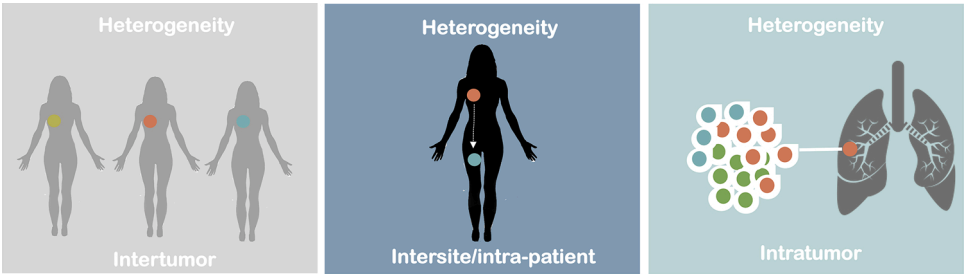

Fig. 3. Illustration of the different levels of cancer heterogeneity. Intertumor heterogeneity: neoplasms from the same primary site can lead to different phenotypic expressions between different individuals. Intersite/intra-patient heterogeneity describes differences between distinct neoplasms within an individual patient (e.g., primary site and metastasis). Intratumor heterogeneity describes differences between cellular populations within a given neoplasm.

ii) Another factor that weakens the demographic argument is the erroneous assumption that life expectancy at birth and longevity can be used interchangeably. While life expectancy at birth (highly influenced by high infant mortality) was quite low in pre-industrial societies (ca. 30–40 years) (Finch, 2012) and in today's foragers (ca. 21–37 years) or forager-horticulturalists (ca. 21–50 years), like the *Hadza* (Africa), *Aché* (South America), *Hiwi* (South America), *!Kung* (Africa), or the *Agta* (Asia) communities, the reported values of the effective end of the life span of these groups is about 70 years (Gurven and Kaplan, 2007; Hill et al., 2007; Pontzer et al., 2018). Hence, the assumption that earlier humans rarely lived past their forties or fifties must be reconsidered (Chamberlain, 2006; Cave and Oxenham, 2016; Pontzer et al., 2018). This assumption has also been questioned in paleodemographic studies over the last two decades (Chamberlain, 2006; Cave and Oxenham, 2016). Chamberlain (2006: 53) notes that there is "no clear historical evidence that maximum lifespan was reduced in earlier historical times".

iii) Cave and Oxenham (2016) emphasize considerations inherent in the archaeological study of human remains. They cite taphonomic processes whereby osteoporotic bones may decay relatively rapidly in situations of marginal preservation and thereby be less amenable to age-at-death estimates. Another key bioarchaeological problem is that past reference population age structures for adults have undergone biased age-estimation methodologies (Milner et al., 2019) A related issue is that many of the traditional, non-invasive methods for estimating age-at-death in adults generally assign a 50+ years category to all those dying in older adulthood (e.g., see Buikstra et al., 2005). Invasive methods, such as tooth cementum annulation counts (Bertrand et al., 2019), and recently developed non-invasive techniques, such as transition analysis (Getz, 2020), hold promise for more precise age estimates for skeletons in older age groups.

iv) Studies in paleo-oncology have also been limited by an absence of population-based studies of cancer in the past, and the crude rate computation is most often the only measure provided. Rarely is the estimation of cancer frequency provided with an age-stratified prevalence in that population. Since cancer is an age-related condition, the age structure of a skeletal assemblage has an impact on comparing data from different archaeological samples (Nerlich et al., 2006; Waldron, 1996; Zuckerman et al., 2016; Marques et al., 2018). This factor is paramount for paleo-oncology because it is the only way to make credible comparisons between groups living in different temporal and socio-environmental contexts.

Although the demographic argument is very important in understanding the cancer landscape today and in the past, it does not fully justify the absence of cancer in ancient human groups, as is often argued. At least a fraction of the population might have reached "the age of cancer". To complete this section, it should further be noted that some parts of the world do not see as much paleopathological work as others and there may also be a lack of paleopathology training opportunities within regions. This can lead to non-recognition of cancer lesions and thus an absence of evidence, which may not directly correlate with *actual* evidence of absence of cancer (see Buikstra and Roberts, 2012 on the history of paleopathology in different parts of the world).

4. Evidence from Paleopathology: the "rarity" of cancers in the past

4.1. Cancers as rare diseases: a paleoepidemiological survey

A recent compilation of case reports describing individuals with malignant neoplasms, as published in the paleopathological literature, shows that they may not be as rare as previously thought. Hunt et al.'s (2018) survey of the paleopathological literature identified 272 individuals with malignant neoplasms from archaeological sites dated to prior to the 1900s (see also Hunt et al., 2017).

First, we compared Hunt and colleagues' (2017) data with our own literature review and then added post-2017 publications. This compilation of published evidence for cancers increases to more than 300 'probable' cases of malignant neoplasms in ancient skeletal remains or soft tissues (mummies) when journal articles (mostly peer-reviewed), books/book chapters, published bioarchaeological reports or theses, and presentations at scientific meetings were surveyed. The diagnoses were accepted as published by the authors, without a critical assessment. Even if some of these diagnoses may need future reappraisal, particularly for older publications and especially if the degree of completeness/preservation of individual bones are not taken into account, they do serve a purpose for the present work, which is to evaluate the rarity of cancers based on a meta-analysis/literature review. Our review aims to summarize, synthesize, and discuss the pitfalls of published information in paleopathology on cancers as published, to date. Despite these limitations, this review is informative when placed into a broader context. Since most publications on cancer in paleopathology are in the case-study format, they often lack detail required for a paleoepidemiological approach, which we illustrate.

From the >300 case-studies published, we next selected publications where the archaeological sites studied contained 20 or more individuals that were originally studied, and where complete information was available regarding the total number of skeletons/humans remains studied. These criteria reduced the sample to 108 archaeological sites.

Of the 108 skeletal populations (a sample of 32,353 skeletons and 151 cancer cases published) the cancer crude prevalence was relatively low, at 0.5 % (95 % CI = 0.39−0.54). The values ranged from a minimum of 0.06 % to a maximum of 4.6 %, with a median figure of 0.7 %, a mean of 1.2 %, and a standard deviation (SD) of 1.1 (95 % CI = 0.96–1.4) (Fig. 4). If we use the mean value of 1.2 %, this would represent a ratio of 2400 individuals per 200 000 people, or 24 individuals per 2000, which does not match current definitions of a RD.

Another common idea explicit in paleo-oncological studies is that small sample sizes are a factor hindering the detection of cancer in the past. Each of these sites had a low number of individuals with cancer reported, with a mean value of 1.4 cases (SD = 1.3) and a minimum of 1 and a maximum of 13 per site. As expected, sites that contained three or more reported individuals (8.3 % or 9/108) were also those from larger sample sizes (number of skeletons ranging from 150 to 2547; mean = 732, SD = 752). The mean number of skeletons studied per site is significantly higher for sites where three or more people had cancer reported, even if values overlap, confirming the idea that sample size is a limiting factor (Table 1).

Obviously, this analysis is limited by several factors, such as differential preservation of the skeletons in the samples, variable degrees of completeness of the skeletal remains, non-uniformity of diagnostic criteria used by different authors, relative experience of researchers, research being oriented towards neoplastic conditions being relatively more common in certain parts of the world, a focus on specific chronological periods, and a lack of age-at-death profiles for the total sample of skeletons/preserved bodies from which the individuals with cancer are reported.

However, of utmost importance are differences in the age-at-death composition of the samples. Most of the publications surveyed did not provide information regarding cancer data stratified by age groups, nor the age-at-death profile of the total skeletal population studied, hindering a paleoepidemiological approach that enabled controlling for age at death differences. This is an important epidemiological bias when studying cancer in the past (Waldron, 1996; Nerlich et al., 2006, Zuckerman et al., 2016, Marques et al., 2018) and particularly in the case of cancer, which is an age-related condition (Weinberg, 2014). Marques et al. (2020) showed that there was minimal temporal variation in

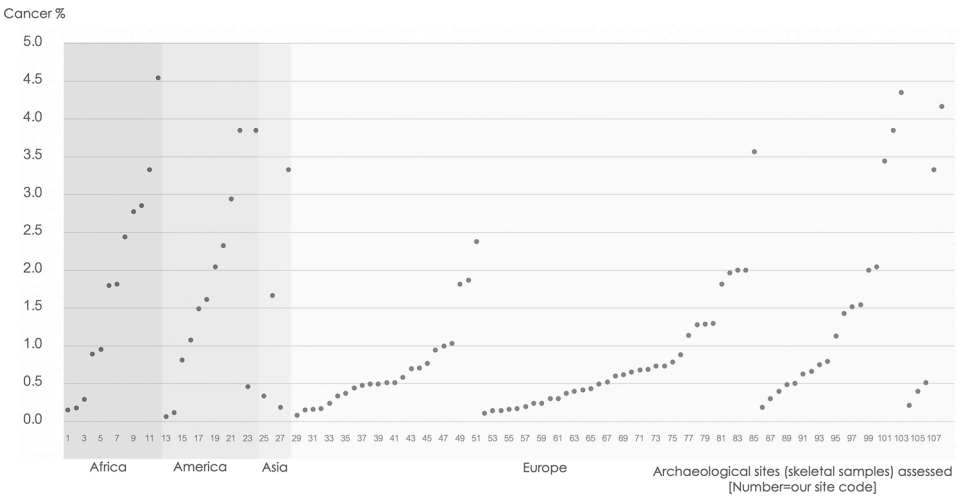

Fig. 4. Distribution of cancer crude prevalence (%=$n_{cancerskeletons}/n_{totalskeletons}$) in individuals from 108 archaeological sites reviewed in our literature survey. The data are organized by continent and from the lowest to the highest prevalence for each continent. The values on the X-axis represent the codes attributed to each site.

Table 1
Relationship between the number of archaeological sites with cancer reported and the number of skeletons in the study base.

	Archaeological sites				
	Number of sites n (%)	Size of the study-base (no. of skeletons)			
		Total (n)	Mean (SD)	Size Range (n)	Statistics*
Sites with 1 or 2 cancer cases	99 (91.5 %)	25,769	260.3 ± 285.5	22–1504	$p = 0.003$ U = 180.000
Sites with >3 cancer cases	9 (8.3 %)	6584	731.6 ± 751.8	150–2547	
Total	108 (100%)	32,353	–	–	

* Mann-Whitney test used because the variables were not normally distributed.

cancer prevalence in 24 skeletal populations dated to between ca. 5000 BCE to 1900 CE when prevalence was age-adjusted. Marques (2018) also showed that the crude prevalence of cancer in four Portuguese documented skeletal collections provided different results when age-adjusted methods were applied.

4.2. Cancers as rare diseases: case study of tuberculosis and metastatic bone disease

To illustrate the need for considering age-at-death structures when debating the rarity of cancer, and in particular "how much rarer" cancer was when compared with apparently more "common" diseases, the next stage in the process was to compare crude prevalence and age-standardized rates for metastatic bone disease (MBD) and tuberculosis (TB). MBD and TB were chosen as comparators because they are both age-associated diseases and the more commonly reported representatives of their categories in paleopathological publications (cancer and "specific" infectious disease, respectively). We focused on two distinct geographic contexts: the UK and Portugal. Since the study-base for the published evidence of bone metastases is particularly well documented for postmedieval sites (1500–1855 CE) in these countries, we used this time period to explore any differences in prevalence for TB and MBD.

Twelve archaeological sites mainly located in London, UK, were selected for study (Museum of London- Welcome Osteological Research database- MOLA 2020), along with one site in Lincolnshire, East Midlands (Barton-on-Humber- Rodwell and Waldron, 2007) and one in Wolverhampton, West Midlands (St. Peters Collegiate Church- Arabaolaza et al., 2007) (see legend, Fig. 5). The Portuguese sample is composed by sites with reports of MBD and TB, from the CIAS Database, Portugal-CIAS (2020) along with one site from Loures (Antunes-Ferreira, 2015) and Castelo Branco (Matos et al., 2011),(see legend Fig. 5). They each fulfilled the following criteria: 20 or more individuals in the total skeletal population; cancer and/or TB evidence clearly described so that the diagnosis could be reassessed/confirmed; information on specific age-at death categories for individuals affected; and availability of demographic data for the whole population from each site. The diagnosis of MBD was considered as described in the original publication or bioarcheological report and re-assessed using descriptions from the databases or reports. A multifocal skeletal distribution with osteoblastic, osteolytic, or mixed lesions, affecting at least one element of the axial skeleton (particularly the pelvic girdle and thoracic cage), as well as the proximal areas of the long bones, was considered as indicative of MBD (for more details on the used criteria see Marques, 2018). A diagnosis of TB was accepted when Pott's disease had been identified or if destructive lesions of hip or knee joints were noted unilaterally. Individuals with proliferative rib lesions, hypertrophic osteoarthropathy, or other possible indicators of TB, without hip/knee damage or Pott's disease, were not included in the dataset. The diagnostic criteria accepted for tuberculosis of the spine (Pott's disease) were taken from clinical information (Resnick and Niwayama, 1995). The damage to the spine is usually located in the lower thoracic and lumbar spine, although the cervical spine can be affected. More than one vertebra is usually affected, but normally at least two adjacent vertebrae are involved in most instances; the neural arches are generally spared. Destructive lesions, with very little or no bone formation, can damage any aspect of the vertebral bodies, but the anterior portion is most affected. Ultimately this can result in collapse of the affected vertebrae and vertebral deformity (kyphosis). Of course, a number of differential diagnoses always must be considered, including non-tuberculous osteomyelitis, trauma, brucellosis, and neoplastic disease, and therefore the characteristics and locations of all pathological changes in a skeleton should be considered when making a diagnosis of TB.

The number of reported individuals with MBD from these twelve sites ranged between one and three individuals whereas individuals with TB ranged from between one and eight. Contrary to our expectations, as seen in Fig. 5, we note that the crude prevalence for both conditions is

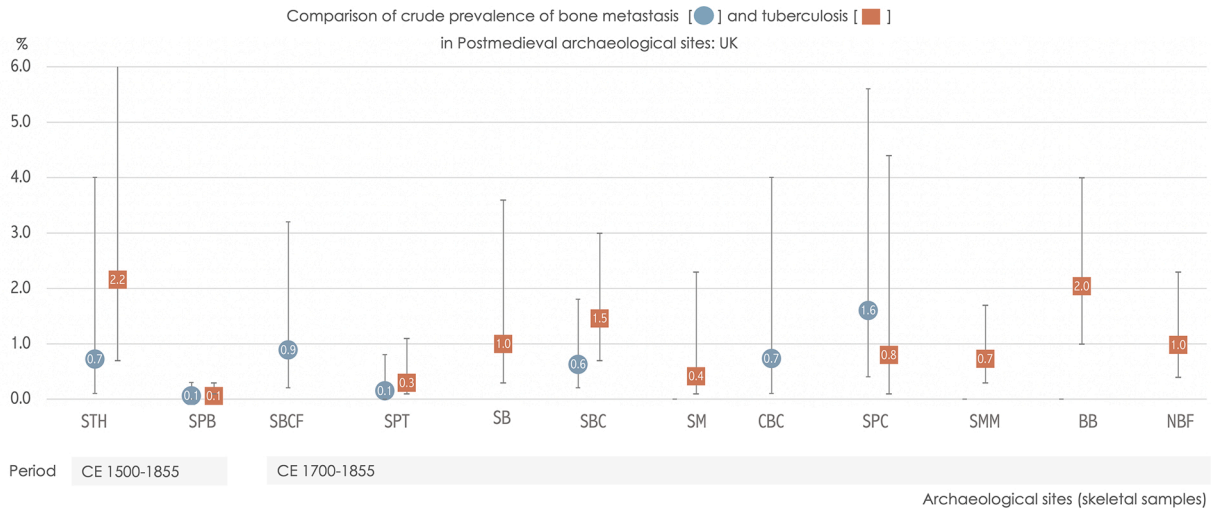

Fig. 5. Distribution of crude prevalence (%=$n_{cancerskeletons}/n_{totalskeletons}$) and 95 % CI for MBD and TB for the 12 postmedieval sites in the UK. Note that skeletons with unknown age-at-death were excluded from the study base, and therefore the prevalence may be different from the original publication.
Legend: Circles and squares represent the crude prevalence and lines the 95 % CI (calculated with Epitools (http://epitools.ausvet.com.au) using the Wilson method for small samples [Brown et al., 2001]). STH- St. Thomas' Hospital, London; SPB- St. Peters, Barton-on-Humber, Lincolnshire; SBCF- St. Brides Church, Fleet Street, London; SPT- Christchurch Spitalfields, London; SB- Sheen's burial ground, London; SBC- St. Brides Lower Churchyard, Farringdon Street, London; SM- St. Marylebone's, Paddington Street (north) burial ground, London; CBC- Cross Bones Cemetery, Southwark, London; SPC- St. Peter's Collegiate Church, Wolverhampton; SMM- St. Mary and St. Michael, Whitechapel, London; BB- Bow Baptist Church, Tower Hamlets, London; NBF- New Bunhill Fields burial ground, Southwark, London. (Data from:Molleson et al., 1993;Arabaolaza et al., 2007;Rodwell and Waldron, 2007;Connell and Miles, 2010;Walker, 2012;Henderson et al., 2013,[Henderson et al., 2015]2015; and the Museum of London- Welcome Osteological Research database (MOLA, 2020).

relatively low for this dataset but, as expected, the prevalence of TB was slightly higher for most sites. However, the 95 % confidence intervals (95 % CI) for the upper and lower boundaries overlap, which indicates that the values are not markedly different for cancer and TB within the same site. The 95 % CI is wide, indicating a low precision of the observed effect (Smith, 2020).

Comparisons between sites can be generated by standardizing ages, thus accounting for biodemographic differences between sites. As observed in Fig. 6, when age is taken into consideration, both MBD and TB age-standardized rates are higher for the majority of these sites. Interestingly, for the SPT, CBC and SPC sites, the MBD age-standardized rates were higher than for the TB rates for most sites (except STH). This shows that age adjustment procedures are always fundamental when comparing sites, and our data suggest that this is particularly important when calculating past prevalence for MBD in comparative studies. Crude prevalence is not informative.

In a different context, i.e., pre-industrial populations of the medieval and postmedieval (1900 CE) periods in Portugal, the situation is also interesting. In Portugal, there are approximately five individuals confidently diagnosed with TB. However, there are more than 76 other individuals who presented either with proliferative rib lesions alone or other skeletal lesions suggesting a "possible" diagnosis of TB, as discussed by Santos and Matos (2019), and six cases of MBD in a dataset of more than 3000 skeletons. The expectation of a much higher occurrence of TB is therefore not met in the Portuguese dataset. We compared MBD and TB prevalence between these Portuguese sites where demographic data made comparison possible (>20 skeletons per site, known age at death of the individual, and age-structure of the total population). As seen in Figs. 7 and 8 , once again the crude prevalence of MBD and TB within the same site was similar for two of the sites, but higher for one of

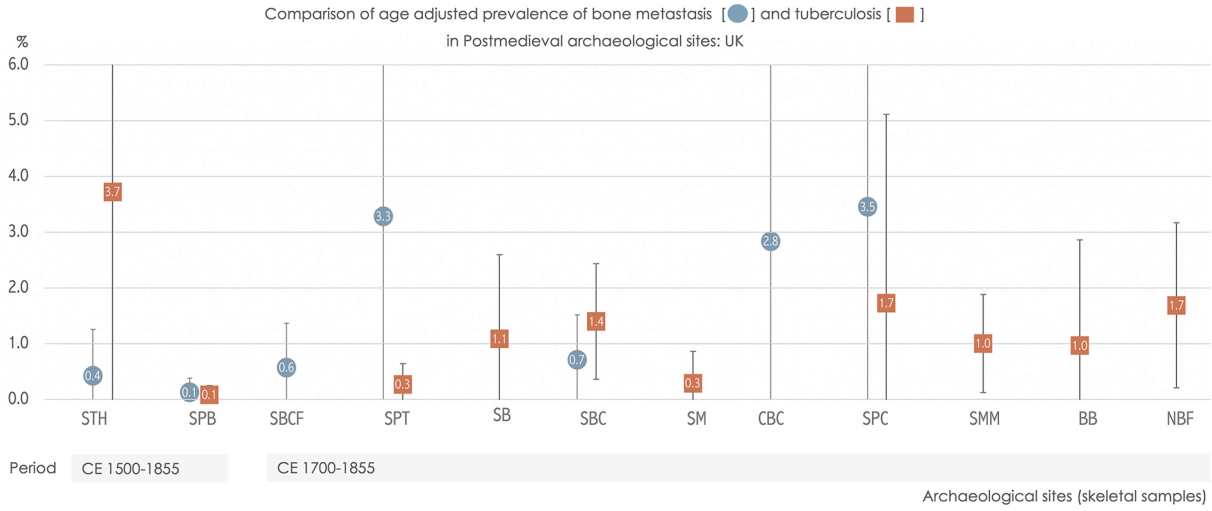

Fig. 6. Comparison of age-standardized rates for the UK sites (see legend of Fig. 5). Age standardization used the direct method (Silva, 1999), using as reference population the demographic distribution of the skeletal sample from the Global History of Health Project (GHHP): European Module (Steckel et al., 2019).

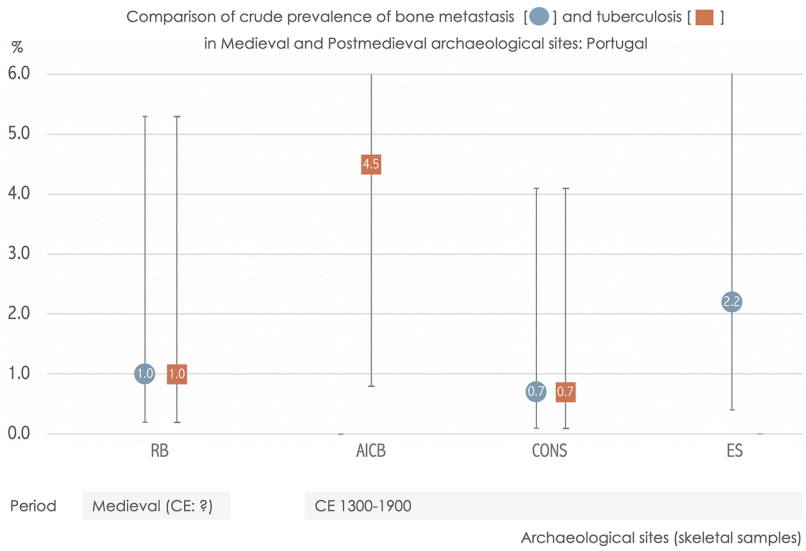

Fig. 7. Distribution of crude prevalence (%=$n_{cancerskeletons}/n_{totalskeletons}$) and 95 % CI of MBD and TB for four medieval/postmedieval sites in Portugal. Note that skeletons with unknown age-at-death were excluded from the study base.
Legend: Circles and squares represent the crude prevalence and lines the 95 % CI (calculated with Epitools (http://epitools.ausvet.com.au) using the Wilson method for small samples [Brown et al., 2001]). RB- Necrópole da Rua dos Barcos, Santarém; AICB- Adro da Igreja de S. Miguel, Castelo Branco; CONS- Necrópole de Constância; ES- Necrópole do Espírito Santo, Loures (Data from: Gomes, 2005;Assis and Codinha, 2010; Matos et al., 2011;Antunes-Ferreira, 2015; CIAS Database-CIAS,2020).

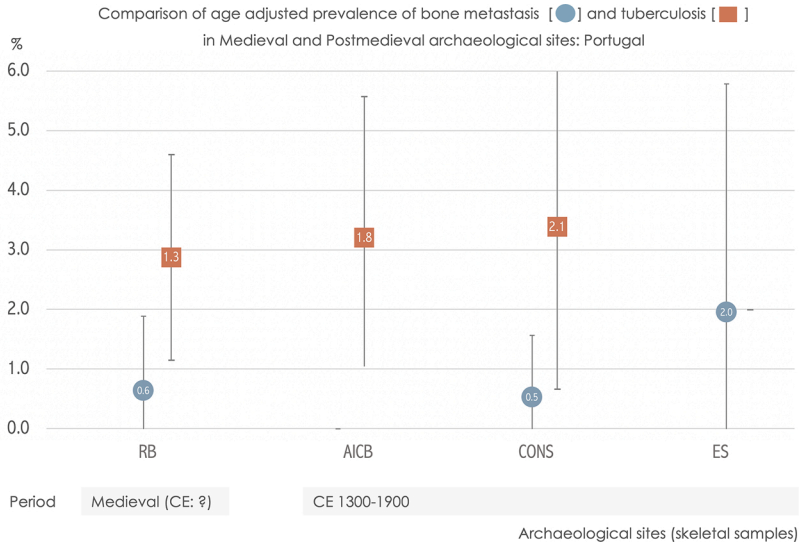

Fig. 8. Comparison of the age-standardized rates for the Portuguese sites (see legend of Fig. 7). Age standardization used the direct method (Silva, 1999), using as reference population the demographic distribution of the skeletal sample from the Global History of Health Project (GHHP): European Module (Steckel et al., 2019).

the sites. Contrary to the above-mentioned patterns for the UK sites, the MBD prevalence in the Portuguese analysis declined following age adjustment, and a similar trend was found for TB prevalence at two of the three sites with evidence for TB. Additionally, in the Portuguese sites both crude prevalence and age-standardized rates for TB were consistently higher than for MBD.

It is important to stress that when analyzing the "big picture" for both the UK and Portugal, all crude and age adjusted rates for MBD and TB are extremely low (not exceeding 4.5 %). These figures challenge the common and generalized view that we often see in publications that MBD is "rare" in the past.

The purpose of this exercise was to explore whether TB frequencies were similar to those of MBD in communities living in the postmedieval period in the UK or in medieval/postmedieval Portugal. Received wisdom is that cancer was a "rare disease" and TB relatively common during this period, a perception based on published data. However, it is acknowledged that only 3–5 % of untreated people may be affected in their skeleton (Jaffe, 1972), but TB does tend to be assumed as more common than cancer in the past. Obviously, the age-adjusted frequencies in this dataset are very close. We really must reconsider the conventional phrase, that "cancer was rare in the past". Most of all, we should also refrain from comparing cancer prevalence and other conditions when data for age at death are not considered.

More large-scale studies of cancer palaeoepidemiology are needed involving comparative analyses and the use of paleoepidemiological methods that control for age-at-death. We also need to compare our evidence of cancer with that for other diseases. This is necessary to critically evaluate the "presumptive" rarity of cancers in the past.

5. Discussion and conclusion

Cancer is an ancient illness, as testified by its occurrence across species in the non-human and human fossil record. Paraphrasing Aktipis and Nesse (2013: 151–153), we can say that "the story of cancer begins about one billion years ago at the dawn of multicellularity". Malignant neoplasms possibly affected the lives of our hominin ancestors (Odes et al., 2016) and cancer has afflicted human populations at least during the last five millennia (Strouhal and Němečková, 2009). Despite this deep-rooted evolutionary phenomenon, the actual history of cancer and humankind is the focus of a heated debate among scholars.

We argue that incomplete knowledge of variation in expression of cancers severely limits our ability to estimate cancer rates in the past. We must be aware of this variation in the types of cancer that affected past populations when compared to Industrial and post-industrial societies, as well as variation in osteotropism and heterogeneity of cancers. These factors limit our ability to make analogies with modern epidemiological and biomedical data (Marques et al., 2018).

Furthermore, there are also several paleopathological biases: the relatively low sensitivity of paleopathological diagnoses, lack of uniformity in diagnostic criteria used by different authors, and the often small number and fragmentary and poorly preserved nature of archaeological samples (Waldron, 1996; Capasso, 2005; Marques et al., 2018). As shown by Marques et al. (2018) and Rothschild and Rothschild (1995), a large proportion of people with cancer in the past either did not manifest externally visible osseous lesions at the time of their deaths or present non-specific lesions in their bones or soft tissues that limit diagnostic specificity. Marques et al. (2018) reported that a mere 17.6 % (n = 23) of the 133 skeletons from Portuguese Identified Collections showed osseous signs compatible with metastatic and/or malignant neoplastic lesions, whereas Rothschild and Rothschild's (1995) study of cancer in 129 skeletons from the Hamann-Todd documented collection (Cleveland, Ohio, USA), showed that lesions were present in 25.5 % of individuals (n = 33) using radiological examination, but in only 8.5 % of individuals (n = 11) using visual inspection, which means that detection of cancer lesions using "radiologic examination was three times that of visual examination" (Rothschild and Rothschild, 1995: 261). Such results emphasize the importance of diagnostic constraints in paleo-oncological studies and the problems of non-systematic use of radiological surveys. In the future, it is crucial in conducting paleopathological research on cancer to use systematic radiological surveys and at the same time re-appraise archaeological skeletal collections using this technique alongside visual inspection (Rothschild and Rothschild, 1995; Hunt et al., 2018; Marques et al., 2018; Western and Bekvalac, 2020). The small proportion of soft tissue neoplasms that produce osseous change is also a well-known constraint in the recognition of these conditions in archaeological settings. Discussions of non-specific bone lesions associated with primary or secondary malignant neoplasms are also under-represented in many publications, and standard diagnostic criteria and careful differential diagnosis may be lacking, particularly with infectious diseases (Brothwell, 2008; Zuckerman et al., 2016; Marques et al., 2018).

It is also relevant to note another source of bias. Different parts of the world have variable trajectories in terms of training in palaeopathology. For example, Hunt et al. (2018) reported a higher frequency of published case studies on cancer in certain geographic regions, particularly in Northern Europe (18.7 %, 51/272), with most coming from the United Kingdom, followed closely by North Africa (16.9 %, 46/272), and mostly Egypt. These results do not necessarily reflect a geographic disparity in cancer in the past, but a bias in availability of training, experience of the researcher, research scope and interest, financial factors, and the availability of skeletal assemblages for study. These biases influence our understanding of the history of cancer in the archaeological record and should be minimized in future paleo-oncological research

In the future researchers should focus on the assessment of cancer frequency in relationship to the age profile of a given human population, with large scale studies also focusing on relevant socioeconomic and environmental variables. The useful nature of case studies of cancer can be increased markedly if they consistently provide enough baseline demographic information for the total number of skeletons studied that enables larger paleoepidemiological approaches and meta-analyses to be achieved, thus surpassing the present epidemiological bias of many studies (Marques et al., 2018). We urge authors and editors of journals to request that a full demographic profile of the complete sample studied from which cases are drawn should be included, along with chronological and cultural data. Furthermore, publications must also indicate the degree of skeletal completeness and preservation reported, but also for the total sample studied. These data will enable an assessment of the impact of preservation on the recording of potential data of interest (cancer lesions), thereby making the data more reliable for comparative studies.

In sum, while we may consider some cancers rare today, depending upon the reference group and its location in the geographic, cultural, and disease landscape, we are only beginning to understand past cancers, which have been with animals throughout their existence. We sincerely hope that this discussion will contribute to rigor in identifying cancer in human remains and analyzing the data in a manner that will enable this important area of paleopathology to advance.

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