

Taking Stock: A Systematic Review of Archaeological Evidence of Cancers in Human and Early Hominin Remains

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ABSTRACT

This study summarizes data from 154 paleopathological studies documenting 272 archaeologically recovered individuals exhibiting skeletal or soft tissue evidence of cancer (malignant neoplastic disease) between 1.8 million years ago and 1900 CE. The paper reviews and summarizes the temporal, spatial and demographic distribution of the evidence and the methods used to provide the cancer diagnoses. Metastasis to bone is the most widely reported evidence (n=161), followed by multiple myeloma (n=55). In the dataset, males were represented more than females (M=127, F=94), and middle-adults (35-49) and old-adults (50+) were represented most among age groups (MA=77, OA=66). The majority of the evidence comes from Northern Europe (n=51) and Northern Africa (n=46). The data are summarized in the Cancer Research in Ancient Bodies (CRAB) Database, a growing online resource for future paleo-oncological research. This systematic review contributes to broader studies of malignant neoplastic disease in antiquity; it provides an overview of paleo-oncological data, discusses the many practical and methodological challenges of paleo-oncological research, and dispels presumptions about cancer's rarity in the past.

1. INTRODUCTION

According to the latest figures from the World Health Organization, there are four major non-communicable diseases (NCD) responsible for 82% of the total NCD related deaths globally (cardiovascular diseases, cancer, chronic respiratory diseases and diabetes); cancers contributed 21.7% (8.2 million). Annual cancer deaths are predicted to reach 12.6 million by 2030 (World Health Organization, 2018). In 2012 an estimated 14.1 million people were diagnosed with cancer, and 8.8 million deaths resulted from cancer worldwide (Stewart and Wild, 2014). Cancer has also become the second leading cause of death globally, following heart disease, with nearly one in six deaths attributed to malignant disease. Given the significance of cancer today and the growing interest in oncological research, the study of the history of cancer is gaining more attention.

Paleo-oncology is the study neoplastic diseases, benign and malignant, as seen in the biological remains and historical records of humans, their ancestors, and other animals (Halperin, 2004). In the case of human remains, paleopathological methods of analysis are used to identify and examine neoplastic diseases in ancient skeletal remains or in preserved bodies. These data are increasingly considered within their original sociocultural and environmental context, alongside genetic and biological understandings of how this disease affects humans. Paleoepidemiological studies of cancer in archaeologically-derived human and early hominin remains are potentially significant for understanding how and why cancer affected past humans and other animals, further contributing to our collective understanding of cancer risk factors as seen in particular time periods and geographic regions (e.g. Whitley and Boyer, this issue).

David and Zimmerman (2010) suggested that cancer is predominantly a modern disease, “limited to societies that are affected by modern lifestyle issues”. Several media outlets accepted this conclusion, supporting public affirmation that cancer results solely from risk factors that people experience today, such as exposure to pollutants and modern diets (e.g. Alleyne, 2010; Choi, 2010). Here we demonstrate that the amount of evidence of cancer in past societies is actually not negligible, which is in accordance with the long established idea that cancer is a result of a combination of risk factors, including changes in our culturally mediated environment (e.g. manufactured carcinogens), exposure to carcinogens in the natural environment (e.g. ultraviolet rays, radon, smoke), and an underlying genetic predisposition (e.g. inherited and incidental gene mutations - Fearon and Bommer, 2008). As such, cancer can be seen throughout and beyond the Holocene (the last 11,700 years), and paleo-oncological studies have repeatedly proven that cancers are not exclusively found in modern societies. In addition to the aforementioned survey of cancer in mummies (David and Zimmerman 2010), to date there have been several large scale paleo-oncological studies. In 2005, Capasso briefly summarized over 125 individuals reported in published literature with evidence of malignant and benign neoplastic disease. In 2008, Strouhal and Němečková published a book written in Czech, followed by an article in 2009, that summarized the skeletal cancer diagnoses of 250 individuals from Europe, Africa, and Asia. In addition, a study of 3967 individual skeletal remains from 12 archaeological funerary contexts in Hungary, 13 skeletons with evidence of bone metastases were identified (Molnar et al 2009). Although it is clear, from these and other studies that cancer existed in the past, the past prevalence of cancer in archaeological human remains continues to be underestimated due to the inherent limitations of paleo-oncological studies (Strouhal and Němečková, 2009).

This study presents a systematic review of published and unpublished studies of neoplastic disease in archaeological human remains, and discusses practical and methodological challenges of paleopathological research. It aims to provide a foundation for conducting future research into the global history of cancer by: a) compiling and synthesizing available and accessible paleo-oncological data, b) identifying methodological trends and challenges and their potential impact on differential diagnoses and comparative studies, and c) introducing the newly created CRAB (Cancer Research in Ancient Bodies) Database, hosted by the Paleo-oncology Research Organization (PRO) (Hunt et al., 2018).

2. MATERIALS AND METHODS

2.1 The CRAB (Cancer Research in Ancient Bodies) Database

This study is based on the analysis of paleo-oncological data recorded in the 2017 version of the CRAB (Cancer Research in Ancient Bodies) Database (see Appendix A). The CRAB Database is an open access collection of paleo-oncological data intended for scholarly collaborative review, discussion, and exploration of data trends (www.cancerantiquity.org/crabdatabase). It was initially created by the first author for the completion of her research dissertation for the Master of Science in Palaeopathology at Durham University, England, supervised by the second author (Hunt, 2013). More recently, Casey L. Kirkpatrick (3rd author), Roselyn A. Campbell [UCLA Cotsen Institute of Archaeology], and Jennifer L. Willoughby [Western Ontario University] have contributed to the database and assisted in the verification of the data therein.

2.1.1. Database Research

Digital libraries and search engines (JSTOR, EBSCOhost, PROQuest, Google Scholar, various university libraries) were surveyed using a broad variety of keywords, including *neoplasm*, *tumor*, *cancer*, *carcinoma*, *sarcoma*, *malignant*, *metastatic*, as well as words related to specific types of cancer (e.g. *osteosarcoma*, *chondrosarcoma*, *melanoma*, *multiple myeloma*, *leukemia*). Additional evidence was identified through personal correspondence with presenters at professional meetings, and from bibliographies of paleo-oncological surveys and studies (Strouhal and Němečková, 2009).

The survey focused on published literature, and therefore “grey literature” (i.e. unpublished bioarchaeological reports) was not specifically sought out, but reports were included in the database if identified during the searches. As a result of this research, the CRAB Database is populated with information on ancient cancer from books, edited book chapters, journal articles, conference presentation abstracts, university undergraduate, masters and doctoral dissertations and theses, and bioarchaeological reports. This represents a mixture of published and unpublished sources, but the data in all sources were critically reviewed for the purposes of this paper.

2.1.2. Data Selection

During this study, it was determined that a number of the same individuals affected by malignancy were reported in multiple sources, sometimes with alternative differential diagnoses. In an effort to maintain consistency and an accurate representation of the history of methods applied to recording paleo-oncological evidence methods, and the resulting prevalence of the evidence, the data from the original (primary source) studies were included in the database whenever possible. If the original source was not accessible, a secondary source was then consulted.

Studies of the remains of people who lived prior to 1900 CE were included in the database; as evidence dated to after 1900 CE were not included, this prevented the use of evidence that may have been influenced by modern medical therapies (DeVita and Chu, 2008). It was not the purpose of this study to judge the validity of paleopathological diagnoses. Therefore, all paleo-oncological studies were included despite potential methodological and technological deficiencies from earlier studies that may have affected their original diagnoses. Studies included in this survey that were not peer reviewed were also accepted as stated despite their increased potential for incorrect diagnosis.

Reports of benign neoplastic disease were excluded from the database to maintain its focus on malignant neoplasms (see Table 1). In addition to the exclusion of reports on benign neoplasms, some additional exclusions were made to refine the data for analysis. These exclusions include neoplastic diseases that are benign but in rare circumstances can become malignant, such as osteochondromas (e.g. Resnick et al., 1995; Buzon, 2005) and teratomas (Jorge et al., 2016; Wasterlain et al., 2017; Klaus and Erickson, 2013). Due to the uncertainty of a diagnosis of malignancy, some studies were not included in order to avoid the misrepresentation of data. For example, histiocytosis X (currently named Langerhans cell histiocytosis) was once considered to be a neoplastic disease, but it was not included in the current study because of current clinical debate regarding whether it results from a neoplastic process or is an immunologic dysregulatory

disorder (Jordan et al., 2012). If the lesions are attributable to an autoimmune phenomenon, then the disease could be seen to be the result of a very different set of processes compared to those of malignant neoplastic diseases. Although most meningiomas are benign (Clarke, 2002), three reports of meningiomas were included because the authors argued for malignancy (Pahl, 1986; Ricci et al., 2015). Reports of neoplasms that were not attributed to malignancy, or deemed possibly benign, were also not included (e.g. Waldron, 1998).

When demographic information derived from population level data was reported, albeit rarely, it was also documented in the 2018 CRAB Database. Consistently assessing detailed population data, with respect to individual “case studies,” is important for gaining a better understanding of potential disease prevalence within a burial population (Marques et al., this issue). However, due to their limited representation in the studies assessed, and thus limited possibility for meaningful comparative analysis, population data are not considered in the current study.

Table 1: Inclusion and exclusion criteria for the 2018 CRAB Database

<u>INCLUSION CRITERIA</u>	<u>EXCLUSION CRITERIA</u>
<ul style="list-style-type: none"> • <i>Malignant</i> neoplastic diseases • <i>All</i> geographic regions • Individuals who died <i>before</i> 1900 CE • Humans and early hominins • Data from skeletons and preserved bodies • Documents in English, in other languages with English translations, or in languages understood by the authors of this paper • Evidence documented in books; edited book chapters; journal articles; conference presentation abstracts; university undergraduate, masters, and doctoral dissertations and theses; and bioarchaeological reports 	<ul style="list-style-type: none"> • <i>Benign</i> neoplastic diseases • Neoplastic diseases with uncertain malignant or benign designation • Individuals who died <i>after</i> 1900 CE • Non-hominin primates and other species • Documents in languages not understood by the authors, or in languages without English translations available • Government required reports (e.g. Cultural Resource Management reports)

From the data selected for inclusion in the CRAB Database, both quantitative and qualitative data were collected with a focus on a number of data categories. These categories fall within four main groups: 1) geography, chronology, and context, 2) demography, 3) methods and diagnosis, and 4) sources. All data categories currently recorded in the Database are listed in Table 2 (data categories included in this systematic review appear in **bold** text). However, this particular paper focuses on the measurable data that are most pertinent to the aim of this study: providing a foundation for conducting future research into the global history of cancer by compiling and synthesizing available and accessible paleo-oncological data, and by identifying methodological trends and challenges and their potential impact on differential diagnoses and comparative studies. The other data are not summarized in this paper because; (a) there was insufficient information reported in previous studies to warrant a useful examination (e.g. associated geographical, chronological and contextual information); (b) they were not necessary for achieving the aim of this study (e.g. burial identification numbers

are not needed); and/or (c) they did not fit into the limited length and scope of this paper (e.g. full description of lesions). The exclusion of specific categories of data are shown in Table 2 in bold.

Table 2: Categories of data recorded in the 2018 CRAB Database

GEOGRAPHY, CHRONOLOGY & CONTEXT	DEMOGRAPHY	METHODS AND DIAGNOSIS	SOURCES
Location of burial site <i>e.g. site name</i>	Sex <i>e.g. Female, Male</i>	Diagnostic methods <i>e.g. macroscopic, radiological, microscopic, biomolecular</i>	Primary source of study <i>i.e. bibliographic reference of original study</i>
Geographic region & Country <i>e.g. Northern Africa, Egypt</i>	Age-at-death/age group <i>e.g. 20-25, Young-adult</i>	Types of cancer(s) diagnosed <i>e.g. metastasis to bone or multiple myeloma</i>	Year of publication and/or dissemination <i>e.g. 1963</i>
Time range of the burial (B.C.E. - C.E.) <i>e.g. 100 B.C.E. – 100 C.E.</i>	Total individuals in the burial population ^{a, c}	Detailed description of evidence/lesions ^c	Source material and publishing body <i>e.g. journal article from IJPP</i>
Time period <i>e.g. Roman Period</i>	No. of individuals analyzed in the burial population ^{a, c}	High quality images of lesions ^c	Abstract ^b
Burial identification number ^b <i>e.g. Burial #1243</i>	No. of males and females in the burial population ^{a, c}	Use of lesion distribution figure <i>e.g. skeletal chart</i>	Secondary source ^b <i>e.g. bibliographic references of sources that describe previous studies</i>
Mortuary context description ^{a, c} <i>e.g. multi-burial tomb</i>	Demographic profile of the burial population ^{a, c} <i>i.e. number of adults in age-at-death groupings with sex-estimations</i>	Differential diagnosis <i>i.e. alternative diagnoses considered</i>	
Associated cultural information ^{a, c} <i>e.g. grave goods, orientation</i>		Completeness of remains <i>e.g. only skull present</i>	
		Level of preservation <i>e.g. excellent, good, fair, poor</i>	
<ul style="list-style-type: none"> – Bold: data categories that were considered in this review. – The regular font data categories were not considered in this review because of the reasons outlined above at the end of 2.1.2 (a), (b), and (c), and have been reserved for future studies. 			

3.2 Methods

In an effort to standardize the collected data and facilitate data synthesis, specific procedures were developed for the recording and assessment of qualitative, quantitative, and often inconsistently reported data. These methods are described below.

3.2.1 Geography, Chronology, and Context

The United Nations (UN) Statistics Division developed an organizational system, known as a geoscheme, that classifies countries of the world into geographic groups, hereafter referred to as regions (1999) (Figure 1). The UN geoscheme was utilized to organize the 2018 CRAB Database for the purposes of standardization, ease of analysis, and for potentially allowing future comparisons with modern health data (keeping in mind that regional borders in antiquity would have been different).

When the time period and/or time range were reported by the original author(s), that chronological information was included in the database according to the Common Era notation system (BCE, CE). Few authors did not indicate the time period or time range of a person's death in the original study due to that information being indeterminate. However, when age-at-death was reported, a chronological interval for age-at-death was usually presented as opposed to a specific year of age. In these cases, the mean of this age interval was used in statistical representations of chronological context.



Figure 1: United Nations geographical subregions, referred to as *regions* in this report. Source: T. Seppelt / CC-BY-SA-3.0

3.2.2 Demography

The estimated sex of individuals was recorded according to the following categories: *female*, *male*, and *indeterminate sex*. All sex estimations were taken at face value from the studies included in this survey, regardless of the methods used. There are still no widely accepted osteological standards for accurately assessing the sex of non-adult skeletons (Scheuer and Black, 2004). Therefore, for the purposes of this study, the sex of non-adults with an estimated age-at-death of less than 19 years, regardless of the author's original assessment, were recorded as *indeterminate*.

The age group assigned to individuals was categorized according to Buikstra and Ubelaker (1994): *non-adult* (under 20 years), *young-adult* (YA, 20–34 years), *middle-adult* (MA, 35–49 years) and *old-adult* (OA, over 50 years). Both specific age-at-death ranges (e.g. 20-30 years) and general age groupings (e.g. young-adult “YA”) were recorded. When the age-at-death estimation could be attributed to two or more age groupings, age group was determined from the mean age of the range. For example, in Molnar et al.’s (2009) study of paleo-oncological evidence in Hungary, one of the described individuals was estimated to be between 40 and 55 years old at the time of their death; an age range that could be attributed to both the aforementioned middle-adult and old-adult age categories was thus calculated for use in this study. Thus, the mean of the given age range (40-50 years) was calculated (mean = 47.5 years) and used to assign this individual to a single age category (middle-adult). Although this method of assigning individuals to age cohorts simplifies a broad comparison of age-at-death data, it is accepted as problematic because the mean of an age-at-death estimation does not accurately represent the age-at-death of the individual. Additionally, by definition, “estimation” of age-at-death reported in the original studies will likely not be entirely accurate either. Therefore, the age-at-death data presented in the results of this study are only to be considered broadly, and perhaps only as a starting point for more quantitatively precise statistical analyses which lie beyond the scope of this particular study.

3.2.3 Methods and Diagnosis

Although methods specifically for paleo-oncological diagnoses currently lack broadly accepted standards, as opposed to more general standards for paleopathological recording (e.g. in the United States: Buikstra and Ubelaker 1994, and in the UK: Brickley and McKinley 2004; Mitchell and Brickley 2017), the detailed documentation of pathological processes evident in human remains is expected as a first step to differential diagnosis in any paleopathological study. Paleo-oncological reports should include: the presence, distribution, and detailed description of bone forming and/or destroying lesions, distribution patterns, potential differential diagnoses, and the analytical methods employed. These reports should also consider the level of preservation of the remains, which could impact a reliable diagnosis. Each study in the 2018 CRAB Database was assessed and scored for the above information.

In studies where two diagnoses were considered equally probable, both diagnoses were quantifiably recorded. For example, in a study where multiple myeloma and bone metastasis were equally considered, both diagnoses received the same data logging treatment. That is, multiple myeloma = 1 and metastatic carcinoma =1. This strategy was employed so as not to skew the diagnostic data when multiple diagnoses were made. As such, there is a duplication of “cases” in some instances, which should be considered when viewing the data resulting from this review.

3.2.4 Sources

Data were recorded in order to observe trends in particular interests, dissemination methods, and accessibility of data in paleo-oncological research. Data collected include the publication type (e.g. book, journal article), publishing body (e.g. *International Journal of Paleopathology*), language of publication, and publication date.

4. Results

4.1 Geographical and Chronological Spread of Evidence

Skeletons and preserved bodies recorded in the database were recovered from 14 of the 23 regions identified in the UN Statistics Division geoscheme (1999) (Figure 1), representing 35 countries (Appendix B). Table 2 is a quantitative summary of the data in the database, organized by geographic region. Two hundred and seventy-two individuals were reported from 198 funerary contexts in 154 studies. Figures 2 and 3 illustrate the global distribution of the evidence. The greatest number of individuals with evidence of cancer was recorded from the region of Northern Europe (18.7%, 51/272), followed closely by Northern Africa (16.9%, 46/272) (Table 3); 88.2% (45/51) of the individuals attributed to Northern Europe were recovered from the United Kingdom, and 89.4% (42/47) of the individuals attributed to Northern Africa were recovered from Egypt.

Table 3: Number of individuals (*n*) with skeletal evidence of cancer distributed by age-at-death, sex estimation, and proposed diagnosis by geographic region, as recorded in the 2018 CRAB Database.

REGION	<i>n.</i>	Age-at-death (<i>n</i>)*					Sex (<i>n</i> **)			Diagnosis (<i>n</i> ***)				
		NA	YA	MA	OA	Unk	M	F	Unk	BM	MM	OS	NPC	Other
Northern Africa	46	--	8	11	9	18	20	19	7	24	12	5	5	4
Southern Africa	1	--	--	--	--	1	--	--	1	--	--	1	--	--
Western Africa	1	--	--	--	--	1	--	--	1	--	--	1	--	--
Northern America	36	4	8	16	5	3	15	17	4	16	14	3	1	2
Central America	1	1	--	--	--	--	--	--	1	--	--	1	--	--
South America	25	3	1	7	1	13	8	4	13	19	1	1	--	4
Eastern Asia	5	--	1	1	1	2	4	1	--	3	1	--	--	0
Southeastern Asia	1	--	1	--	--	--	--	1	--	1	--	--	--	1
Southern Asia	1	--	--	--	--	1	--	--	1	--	--	--	1	--
Australia & New Zealand	4	--	--	2	1	1	3	1	--	1	1	--	2	--
Eastern Europe	38	--	3	9	21	5	24	10	4	28	7	3	--	--
Northern Europe	51	--	10	10	15	16	26	19	6	35	7	5	--	6
Southern Europe	24	3	4	5	5	7	9	8	7	13	2	5	--	5
Western Europe	38	3	3	16	8	8	18	14	6	21	10	7	--	2
Total	272	14	39	77	66	76	127	94	51	161	55	32	9	24

n = total number of individuals identified and represented in the review

*Age-at-death: NA = non-adult (0-20), YA = young-adult (21-34), MA = middle-adult (35-49), OA = older adult (50+), Unk = unknown or indeterminate

**Sex: M = male, F = female, Unk = unknown or indeterminate because a non-adult or a poorly preserved adult

***Diagnosis: BM = bone metastases, MM = multiple myeloma, OS = osteosarcoma, NPC = nasopharyngeal carcinoma, Other = other malignant neoplasms. In studies where two proposed diagnoses were considered equally probable, both diagnoses were quantifiably recorded. As a result of this duplication, the total number of diagnoses equals 281 despite there having been only 272 individuals studied.

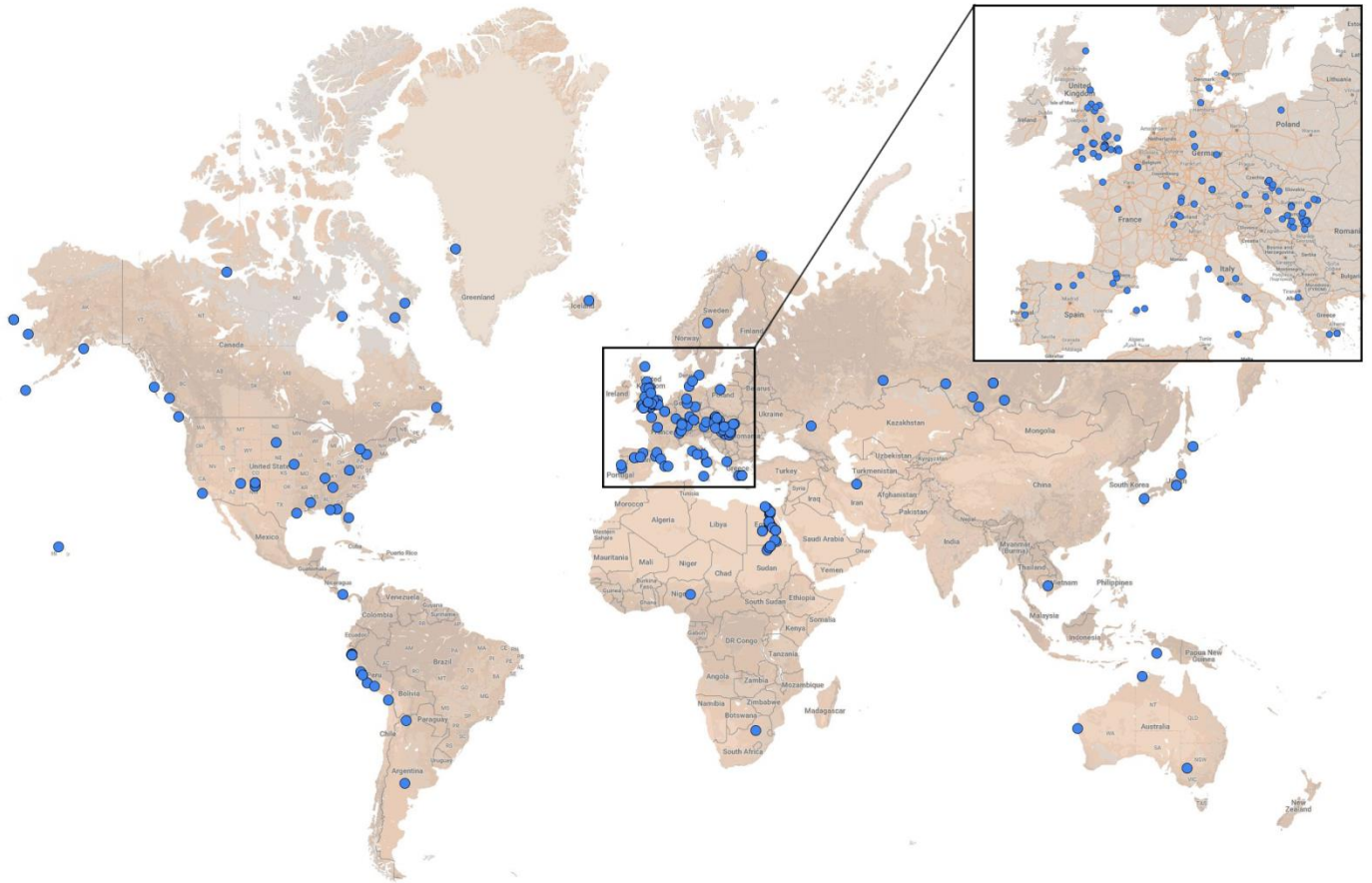


Figure 2: Global distribution of archaeological sites and funerary contexts containing individuals exhibiting evidence of cancer ($n=272$ from 198 archaeological contexts)

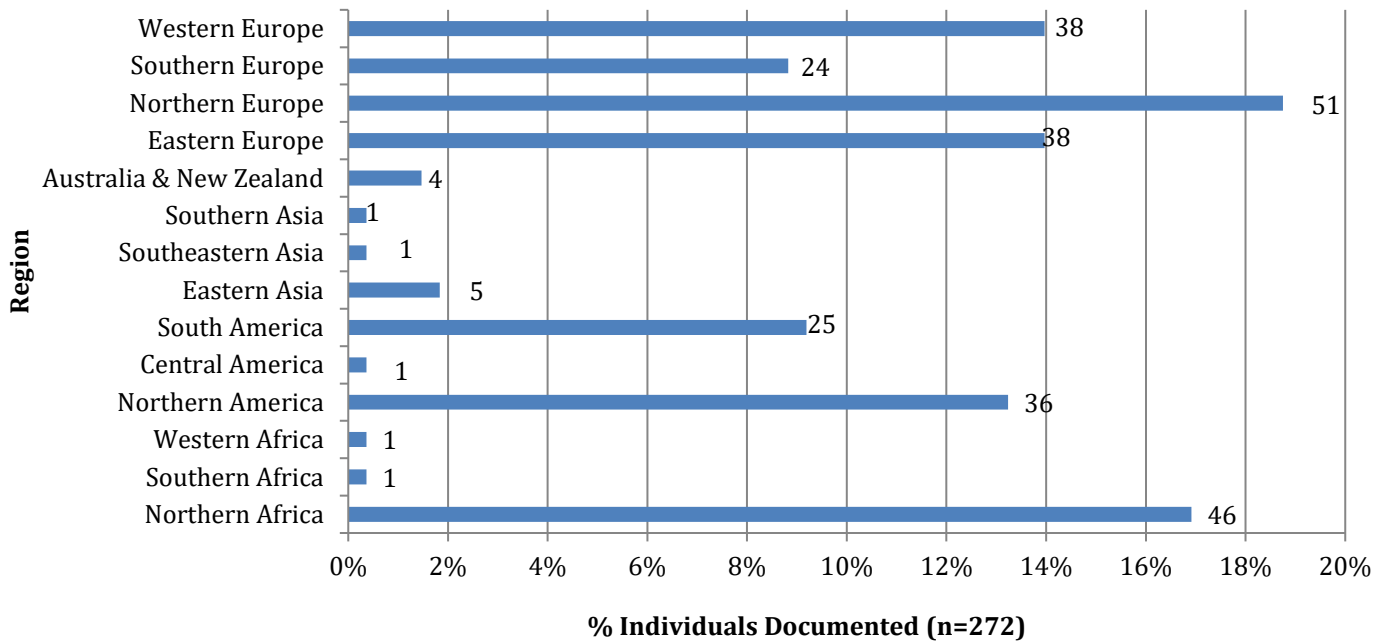


Figure 3: Global distribution of the number and percentage of individuals recovered with evidence of cancer by geographic region. *Percentage (%)* is indicated on the x-axis and *number (n)* is given at the end of each column.

Of the studies that provided time ranges for the paleo-oncological evidence (87.1%, 237/272), many relied upon relative dating provided by grave good seriation, and many did not indicate a dating method. However because dating methods were not systematically recorded, they will not be discussed in this study. Aside from paleoanthropological evidence from three early hominins (Odes et al., 2016; Tobias, 1960; Domett and Buckley, 2012), for which one is highly controversial (Tobias, 1960), the documented individuals with bioarchaeological evidence of cancer date from as early as 4000 BCE (Strouhal and Kritscher, 1990). The evidence generally increases as time progresses and the majority of evidence documented in this study dates to between 1000 CE and 1499 CE (Figure 4).

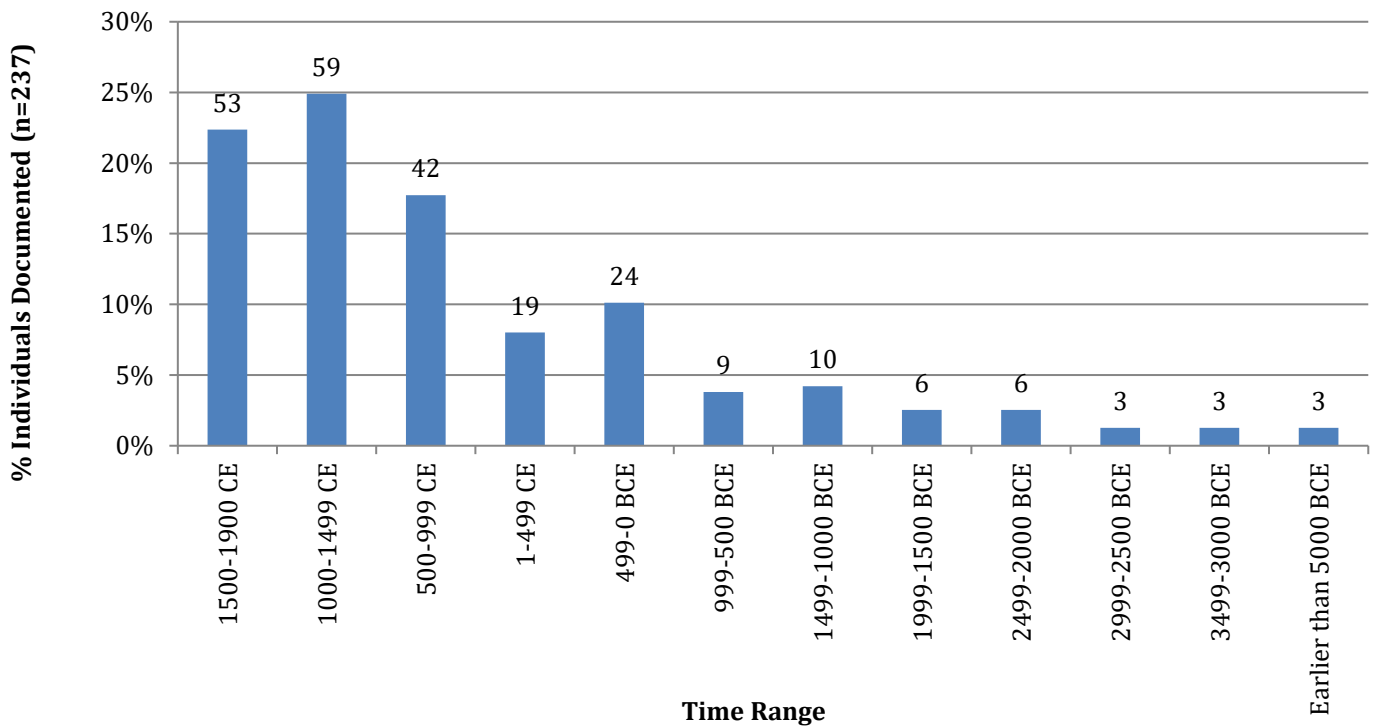


Figure 4: Temporal distribution of cancer in the studies where time period was recorded (n=237). *Percentage (%)* is indicated on the y-axis and *number (n)* is given at the top of each column.

4.2 Demography

In the studies documented, sex had been estimated in 81.3% (221/272) of individuals and the remaining 18.8% (51/272) were either reported as *indeterminate sex* or a sex estimation was not given. Adult males are represented more than adult females at 127(M) to 94(F). Females outnumber males in the young-adult age group at 22(F) to 16(M), and males outnumbered females in the two dominant age groups: middle-adults at 49(M) to 28(F), and old-adults at 43(M) to 23(F) (Figure 5). Fourteen individuals documented as non-adults were recorded in the database with indeterminate sex.

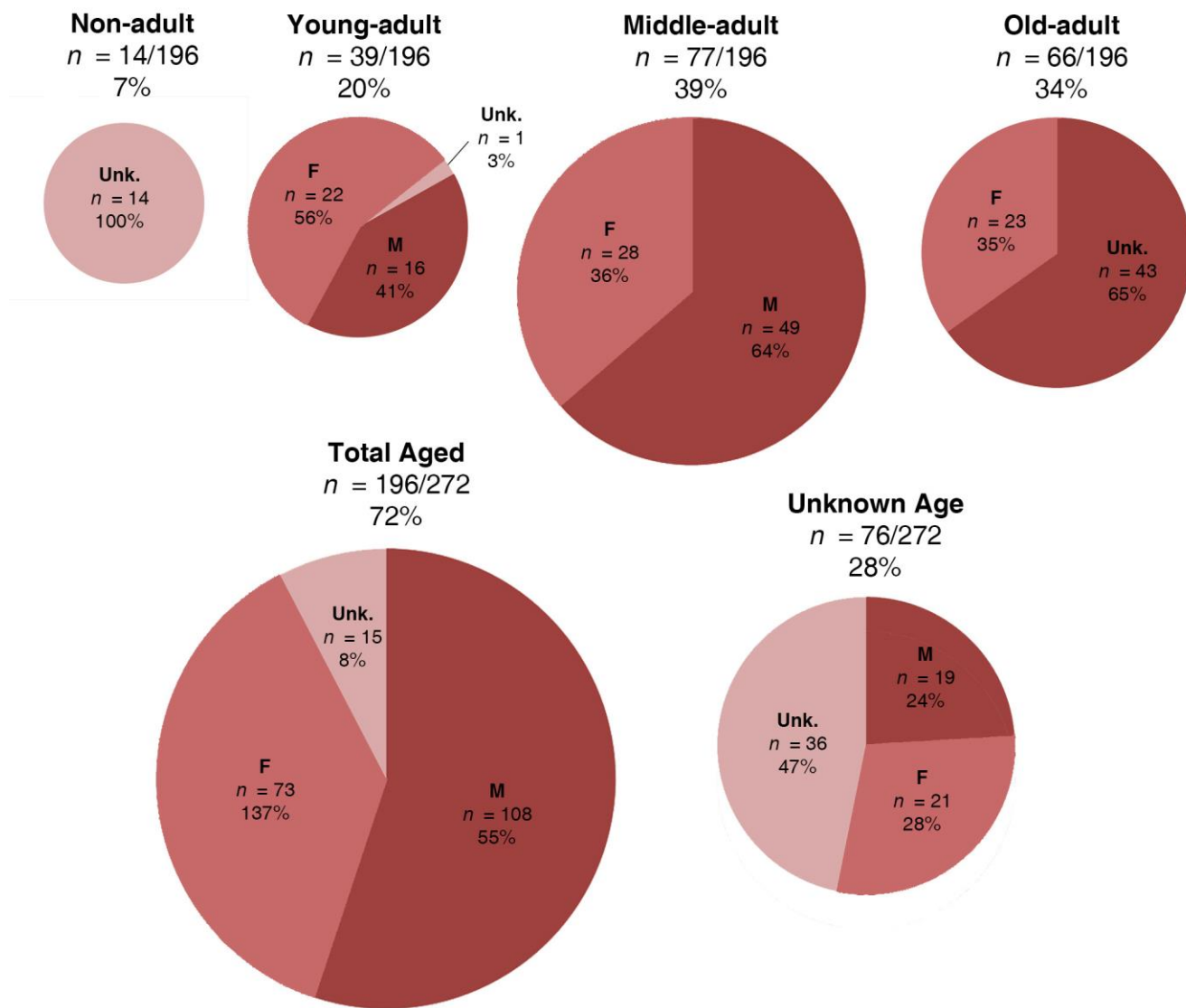


Figure 5: Age-at-death and sex estimations of individuals with evidence of cancer in the studies in this review

Figure 5 shows the age-at-death and sex distribution of the individuals with evidence of cancer. Age-at-death was estimated for 72.1% (196/272) of the individuals. The data recorded show that 7.1% (14/196) of those individuals were classified as non-adult (0-19), 19.9% (39/196) were classified as young-adult (20-34 years), and 39.3% (77/196) were classified as middle-adult (35-49 years). The combined number of individuals under 49 years-at-death is 130 (47.8%), surpassing the 66 (24.3%) individuals in the old-adult age group (over 50 years-at-death).

4.3 Diagnostic Methods Used for diagnosis

Macroscopic methods of analysis were used in 211 studies where methodological information was given. Radiography was used in 58.3% of the studies (123/211), microscopy in 22.3% (47/211), and biomolecular methods in 2.8% (6/211) (Figure 6). The distribution pattern of skeletal or soft tissue lesions were included in only 9.5% (20/211) of studies.

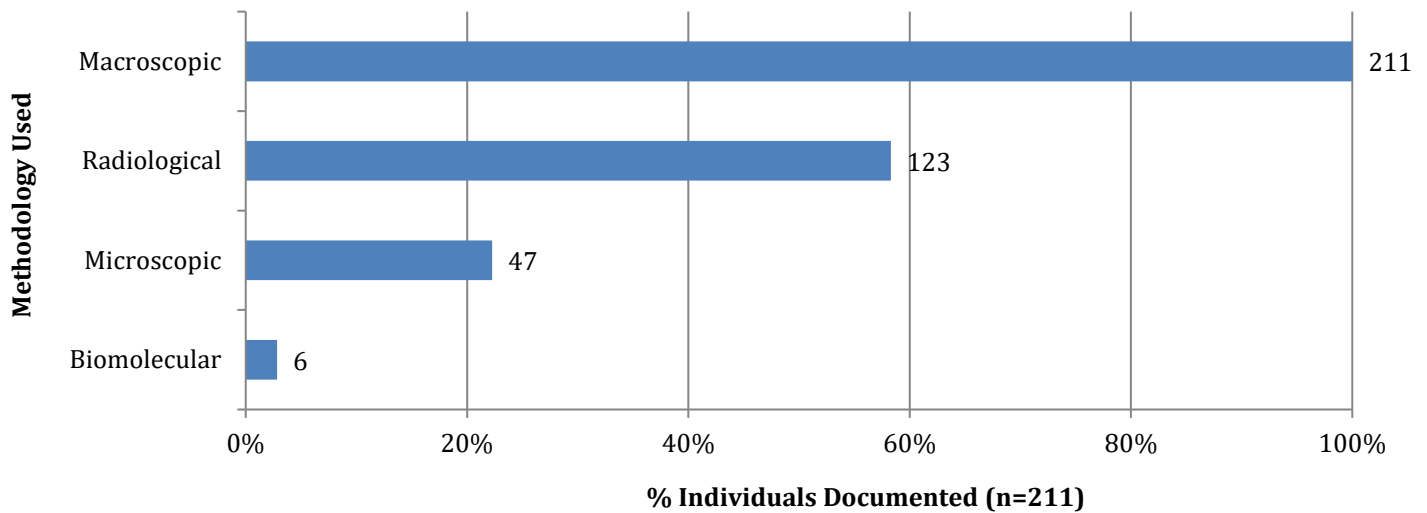


Figure 6: Diagnostic methods used. *Percentage (%)* is indicated on the x-axis and *number (n)* is given at the end of each bar.

4.4 Types of Cancers Diagnosed

There were 281 diagnoses of neoplastic disease reported in the 272 individuals studied. Several authors gave multiple diagnostic options deemed equally likely for a single individual with neoplastic lesions, and therefore the number of diagnoses exceeds the total number of individuals. Bone metastasis was diagnosed in the majority of individuals, representing 57.03% (161/281) of studies; multiple myeloma was diagnosed in 19.6% (55/281), osteosarcoma in 11.4% (32/281), and nasopharyngeal carcinoma in 3.2% (9/281). Twenty-four other cancers were also documented (Figure 7).

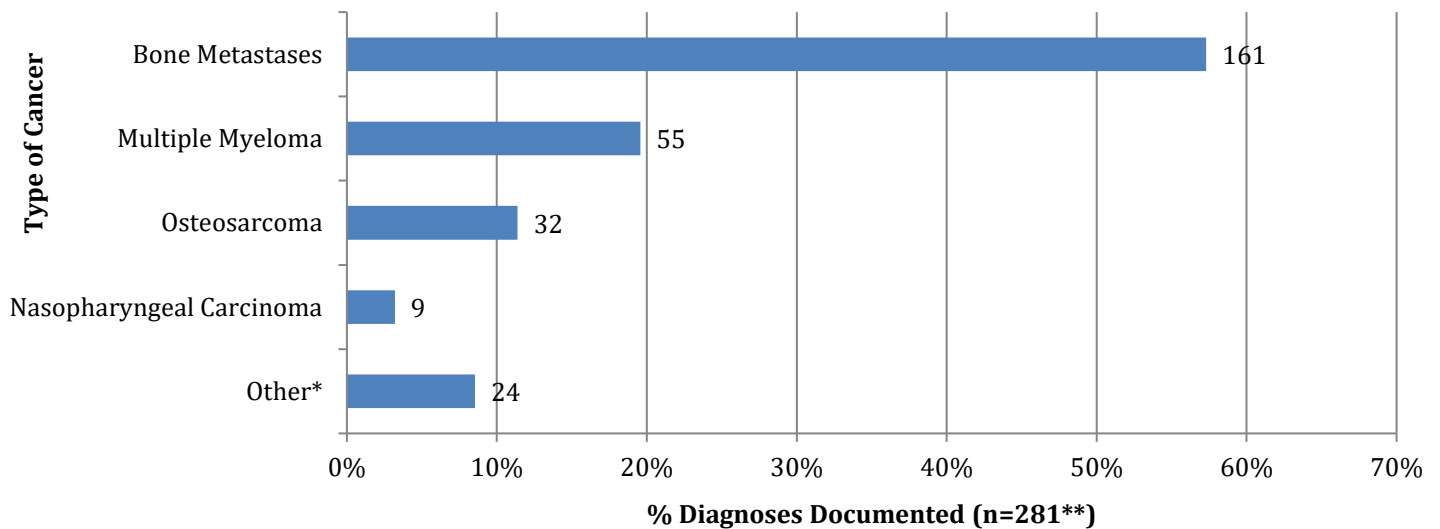


Figure 7: The number and percentage of paleo-oncological diagnoses (several authors gave multiple diagnoses deemed equally likely for a single individual). *Percentage (%)* of all recorded diagnoses is indicated on the x-axis and *number (n)* of diagnoses is given at the end of each bar.

*Other types of cancer documented: adenocarcinoma of the colon (n=1), chondrosarcoma (n=3), Ewing's sarcoma (n=1), gingival carcinoma (n=1), malignant hemangioendothelioma (n=1), malignant hemangioma (n=1), leukemia (n=3), malignant intradiploic cyst (n=1), malignant meningioma (n=3), gingival carcinoma (n=1), rhabdomyosarcoma (n=2), rectal carcinoma (n=1), Paget's sarcoma (n=1), myeloid epulis (n=1), an unknown sarcoma, and three unknown malignancies (n=3).

** 281 = number of diagnoses of 272 individuals (i.e. several authors gave multiple diagnoses)

Authors suggested the tissue of origin for metastatic cancers in 72 of the 161 (44.7%) individuals with a diagnosis of bone metastasis (Figure 8). Prostate cancer was the suggested origin of the malignancy in 17.4% (28/161), breast cancer in 11.2% (18/161), malignant melanoma in 5.6% (9/161), and lung cancer in 5.0% (8/161) of the documented individuals.

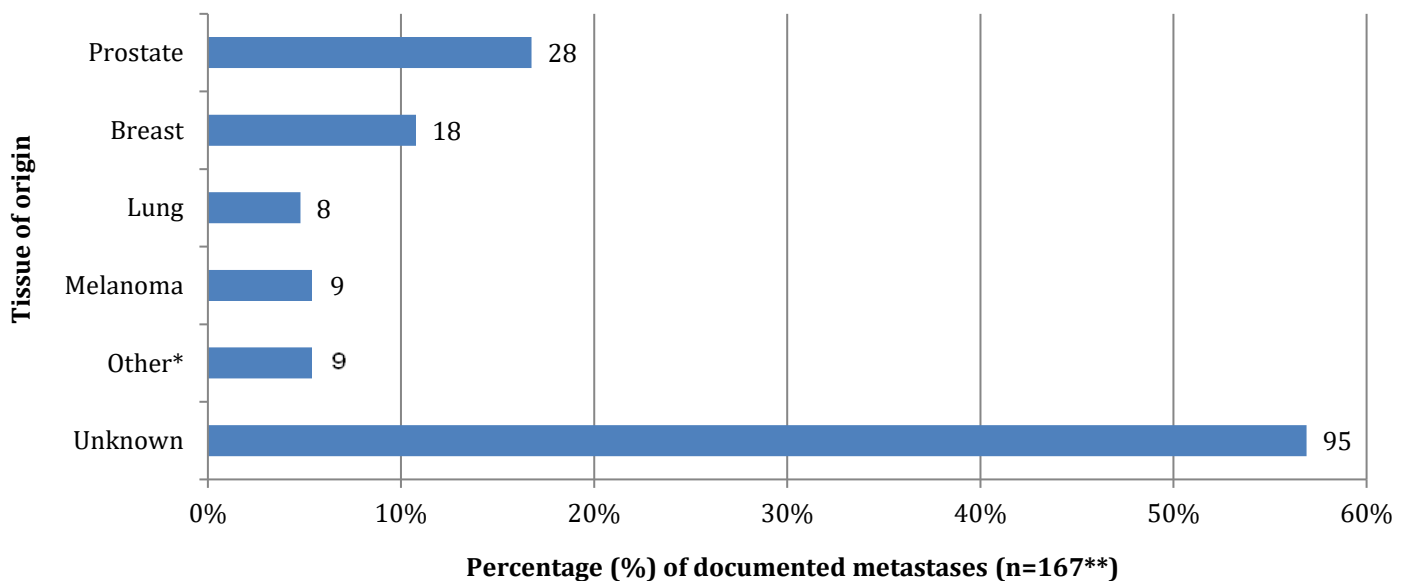


Figure 8: Estimated tissues of origin for metastatic cancers identified in this study. *Percentage (%)* is indicated on the x-axis and *number (n)* is given at the end of each bar.

*Other tissues of origin suggested for metastatic cancers were: 1) Kidney (or lung) (Strouhal et al., 1996); 2) Mouth, tongue, or throat (Walker, 2012); 3) Thyroid, esophagus, or salivary gland (Cassidy, 1977); 4) Cervix or stomach (Mark, 2007); 5) Testis or extragenital (Zink et al., 1999); 6) Nasopharyngeal carcinoma (Pahl et al., 1987; Wells, 1963)

** 167 = number of diagnoses of 161 individuals (i.e. several authors gave multiple diagnostic options)

Diagnostic information was collected from reports on 211 of the 272 (78.7%) individuals recorded in the CRAB Database, as methods of diagnoses were not found for the remaining individuals. Among the studies that provided methodological information, only 51.7% (109/211) reported a full differential diagnosis or explored alternative diagnoses for the described lesions. These included benign tumors, non-neoplastic conditions, and alternative cancer diagnoses. Among other malignancies, bone metastases (35.8%, 39/109) and multiple myeloma (35.8%, 39/109) were the most common alternative diagnoses. Multiple myeloma was most often referenced as an alternative to bone metastasis, and vice versa. Tuberculosis (TB) was the most common non-

neoplastic disease mentioned (15.6%, 17/109) (e.g. Ortner, 2003), and localized infection was considered an alternative diagnosis in 16.5% (18/109) of the studies (e.g. Lieverse et al., 2014).

4.5 Publishing Trends

The majority of studies recorded were published in peer-reviewed journals. Books and edited book chapters, conference presentation abstracts, and bioarchaeological reports comprise the rest of the source types (Figure 9). In total, 154 documents presented information on 272 individuals in this study.

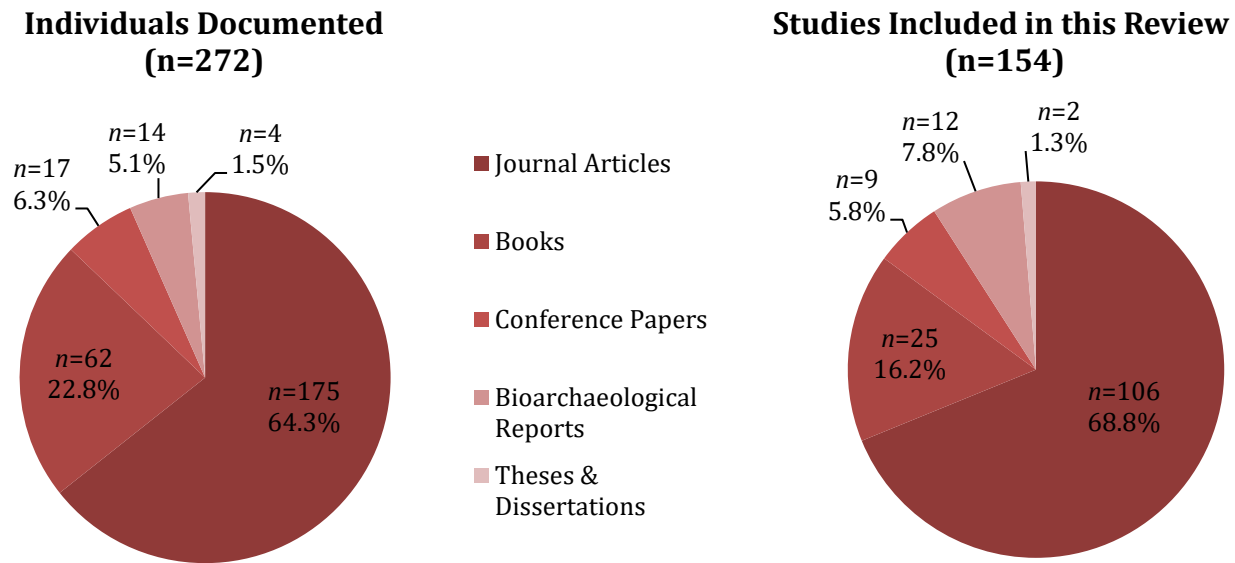


Figure 9: Number and percentage of paleo-oncological reports and individuals with paleo-oncological evidence per publication type.

Fifty different journals contained reports of cancer in skeletons or preserved bodies. The three journals containing the majority of studies are the *Journal of Paleopathology* (28), the *International Journal of Osteoarchaeology* (15), and the *International Journal of Paleopathology* (13). Papers written in seven languages other than English represent 14.3% (22/154) of the studies (Czech, French, German, Hungarian, Italian, Slovenian, Spanish). There are undoubtedly other non-English language sources concerning paleo-oncological research. However, they were either inaccessible to the authors, or translations were not found.

Most studies of individuals with evidence of cancer in this review were conducted in the 1990s and between 2000 and 2010, in total representing 39.3% (107/272). Figure 10 illustrates the temporal distribution of studies and the number of individuals documented. The two present a similar pattern, increasing after the 1940s.

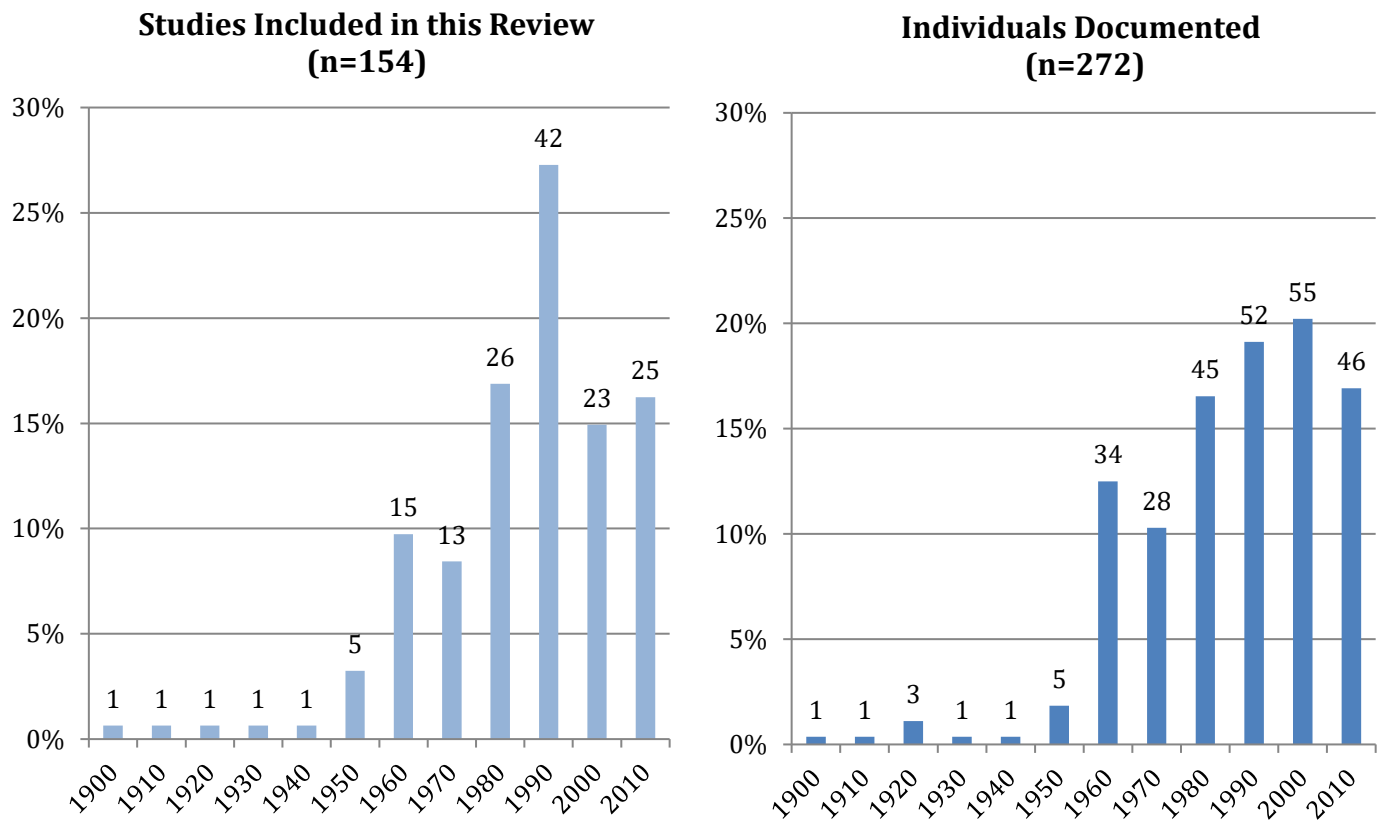


Figure 10: The percentage of studies included in this review (n=154) and individuals documented (n=272) with evidence of cancer, presented by publication or dissemination date. *Percentage (%)* is indicated on the y-axis and *number (n)* is given at the top of each column.

5. DISCUSSION

The aim of this systematic review was to synthesize and discuss the paleopathological evidence for cancers in surveyed studies. These data are now discussed, followed by some practical and methodological limitations that challenge paleo-oncological research, and some recommendations. Prior to discussing the data presented, it is important to understand that data concerning malignant neoplastic diseases in the past cannot be realistically compared to modern cancer data, and thus such comparisons are not attempted in this review (cf. Wood et al., 1992 and Wright and Yoder, 2003). There are also other limitations that will be considered through this discussion.

5.2 Geographic Distribution of Evidence

Geographic distribution of cancer is considered in this study as it may provide information on the global distribution of reported paleo-oncological evidence. It should also be noted that the geographic distribution of cancers in antiquity only reflects each individual's burial place or findspot, and does not account for migration before or after the development of cancer. Some people buried in the cemetery may not have been local to the region, and others who were local may have been buried elsewhere. Furthermore, the complete cemetery may

not have been recovered during excavation and cemetery populations cannot be assumed to represent the living population, thus further complicating data integration and interpretation, and restricting interpretation of this data set to the worldwide distribution of paleo-oncological evidence studies to date (cf. Waldron, 1994: 12-16; Wilson, 2014).

As a result of these aforementioned limitations, the geographic clustering of evidence seen in this study is not reflective of the epidemiological distribution of cancers in antiquity, but instead represents regional variations including, but not limited to: preservation environment, population size, selective scholarly attention, accessibility to study human remains, and the history of paleopathological study in a particular region (Buikstra and Roberts, 2012). The regions with the most evidence of cancers (Northern Europe and Northern Africa) reflect some of these biases in the data: the arid climate of Egypt and Sudan is excellent for the preservation of human remains, and paleopathological attention is strong in both Europe and Egypt.

Although studies of geographical distributions of paleo-oncological evidence will always be heavily biased by preservation environment, it is important to encourage the continued search for paleo-oncological evidence in areas with limited evidence to date. Furthermore, it is important that all paleo-oncological studies include information regarding the findspot of the affected human remains. This is because the occurrence of cancer can be caused by genetic mutations that are endemic specific geographical regions and populations (e.g. people with Ashkenazi Jewish ancestry are more likely to carry the BRCA1 and BRCA2 mutations, making them more susceptible to breast, ovarian, and prostate cancers [Rich et al., 2015]). As such, outlying prevalence rates may be explained by the known increase in susceptibility to oncogenic mutations in the population and differential diagnoses can be conducted with the consideration of known genetic and environmental carcinogens.

5.3 Temporal Distribution of Evidence

The chronology of cancer has been an issue of debate for many years (e.g. Sigerist, 1951; Putschar, 1966; Brothwell, 1967; Strouhal, 1994; Waldron, 1996; Zink et al., 1999; Nerlich et al., 2006; David and Zimmerman, 2010; Faltas, 2011; Binder et al., 2014; Marques et al., this issue; Ewald, this issue). This issue is considered to be important as the paleo-epidemiology and evolution of cancer may provide more information about the factors contributing to oncogenesis. The synthesis of these studies contradicts a common belief that cancers are modern human-influenced diseases. Evidence of cancer in early hominins may date to as early as 1.8 million years ago (Odes et al., 2016), with evidence from anatomically modern humans currently dating as far back as 4000 BCE, as seen in an individual from Mauer, Austria diagnosed with multiple myeloma (Strouhal and Kritscher, 1990). In later evidence, Steinbock (1976) reported an individual with multiple myeloma from Indian Knoll, Kentucky, dated to 3300 BCE, and Webb (2009) reported a mature male individual with nasopharyngeal carcinoma from the Murray River in Euston, Australia dating to the Middle Holocene (broadly between 3050-550 BCE). The remaining evidence dates to later than 2700 BCE, showing a progressive trend toward increasing frequency over time, with the majority of the evidence occurring in the 2nd millennium CE.

It should be noted that older burials are more prone to taphonomic destruction and in some cases may not be recovered at all due or the halting of excavation at a higher layer that is deemed to be more interesting to the researchers and/or the public. Some of the more modern burials are also inaccessible due to cultural restrictions on excavations (e.g. Muslim burials must generally be left untouched). This may help explain why evidence of cancer BCE is dominated by studies from Northern Africa, whereas Northern Europe contains most of the more recent evidence in history.

5.4 Demographic Analysis

Biological sex and age as well as other variables, such as ancestry, often influence susceptibility and exposure to disease (Roberts and Manchester, 2007) and when documented in paleoepidemiological studies, can contribute to a stronger paleopathological profile of a population (Waldron, 1994). In the case of neoplastic diseases, detailed demographic (and cultural context) information could help to identify potential cancer risk and possible exposure to etiological factors (Roberts and Manchester, 2007). These age and sex trends should be taken into account, when appropriate, during differential diagnoses.

Some cancers preferentially target specific age groups ; for example, osteosarcomas originate at the metaphyses of long bones during periods of rapid growth, and therefore mainly affect non-adults (DeVita et al., 2015). Cancers of the blood, brain and nervous system are also more common in non-adults but can often be seen in young-adults, whereas cancers of the breast, prostate, lung, and colon significantly affect older adults over 50 years (Gebhardt et al., 2008). Some cancers today are also seen more in females or males. For instance: prostate and testicular cancers are specific to males whereas gynecological cancers are specific to females, and breast cancer is seen more in females than males (Virk and Lieberman, 2007).

As presented in the data, cancers were observed more in males than in females but, as previously mentioned, there are challenges in the estimation of overall population frequencies without demographic data for the population from which the individual derives (Marques et al., this issue). Recent clinical research shows that the current global trend in cancer susceptibility and mortality is consistently weighted toward males, with a cancer mortality rate 18% higher than that of females (Dorak and Karpuzoglu, 2012). According to the same study, men have a 44% chance of developing cancer within their lifetime, compared to women at 38%. Furthermore, the sex differential in the susceptibility to any disease is dependent on various risk factors, such as those experienced in people's socio-cultural environments, or through genetic predisposition, reflecting susceptibility and resistance. A more in-depth assessment of the sex-specific results of this review will require detailed exploration of contextual information in the future.

Furthermore, in the absence of sex-specific population data for the individuals studied in this review, it is impossible to estimate the percentage of males or females affected by cancer. As such, comparison of the sex-specific data in this study should be taken at face value, without trying to extrapolate sex-specific trends in cancer's past prevalence in the population from which the individual derived and indeed more widely from a global perspective. The same principles should be applied to the age-at-death profiles presented in relation to the paleo-oncological evidence.

Today, cancers are primarily considered diseases of old age, and therefore finding a higher cancer prevalence in old adults might be expected in the archaeological record (Ortner, 2003, Howlader et al., 2017). However, young-adult cancers are steadily increasing today (Howlader et al., 2017). In this survey, the old-adult cohort was represented in nearly one-third of studies, while most of the other two-thirds were documented as young and middle-aged adults. It is possible that taphonomic processes and/or funerary practices may have contributed to these age-at-death-specific differences, but also the area of a funerary site that was excavated as the (often) partial excavation of some cemetery populations can lead to biases in the sex and age distribution (and thus the inherent absence of specific sex or age group related cancers). Although it has not been investigated in this survey of data from multiple sites and funerary contexts, it is important to consider the possibility of an underrepresentation of old-adult and non-adult burials due to lower bone mass and density, respectively, making their bones more susceptible to decay and survival into the archaeological record (Aufderheide, 2011; Stodder, 2008). Likewise, non-adults may have been buried non-normatively for the region and time period and were therefore not exhumed during the excavation of a particular site.

Furthermore, It is probable that there is an underrepresentation of individuals older than 50 years-at-death in the archaeological record primarily due to (a) the problems of accurately ageing skeletons into older age-at-death categories (Hoppa and Vaupel, 2002:), (b) the fact that some of the current age estimation methods were not developed at the time that many of these studies were written, and (c) that bones of older individuals can be more susceptible to taphonomic damage (e.g. having underlying osteoporosis), and are therefore less likely to be preserved enough for sex and age-at-death estimations or pathological observations to be made (Milner et al., 2008). Although the limitations of adult age-at-death estimations are far more complex than can be discussed in this paper, it is important to consider possible age estimation errors when conducting differential diagnoses or discussing whether the amount of neoplastic disease evidence in human remains correlates to life-expectancy estimations. The questionable accuracy of osteological methods for accurate age-at-death estimation in adults, and particularly for older adults, suggests that adult age-at-death estimations should be regarded carefully. Therefore, it may be hypothesized that the underestimation of actual adult age-at-death may have consequently resulted in selection of evidence for cancers affecting young- to middle-adults more than non-adults and old-adults. Newer methods for addressing the ages of adult skeletons, such as *transition analysis*, may be more reliable (Milner et al 2008; Milner and Boldsen 2012) and should be accounted for in future data comparisons.

Individuals who survived into old age may have been “healthier” than others in their cohort. Therefore, they were less susceptible to cancers. Conversely, those individuals who lived shorter lives following an expression of cancer would have been less likely to experience cancer metastasizing to their bones, and could be easily overlooked in the archaeological record (Wood et al. 1992).

The *osteological paradox* may also explain the higher prevalence of young- to middle-aged adult individuals with cancer in this study. This paradox covers three principles relating to archaeologically-derived human remains, and why they cannot be representative of the health of the population at any given moment (Wood et al., 1992): *demographic non-stationarity* (the population does not maintain a consistent rate of fertility, mortality, and age-at-death, making paleoepidemiological studies challenging), *selective mortality* (each age group is variably susceptible to specific diseases which may increase their risk of death), and *hidden*

heterogeneity of risks (individuals are variably susceptible to risks for disease). With these principles in mind, variations in the archaeological evidence of cancers within certain age-estimated groups may occur. Thus, the evidence of cancers identified within this review could reflect the limitations of skeletal and soft tissue preservation and recovery as well as the inability to calculate prevalence due to the limitations of the content of some sources on which this study is based (e.g. missing population data), or perhaps is reflective of a significantly different pattern of cancer than initially expected. In any case, it is becoming clear that the correlation of age-at-death and cancer prevalence is highly complex, and deserves more in depth research and discussion in paleopathology.

Although this study, and studies like it, may be useful for reflecting upon the relationship between modern and ancient occurrences of cancers, it is important to understand that data on mortality rates today are not directly comparable to the past. It is not possible to see *all* evidence of cancer due to previously discussed limitations, but it is also not possible to determine whether the deaths of the affected individuals considered in this review were specifically caused by cancer; other factors, unrecognizable in the skeleton, may have co-occurred and contributed to the death of the individual.

5.5 Diagnoses: Types of cancers represented, methods used, and differential diagnoses

5.5.1 Types of cancers

Bone metastases were identified in over half of the individuals reported (56%) while primary cancers were identified in 44% of individuals. In most instances, soft tissues are not preserved archaeologically, and only cancers that have affected the bone can be recognized. Therefore, it is expected that evidence of metastasis to bone would dominate the data. Authors attempted to identify the location of the primary tumor for almost half of the individuals documented with bone metastases. However, without preserved soft tissue or the identification of specific biomolecular markers, the location of the primary tumor cannot be definitively determined. Instead, many authors use the distribution of metastatic bone lesions, the probability of metastasis to bone from different primary tumors, and modern trends in specific cancer prevalence to estimate the most likely source of the metastasis. In addition to lesion analysis, sex- and age-specific risks for certain cancers were heavily referenced by authors when discussing the possible primary site of metastases in the sources reviewed. As a result of these combined considerations, breast and prostate cancers were the most commonly attributed sources for metastases. However, it should be remembered that modern data regarding cancer risk and metastasis are not necessarily directly comparable to paleo-oncological data and should be referenced with caution (Ragsdale, 1995; Ragsdale et al., this issue). Furthermore, consistent reference to the most common metastatic cancers runs the risk of overlooking less common metastatic cancers. As a result, preferred diagnoses for metastases lacking soft tissue or biomolecular evidence should always be considered with a consideration of the limitations.

5.5.2 Methods of analysis

All information from the paleo-oncological studies surveyed in this review was assumed to be accurate as verification of all evidence and interpretation was not within the scope of this paper. However, researchers in

early dated studies did not have access to techniques and technologies we have today to record all information to a standard. As such, without reappraisal studies, some of these data cannot be confirmed as accurate, especially considering the limitations of the methods used in studies from the early 1900s.

Diagnosis of neoplastic disease in paleopathology predominantly relies on the macroscopic detection of irregular new bone formation or destruction without the aid of radiological and historical methods, for example. Unfortunately, macroscopic evidence underrepresents the actual occurrence of all cancer because not all neoplasms are visible on the surface of the bone, and tumors originating in, or spreading to, *bone* only represent a fraction of all malignancies (Howlader et al., 2017; Marques et al. this issue). Applying multiple types of methods to diagnosis of cancers will be essential in the future to ensure more accurate diagnoses and a better understanding of cancer's presence throughout history. However, in most circumstances, due to financial and time constraints, and limited equipment accessibility, it is unreasonable to hope for or expect that a paleopathologist would apply radiographic, histological, and/or biomolecular analysis to every skeleton and preserved body in a population assemblage in order to suggest a diagnosis of cancer. Therefore, due to limited access to these analytical methods, a comprehensive paleo-oncological profile of a population is very unlikely (Rothschild and Rothschild, 1995).

The accurate recording and evaluation of cancerous lesions relies heavily on the state of preservation and completeness of the skeleton (or preserved body), as does the process of differential diagnosis. Over time, taphonomic processes can severely impact what can be recorded and the ability to ascertain demographic and pathological information. Furthermore, bones affected by disease that destroy bone (often seen in malignant disease) decay faster and are more susceptible to postmortem damage; this can impact the recognition of pathological characteristics and thus accurate diagnoses (Roberts and Manchester, 2007). Unfortunately, the relevant data regarding preservation and completeness of the remains were not regularly reported in the sources considered. Figures of the skeleton showing the distribution pattern of lesions and related completeness of the skeleton were only seen in 9.5% (20/211) of the studies (e.g. Luna et al., 2008). Understanding the complete distribution pattern of pathological lesions is imperative for developing differential diagnoses and the creation of these distribution figures is immensely valuable. Lesion distribution figures conceptualize both the preservation of the individual (e.g. bones preserved), *and* the pattern of skeletal and/or soft tissue involvement; these are two important factors in creating a more specific, accurate, and comparable diagnosis. Primary cancers affecting the skeleton are likely overrepresented in paleopathology because they are more visible in the archaeological record than primary cancers affecting soft tissues; primary tumors of the bones also occur much less often than primary tumors of the soft tissues (Howlader et al., 2017). Furthermore, many individuals who developed primary malignant tumors of the soft tissue may have died before the disease metastasized to the skeleton (Wood et al. 1992). In these cases, it is unlikely that a paleopathologist would detect cancer by macroscopic examination alone.

Radiology (plain film radiography and computed tomography) was the second most commonly used method for recording, analysis and diagnosis, as seen in over half of the studies. Rather than for routine "screening", this was generally used to confirm or supplement macroscopic analysis. Radiology may reveal early metastatic malignant lesions, and could be vital for accurate diagnosis in paleopathology (Mays, 2012; Rothschild and Rothschild, 1995). Radiology also has the potential to detect cancers affecting the skeleton or

soft tissue in preserved bodies, as demonstrated by Prates and colleagues (2011) and Willoughby and colleagues (2016). Despite the potential of radiological methods, they are not uniformly applied. This is likely due, in part, to time and monetary constraints, as well as limited access to equipment; the lack of radiological analysis affected the completeness of the data included in this study.

Microscopic methods (including histology) were employed in 21.8% of studies (stereoscopic, and scanning electron microscopy - SEM). These methods can potentially confirm or refute neoplastic diagnoses, and significantly contribute to more specific diagnoses (de Boer and Van der Merwe, 2016; Fornaciari et al., 1999).

Biomolecular methods also have great potential to expand on data collected using traditional diagnostic methods through the detection and analysis of micromolecules specific to cancers such as proteins, genes and other biomarkers, further contributing to our collective understanding of cancer paleoepidemiology (Nerlich, this issue). However, the detection of specific gene mutations is only one piece of evidence that may suggest a predisposition for the development of cancers, but it will not necessarily indicate whether a cancer was actually present in the remains of an individual from the past. For example, today the presence of BRCA1 and BRCA2 gene mutations indicates an increased risk of developing breast cancer, but cannot predict if it will occur (Antoniou et al., 2003; Chen and Parmigiani, 2007; Howlader et al., 2017). As with other paleopathological diagnoses, the use of multiple methods of analysis will potentially increase the specificity and accuracy of a diagnosis. However, due to the destructive nature of biomolecular and histological methods, paleopathologists must carefully weigh the benefits of this type of analysis against the risk to the integrity of the remains before proceeding with these methods. Furthermore, serious consideration should be made as to whether these methods should be employed if there is no reasonable macroscopic or radiographic evidence to suspect cancer. Biomolecular analyses (immunological, aDNA, proteomics) were only employed in 2.8% of the studies included in this review (e.g. Cattaneo et al., 1994; Fornaciari et al., 1999; Schultz et al., 2007) (Figure 8). In addition to being a relatively new method for paleo-oncological investigation, the low number of biomolecular studies may also be attributed to constraints on time, money, and the level of expertise required.

5.5.3 *Differential Diagnoses*

Conducting a detailed differential diagnosis is essential. This is especially true for cancers, being that they are a collection of diseases that present similarly to a number of other diseases in the skeleton and preserved soft tissue. Additionally, the publication of complete differential diagnoses is important for the scientific process, because future researchers are able to revisit the thought processes of the original authors and re-evaluate those alternative diagnoses, especially when there are methodological advances (or the human remains have been reburied).

Further research is particularly needed regarding the skeletal manifestations of bone metastases and multiple myeloma as they share some common features and are often given as a preferred diagnosis, based on modern clinical and epidemiological studies. Other non-neoplastic abnormalities that share characteristics with cancers in the skeleton (among others) include the destructive lesions of TB, treponematosi, fungal infection, and post-mortem destruction by insects, all of which should be included in a differential diagnosis (Waldron, 1987; Mann

et al., 1990; Aufderheide and Rodriguez-Martin, 1998; Arkun, 2004; Rothschild et al., 1997; Hershkovitz et al., 1998; Marques et al., 2013)

Because of these challenges in the differential diagnosis of neoplastic disease in paleopathology, Brothwell (2011), Marques and colleagues (2013), and Ragsdale and colleagues (this issue) have recommended broader diagnoses of neoplastic diseases rather than specific diagnoses when pathognomonic evidence is lacking. They argue that making a specific diagnosis has more potential to end in a misdiagnosis, consequently impairing comparative studies. This is a valuable perspective, also noted by Miller et al (1996). Although it is important to derive a certain amount of information even from limited data in order to develop further study, it is equally important to consider those limitations when interpreting the data. Differential diagnosis in this case (i.e. listing possible diseases in order according to their likelihood of being the specific diagnosis) is a valuable tool. Three key parameters important for distinguishing malignant neoplastic diseases from other neoplasms and tumor-like conditions are usefully described by Marques et al. (2013): (1) lesion morphology (destructive vs. bone forming lesions, periosteal reaction patterns, lesion margin typology, matrix patterns; see also Ragsdale et al, this issue); (2) skeletal or soft tissue distribution chart of lesions and/or tumors; and (3) age-at-death and sex of the individual. These three parameters should always be addressed while conducting proper differential diagnoses of neoplastic diseases.

5.6 Further Limitations to Consider

It is essential that readers are aware of the challenges in analysis potentially affecting the data from this study. While a number of limitations have already been outlined and discussed above, it should be emphasized that limitations are increased in systematic reviews because both the limitations of the original studies and those of synthesizing the data from these studies must be considered. As Waldron (1994:42) wrote: ‘if we are aware of the potential biases in our material we can make allowances in the inferences we draw from it’.

Although this study is the largest review of paleo-oncological evidence of cancer to date, language barriers and limited accessibility to “hard to access” publications may have prevented the incorporation of additional relevant primary studies, including those in other non-English language sources. Certain restrictions may have also influenced the completeness of data collected, including: absence of certain information within studies (e.g. age-at-death and sex), and the relative accuracy of non-English to English translations.

Additionally, there are very few published diagnostic reference points available to aid in the differential diagnosis of neoplastic disease in archaeological human remains (e.g. Ortner, 2003; Brothwell, 1967; Aufderheide and Rodríguez-Martín, 1998; Madewell et al., 1981; Ragsdale et al., 1981; Sweet et al., 1981; Ragsdale et al., this issue), although guidance is available in clinical literature. However, clinical literature may not always be applicable to archaeologically recovered human remains (see Mays, 2012; Ragsdale et al., this issue). It should also be noted that many paleo-oncological studies do not provide socio/cultural/economic/political or environmental contextual information to: a) enable inferences to be made about etiological factors that may have been present for cancer to develop in the populations, and subsequently b) allow for comparison of the data with the risk factors outlined for populations today. It is also important to recognize that in some parts of the world paleopathological analyses are relatively rare compared to regions

such as Europe and North America, and therefore the amount and quality of information available will vary (Buikstra and Roberts, 2012).

5.7 Recommendations for Standardization of Data Reporting

Buikstra and Ubelaker (1994) recommended guidelines for the documentation of lesions and their distribution pattern, as have Roberts and Connell (2004) and Roberts (2017), but these guidelines are not always followed and not all relevant information is always included in published reports (e.g. lesion distribution maps). Several papers have also provided guidelines for the differential diagnosis of neoplastic disease and, in doing so, have demonstrated the types of bony reactions that should be noted in paleo-oncological analysis (Madewell et al., 1981; Ragsdale et al., 1981; Sweet et al., 1981; Ragsdale et al., this issue). Despite these guidelines, there continue to be significant differences in reports on neoplastic disease in paleopathology.

Thus, we recommend that existing general standards for reporting neoplastic disease are expanded to ensure inclusion of contextual information for interpretation. This development will be invaluable for understanding the origin, evolution, history and frequency of cancer, and will facilitate comparative study. Given that these reporting guidelines have not been a standard protocol that have been followed by scholars in the past for studies of neoplastic disease, and that older studies did not have the benefit of the aforementioned guidelines for recording, some inconsistency in data quality and quantity is inevitably present in the studies included in the CRAB Database. These inconsistencies contribute to significant challenges associated with data synthesis, comparative study, and meta-analysis. Although detailed descriptions of skeletal and/or soft tissue evidence are given in many studies, as would be expected in any paleopathological study, some authors did not describe the criteria on which they based their diagnoses, and thus these diagnoses cannot be effectively peer-reviewed or realistically compared to other studies. Ideally, a standard reporting method should include as much specific information as possible concerning the circumstances surrounding the life, death, burial, recovery, and analysis of the individual so that diagnoses can be compared with other studies exhibiting similar or different characteristics.

We recommended that paleo-oncological reports include the following information, if known:

- Site name;
- Site location (e.g. city, GPS coordinates);
- Time period (e.g. BCE/CE, BC/AD);
- Social/cultural/economic/political and cultural affinity of the individuals (e.g. rich, poor, hunter gatherer, farmer, or industrialist);
- Environmental context (e.g. urban/rural);
- Burial number;
- Burial context (e.g. treatment of the body, grave structure, grave goods, orientation, position of the body);
- Burial preservation and completeness, including diagrams (e.g. bones and teeth preserved)
- Age, sex and ancestry estimations for the individual and methods used;
- Detailed description of abnormal skeletal and/or soft tissue evidence;

- Skeletal and/or soft tissue distribution chart of the abnormal evidence;
- High-quality images of lesions illustrating the results of each methodological finding (e.g. histological and radiological imaging);
- Detailed description of the methods used for diagnosis, with references;
- Detailed description of differential diagnostic options considered with references;
- Description of other paleopathological evidence (to explore co-occurring conditions);
- Excavation/recovery methods; and
- Curation location

If an individual diagnosed with cancer is part of a larger burial population, it is also suggested that researchers report:

- The demographic profile for the burial population that shared the same “lived environment” (including total number of individuals, number of individuals analyzed, number of adult females and males, number of adults of unknown sex, number of non-adults, and the number individuals in each age cohort);
- All the methods used to screen for pathological evidence in the population; and
- Other cancers present in the burial population and any other paleoepidemiological information from the population that may help to provide insight into potential risk factors and allow for contextualization of a broader perspective.

Bearing this in mind, the first author will be developing standardized documentation forms and guidelines for data reporting in the CRAB Database to help ensure that more complete information is reported in the future, which will enable effective comparative studies. It is hoped that this will facilitate the documentation and reporting of possible evidence of neoplastic disease and streamline data submission to the CRAB Database, should the researcher be interested in contributing.

5.8 Future of the CRAB Database

The CRAB Database was seen as an opportunity to synthesize data regarding the global history of cancer evidence. It has developed into an active and ongoing resource accessible to researchers who want to study paleo-oncology, and scholars are encouraged to suggest additions to the database by contacting the database administrators (<https://www.cancerantiquity.org/crab-database-additional-data>). It will continue to grow with new evidence and pathways for presenting that evidence to researchers, including the development of open resources and discussions. The variables suggested in Section 6.5 above will be recorded.

In the future, the database will have a separate section for “grey” literature (i.e. non-peer reviewed sources), which will be populated with conference presentation abstracts, university undergraduate masters and doctoral dissertations and theses, and bioarchaeological reports that are not published). Future versions of the CRAB Database will also indicate whether re-evaluation studies were conducted, and whether the results of those studies conflict or agree with the original diagnoses. Longer-term plans for the CRAB Database will lead to the inclusion of evidence of benign neoplastic diseases as well as neoplastic diseases with uncertain benign or malignant designations. Researchers using the database will also be able to sort information based on any of the documented data categories, and a controlled discussion forum is currently being developed. Researchers are

welcome to visit the associated monitored forum (www.cancerantiquity.org/forum/) to make constructive suggestions for the CRAB Database improvement, or to discuss the evidence with other scholars.

6. CONCLUSION

Environmental and cultural changes today, such as industrialization, heavily processed foods, sedentary lifestyles, synthetic and chemically manufactured products, and changes in the quality of our environments have largely been held responsible by the public for the recent surge in modern cancer prevalence (Schoenfeld and Ioannidis, 2013). However, it is clear from this study and the collective research of all authors cited in the 2018 CRAB Database, that cancers and their etiologies have complex and long histories.

The aim of this study was to provide a foundation for conducting future research into the global history of cancer by: a) compiling and synthesizing available and accessible paleo-oncological data, b) identifying methodological trends and challenges and their potential impact on differential diagnoses and comparative studies, and c) introducing the newly created CRAB Database. The resulting data collated from 272 individuals were recovered from 298 archaeological sites and funerary contexts in 35 different countries and dated from as early as 1.8 million years ago to 1900 CE. Summary data revealed higher numbers of males (46.7%) with evidence of cancer than females (34.6%), as well as higher numbers of younger individuals with evidence of cancer (47.8% under 49) than older individuals (24.3% over 50). This result raises important questions about the challenges of age-at-death estimation of older individuals in bioarchaeology, which deserves further analysis and discussion in relationship to paleo-oncology. The data also show that interest in, and subsequent publication of paleo-oncological analyses are concentrated in certain geographic areas (e.g. Egypt and Europe), indicating a need for more work in underrepresented regions. Furthermore, this study demonstrates the need for further standardization of recording and reporting methods, including the presentation of complete differential diagnoses, and the progressive use of innovative methodological techniques.

It is not surprising that cancers have a long and interesting history (Nriagu, 1996; Weiss, 2000; NTP, 2014) because natural carcinogens have been variously present throughout the history of humans and our human ancestors (e.g. blue and ultraviolet light, solar radiation, tannins, radon gas, heavy metals, certain viruses). In addition, human induced carcinogens resulted from cultural shifts that led to rapid changes in lifestyle and diet (e.g. the agricultural and industrial revolutions), poor air quality (e.g. indoor fires and poor ventilation), and an increase in urban pollution (e.g. industrialization). Nevertheless, the past and present limitations facing paleo-oncological research have certainly led to an underestimation of cancers in past populations, as seen in the paleopathological record. As data continue to be critically evaluated, and areas for improvement in diagnostic methods are explored, the scientific and cultural understanding of the history of cancers will advance. Understanding that cancers are diseases of the past as well as the present, and conducting further contextually based research into the history of these complex and enigmatic diseases, could provide valuable insight into the development and epidemiologies of cancers and the reasons for their considerable presence in populations today. This review supports the conclusion that cancers are not recent diseases; indeed they have been affecting humans around the world for thousands of years, and our human ancestors long before that (Strouhal and Kritscher, 1990; Stathopoulos, 1986; Suzuki, 1989).

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