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Ali Shilatifard 's homepage: http://research.stowers-institute.org/shilatifardlab/index.html

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SCIENCE AND SOCIETY

Cancer: an old disease, a new disease or something in between?

A. Rosalie David and Michael R. Zimmerman

Abstract | In industrialized societies, cancer is second only to cardiovascular disease as a cause of death. The history of this disorder has the potential to improve our understanding of disease prevention, aetiology, pathogenesis and treatment. A striking rarity of malignancies in ancient physical remains might indicate that cancer was rare in antiquity, and so poses questions about the role of carcinogenic environmental factors in modern societies. Although the rarity of cancer in antiquity remains undisputed, the first published histological diagnosis of cancer in an Egyptian mummy demonstrates that new evidence is still forthcoming.

Every year, more than 1,350,000 US and UK citizens learn for the first time that they have cancer. Although many may be cured, cancer still causes 165,000 deaths every year and is second only to cardiovascular disease as a cause of death. The history of cancer has the potential to improve our understanding of disease prevention, aetiology, pathogenesis and treatment. However, a chronological assessment of the occurrence of cancer in early fossil, animal and human remains demonstrates the rarity of malignancies in antiquity.

Evidence for the occurrence of this disease in antiquity includes inscriptions, archaeological material and palaeopathological specimens. There are few, often uncertain, references to cancer in Egyptian and Classical literature.

The few reports in the modern literature of tumours in ancient remains are based on defects or masses on bones (for a description of diagnostic techniques used on ancient specimens, see BOX 1). Strouhal[1] has tabulated a total of 176 examples of skeletal malignancies, primarily metastatic, in the archaeological record. Histological studies of rehydrated mummy tissues have resulted in the documentation of only a few benign neoplasms, including examples from Egypt and Chile[2–5]. Most recently, Zimmerman and Aufderheide have diagnosed a rectal cancer[6] in an Egyptian mummy — the first such histological diagnosis in the palaeopathological literature relating to ancient Egypt.

In this Science and Society article, we discuss the evidence of cancer in the literature and palaeopathological specimens primarily from ancient Egyptian and Greek societies. Evidence of cancer in fossilized animals and early humans is discussed only briefly, but readers can refer to other reviews on this topic[7]. Although there are other forms of evidence of the presence of cancer in other ancient populations, owing to space constraints these are not discussed at length here. Interested readers can find further information in Aufderheide's survey[8].

Fossil animals and early humans

How old is cancer? Evidence of cancer in animal fossils, non-human primates and early humans is scarce. Scientific literature has provided a few dozen, mostly disputed, examples in animal fossils, although a metastatic cancer of unknown primary origin has been reported in an Edmontosaurus fossil[9], and Capasso[7] lists several possible neoplasms in fossil remains. Various malignancies have been reported in non-human primates; generally, these do not include many of the cancers most commonly identified in modern adult humans. In studies of thousands of bones that represent the fossil record of Neanderthal man in Europe, the Stetten II skull bone from Stetten, Germany, (*c.*35,000 years BP) provides the only example of a lesion (new bone formation) that might be related to a neoplasm — possibly a meningioma[10]. One early example of a human tumour, in the femur of the first *Homo erectus* fossil, discovered in Java, Indonesia, in the early twentieth century, is probably not a cancer but a benign bony proliferation (FIG. 1) and has been diagnosed as myositis ossificans (bone tissue that is generated in muscle tissue as a result of trauma and haemorrhage) or as an example of fluorosis.

Generally, the scarcity of cancer in the earliest remains supports the theory that age at death, diet and environmental factors substantially influence the incidence of cancer in humans. However, other possible

factors to explain this lack of evidence include the limitations of the diagnostic methods used by early investigators to study these remains, and the insufficiency of data to provide a reliable rate of cancer incidence.

Evidence from antiquity

Palaeopathology has tentatively identified cancer in ancient remains found in many parts of the world. However, two early societies — Egyptian and Greek — are of special interest because their well-preserved inscriptional evidence provides information about the possible diagnosis and treatment of cancer. Therefore, these are the primary focus of this article. Egypt, in particular, with its rich legacy of human remains and antiquities, presents a unique opportunity to study cancer in an ancient society. The survival of well-preserved inscriptions, art representations and palaeopathological specimens is due to environmental conditions and the Egyptian custom of burying tomb goods with the dead. All ancient Egyptians were mummified, either naturally as the result of environmental factors or by means of intentional procedures. Although some studies have concentrated on the well-equipped burials of wealthier people who could afford intentional mummification as a means of preserving their bodies, the examination of all the remains, and primarily those of the common people, constitutes an adequate sample for the study of this ancient population[3]. In Greece, evidence for cancer is restricted to literary sources that describe and identify symptoms and indicate methods of treatment.

Few medical texts have survived, and these can provide an inaccurate view of disease incidence. It is not known whether, in Egypt or Greece, all social classes had equal access to doctors and medical treatment. Any difference might have given physicians an uneven knowledge of the health status of all sections of the population, a situation that would be reflected in the medical documents they composed.

Literature and art

Egypt. Twelve documents, known as the Medical Papyri, provide the surviving literary evidence of the ancient Egyptians' concept of physiology, and their use of pharmaceutical and surgical treatments. The Papyrus Ebers (*c.*1538 BCE)[11] includes a series of prescriptions that provides the most extensive description of swellings in the Medical Papyri. The manner in which the diagnoses and treatments are organized and arranged suggests that they could preserve the main elements of an earlier, undiscovered 'Book on Tumours'. The physician is instructed how to inspect the features of each tumour, categorize it and provide treatment. However, evidence for cancer in these texts is tenuous, and modern readers have usually interpreted such descriptions simply as swellings, leprosy or perhaps varicose veins. Possible references to cancer in the Papyrus Ebers include one treatment (paragraph 813) for 'eating of the uterus', and an incantation for the breasts (paragraph 811), to prevent bleeding, discharge and 'eating' (BOX 2). Any explanation of the term 'eating' is speculative, although it might refer to ulceration. The Papyrus Kahun (paragraph 2) (*c.*1825 BCE) possibly describes another case: a condition of the uterus, diagnosed on the basis of a smell of roast meat, perhaps referring to a vaginal discharge. Although tenuous, it is possible that this could represent cancer, as the description relates to an unidentified uterine disorder.

Egyptian art is an unreliable source for identifying the presence of disease. In most religious art, royalty and the elite were usually idealized as youthful and fit, and even rare examples apparently depicting swellings cannot be categorically identified as a specific disease.

Greece. Several authors wrote about cancer (from the fifth century BCE to 1300 CE), and the earliest texts, the Hippocratic Corpus (from *c.*410 to *c.*360 BCE), are attributed to Hippocrates, the 'Father of Medicine'. This work identifies the cause of cancer as an excess of black bile, an opinion adopted and developed by Galen of Pergamum (*c.*200 CE). The crab-like nature of cancer was noted by the Greeks *c.*200 CE: Hippocrates used the words carcinos (crab) and carcinoma to describe a range of tumours and swellings; according to Galen, it was the characteristic crab-like appearance of some cancers that gave rise to the association of these names with the disease. Classical texts acknowledged breast cancer as the most common form of a disease that was known to occur at many sites throughout the body.

The extent of ancient Egypt's legacy of general medical knowledge to ancient Greece is uncertain. However, the evidence suggests that the Greeks were the first to identify cancer as a specific disease and that, although they distinguished between benign and malignant tumours, the Egyptians probably did not. The conclusion from palaeopathological studies that cancer was scarce in antiquity is supported by the literary evidence from Egypt, in which there are a few tenuous references to the disease. However, references to cancer in Greek texts imply that it was common enough to be widely studied and recorded. This might represent a real increase in the incidence of cancer or, more probably, an increased awareness and knowledge of the disease by the Greek physicians.

Box 1 | **Diagnostic techniques used to examine ancient specimens**

The techniques currently used to analyse cancer in skeletal and soft tissue remains are:

- Macroscopic inspection
- Radiographic examination: this should be applied to any example in which macroscopic inspection suggests that a tumorous process might be present
- Histological examination: in most cases, this will provide the final diagnosis[53]. The standard histological process for soft tissue is based on a technique developed in Cairo, Egypt, in 1921 by Sir Marc Armand Ruffer, the founder of modern palaeopathology[30]. A combination of water, alcohol and sodium carbonate ('Ruffer's solution') is used to rehydrate the mummified tissue, which is then fixed in absolute alcohol and processed for microscopic examination, in the same way as fresh tissue. The microscopic slides are stained with standard stains of haematoxylin and eosin and various specific stains. Scanning electron microscopy and transmission electron microscopy are sometimes used as additional diagnostic tools.

Disease diagnosis in ancient tissue can sometimes be compromised by pseudopathology. The post-mortem process can produce a structural change in normal bone or soft tissue that resembles a lesion, which palaeopathologists sometimes erroneously associate with ante-mortem disease.

Other diagnostic tools may be added in the future[54]. Primary and metastatic cancers in ancient remains might be detected through analytical identification of cancer-associated markers such as carcinoembryonic antigen and prostate-specific antigen[55].

Another means of detecting traces of this disease in ancient remains could be provided by DNA-based techniques used to search for appropriate sequences that are characteristic of cancer[56].

Palaeopathology

Studies carried out on many skeletal remains and mummies — bodies preserved either naturally (by freezing, drying or tanning) or artificially— have all been largely unrewarding.

Skeletal evidence. Tens of thousands of skeletons have been examined but only a few diagnoses of possible and/or probable malignancies — based on gross appearance and occasional X-ray scans showing defects in or masses on bones — have been made. Gray[12] specifically noted the total absence of any radiological evidence of malignancy in his survey of 133 mummies. Bone can be invaded by local tumours, and there are many primary reports of benign lesions in antiquity[2,13–15]; a summary of the evidence that was available until 1991 is given by Ortner and Aufderheide[16]. However, the bone metastases that are common in the modern world have been diagnosed only rarely in ancient material, perhaps because metastatic carcinoma and post-mortem erosion can produce similar changes, such as the formation of multiple round defects in the bone. There are a few reports of osteosarcoma, a primary bone tumour, in the literature[2,17]. Bone can be invaded by a local soft tissue tumour[18] and metastatic carcinoma[19–27]. A primary source, malignant melanoma, is suggested in only one report[21]; however, this was based on gross appearance of pigmentation, without histological confirmation, and such examples are rare[8]. Aufderheide[8] provides a summary of the evidence. These studies examined defects or masses on bones, with diagnosis on the basis of gross appearance and occasional X-ray scans. Histology is obviously impossible on bony defects (holes in the bone): with regard to bone masses (lumps on the bone), sectioning of mummified or fossilized bone is difficult and the results are rarely rewarding. Schultz[28] pioneered the use of bone histology by polarized light, but this technique is useful only in the study of proliferative lesions caused by vitamin deficiency or infectious diseases, for example. Radiology of the margins of bone defects can provide clues as to the nature of the lesion, with metastatic lesions usually showing little or no marginal bone reaction, but histological study of the contents of such defects during life remains impossible. Tumours described by Smith[29] and Ruffer[30] in Egyptian skeletons as osteosarcoma are unlikely to be so, based on the gross morphology. Some more likely cases have been reported from Europe and Peru, although these could be reactive processes that were secondary to infection. Osteosarcoma is not currently an exceptionally rare tumour and, as it usually produces bone, one might expect to encounter it more frequently in archaeological material than is the case, especially as this is a tumour associated with young people. Bone is notorious for trapping radioactive minerals, and one can speculate about the role of radiation in our modern world in causing bone tumours.

Figure 1 | **Benign bony proliferations of the femur can be mistaken for tumours.** An outgrowth on the femur of *Homo erectus* is not a true tumour but more probably an example of myositis ossificans. This is a Kodachrome of a cast taken by M. R. Zimmerman.

Evidence from mummies. Studies carried out on hundreds of mummies from sites across the world have been equally unrewarding. Tissues from mummies are rehydrated with a solution of water, sodium carbonate and absolute alcohol — a technique developed by Ruffer in the early twentieth century for the histological study of mummified tissues (BOX 1); these tissues are then processed in the same way as modern tissues, and slides are prepared for microscopic examination.

Ruffer examined hundreds of mummies. The Paleopathology Association, founded in the 1970s by the late Eve and Aidan Cockburn, has sponsored the examination of several Egyptian mummies that are in museum collections, and the Paleopathology Club of the Medical College of Virginia, USA, has studied hundreds of Chilean and Peruvian mummies.

Glossary

Black bile
According to the Greek physicians Hippocrates and Galen, an excess of this bodily fluid might cause cancer. This humoral theory survived until the late eighteenth or early nineteenth centuries.

Edmontosaurus
A Cretaceous duck-billed dinosaur.

Fluorosis
Soft tissue ossification (bone formation) owing to excessive exposure to fluorine. This condition is seen today in animals grazing in volcanic areas, which are high in fluorine.

Hippocratic Corpus
Earliest Greek medical treatises (*c.* 410 BCE to *c.* 360 BCE), attributed to Hippocrates of Cos, although authorship is unproven. It contains diverse writings on many topics, and includes fragments of other authors' texts[60].

Palaeopathological specimens
Ancient human or animal remains in which the evidence of disease is preserved and can be studied.

Papyrus Ebers
Purchased by Edwin Smith in Luxor, Egypt, in 1862, this document was published by Georg Ebers in 1872. The longest of the Egyptian medical papyri, it dates from *c.* 1538 BCE and contains texts apparently drawn from many sources. These include an important treatise on the function of the heart and its vessels, and pharmaceutical, surgical and magical treatments for a range of diseases[61].

Papyrus Kahun
This earliest extant Egyptian medical papyrus (*c.* 1825 BCE) was excavated at Kahun, Egypt, the site of a pyramid workers' town excavated in 1889 CE. The world's earliest known gynaecological treatise, it provides prescriptions relating to gynaecological diseases and conditions, contraception, pregnancy testing, sterility and identifying the gender of unborn children.

These studies have resulted in the microscopic diagnosis of several benign tumours, including a squamous papilloma of the hand[2], a fibrous histiocytoma of the foot[31] and a sacral neural tumour[4]. There are a few examples from other geographical areas[13,14,32–34], including a chest wall lipoma in the mummy of a 14-year-old Chilean girl (from 1100 CE to 1200 CE)[5].

There have also been rare histological diagnoses of malignancy. The first was of a tumour that is rare in modern populations, a rhabdomyosarcoma in the right cheek below the eye of a Chilean mummy, a child aged between 12 and 18 months, dated between 300 CE and 600 CE[5]. Diagnosis was based on the child's age, the location of the tumour and the histological picture of markedly pleomorphic cells in a loose fibrous stroma. Fornaciari[35] published a case of colorectal adenocarcinoma in a mummy from the fourteenth century CE, confirmed by a DNA test for a mutation in exon 12 of *KRAS*[36]. More recently, Zimmerman[6] made the first histological diagnosis of cancer (a carcinoma of the rectum) in an Egyptian mummy of the Ptolemaic period from the Dakhleh Oasis (from 200 CE to 400 CE). Although several biochemical tests for cancer have been recently developed, such as prostate-specific antigen[37] and carcinoembryonic antigen, a substantial incidence of false-positive results has limited these tests in modern medicine to post-treatment follow-up. False positives mean that these tests cannot be considered diagnostic in mummified material, and so histology remains the ultimate means to diagnose cancer.

Why are ancient tumours rare?

It has been suggested that the short lifespan of individuals in antiquity precluded the development of cancer. Mortality tables are not available for ancient populations; in fact, even total population figures are largely estimates, and standardized epidemiological studies are lacking[38]. However, there is conclusive evidence from ancient Egypt, for example, that the average life expectancy of the whole population, over a period from *c.*4000 BCE to *c.*400 CE, was much lower than in contemporary society. Information about an individual's life and career that is provided by tomb and coffin inscriptions, together with the palaeopathological evidence, confirms that the average lifespan of the wealthier classes was between 40 and 50 years, and a lower age-at-death of between 25 and 30 years is shown in palaeopathological studies of non-elite groups. Although life expectancy was statistically lowered by infant and maternal mortality and infectious diseases, many individuals did live to a sufficiently advanced age to develop other degenerative diseases, such as atherosclerosis[39], Paget's disease of bone[40] and arthritis[41]. As recently as fifteenth century England, life expectancy was 50 years for males and 30 years for females[42]. It must also be remembered that, in modern populations, tumours arising in bone primarily affect the young, so a similar pattern would be expected in ancient populations. Therefore, the rarity of tumours in ancient populations could be a result of factors other than life expectancy.

Another explanation for the rarity of tumours in ancient remains is that tumours might not be well preserved; however, experimental studies[43] show that mummification preserves the features of malignancy (FIG. 2). In an ancient society lacking surgical intervention, evidence of cancer should remain in all preserved specimens. Although the palaeopathological diagnosis of cancer is subject to many difficulties[7], we propose that the minimal diagnostic evidence for cancer in ancient remains indicates the rarity of the disease in antiquity. Carcinogenic environmental factors have been linked to up to 75% of human cancers[44], and the rarity of cancer in antiquity suggests that such factors are limited to societies that are affected by modern lifestyle issues such as tobacco use and pollution resulting from industrialization[45,46].

The treatment of cancer

Remedies for tumours described in the Egyptian papyri (from 1825 BCE) include excision with a knife, burning with red-hot irons, fumigations, topical applications of pastes, spells and advice to leave the swelling untreated (BOX 2).

With regard to tumours, or the three cases tenuously identified as cancer in the Papyrus Ebers and Papyrus Kahun, there is no evidence that any of the recommended Egyptian treatments have continued in use in modern times. However, for many medical conditions other than cancer, therapeutic efficacy can now be demonstrated for 64% of all the pharmaceutical ingredients mentioned in the Egyptian medical papyri[47].

The Greeks found that surgical treatments could be used for superficial cancers but were not suitable for deep-seated cancers. Attention to the patient's diet as well as post-operative care and physiotherapy during convalescence were also indicated. Systemic medication and topical applications included heavy metal preparations (primarily for external use) and plant products (BOX 2). Like the Greeks, the Romans found that some tumours could be removed by surgery and cauterised (burnt), but no medicine

Box 2 | **Treatments used in ancient societies**

Ancient Egyptian and Greek literary sources provide details of prescribed treatments.

Egypt

The medical papyri provide around 2,000 remedies for diseases. Although spells or incantations are recommended for some conditions, many prescriptions give details of ingredients, methods of preparation, dose and route of administration. Incorporating minerals, plants and animal-based products, ingredients were sourced from Egypt, the Near East, Africa and Mediterranean lands. Although many are now synthesized, 50% of the drug sources used by the ancient Egyptians for various ailments remain in use today[57]. Treatments for those cases tentatively identified as cancer are:

- Papyrus Ebers (811): a spell to prevent bleeding, discharge and 'eating' of the breasts — a combination of symptoms that might indicate carcinoma of the breast, arising from the milk ducts[58]
- Papyrus Ebers (813): for 'eating of the uterus', a prescription to take a stone from the shore, break it with water, leave it overnight in dew and then pour it into the vagina
- Papyrus Kahun (2): fumigation of everything the woman associated with the smell of roast meat, in connection with a uterine condition

Greece

The Greeks used surgical treatments such as resection and cautery for cancer. They also used systemic and topical medications. The pharmaceutical ingredients in these included washed and burnt lead, calamine, litharge, soot, copper-based styptic, orpiment, realgar, swallow-wort, stinging nettle, birthwort, edderwort, chickpea, Hellebore, cucumber, heather, hedge-mustard, frankincense, human milk, asses' milk, river crabs and honey[59].

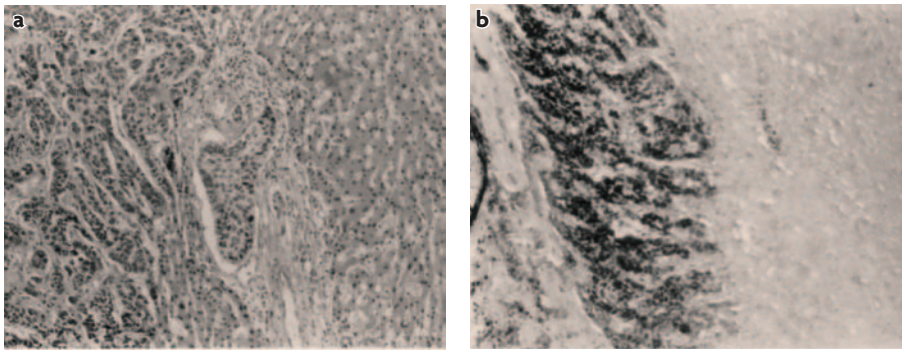

Figure 2 | **Mummification preserves features of malignancy. a** | Metastatic colonic adenocarcinoma (left) in liver (right), 100X magnification, haematoxylin and eosin stain on fresh tissue. The enlarged hyperchromatic nuclei of the tumour are evident. **b** | Metastatic colonic adenocarcinoma (left) in liver (right), 100X magnification, haematoxylin and eosin stain on mummified and rehydrated tissue. The enlarged hyperchromatic nuclei of the tumour are evident as a large dark staining mass with a preserved glandular pattern. Figure is reproduced, with permission, from REF. 43 © (1977) Wiley.

seemed to work. They found that surgery sometimes increased the spread of the cancer, or that tumours occasionally grew again. Breast cancer treatment by mastectomy was attempted early on, but in the ninth century, an Arab physician, Rhazes, warned that inadequate excision worsened the condition[48].

From 500 CE to 1500 CE, little progress was made in understanding cancer, which was still thought to be caused by too much black bile. Textual evidence from Western Europe and the Near East indicates that surgery and cautery, although applied to smaller tumours, were primarily used for haemostasis and the treatment of ulcers and other wounds[49]. Caustic pastes, usually containing arsenic, were adopted for the control of more extensive cancer. Phlebotomy (blood-letting), diet, herbal medicines, powder of crab and other symbolic charms were also used, but there is no evidence that they were effective cures. It was not until the seventeenth century that Wilhelm Fabricus[48] adequately described operations for breast and other cancers, and the first reports in the scientific literature of several distinctive tumours have occurred only over the past 200 years. Examples include scrotal cancer in chimney sweeps in 1775 (REF. 50), nasal cancer in snuff users in 1761 (REF. 51) and Hodgkin's disease in 1832 (REF. 52).

Conclusion

It is hoped that research in palaeopathology will contribute to the elucidation of the pathogenesis of cancer. The publication of the first histological diagnosis of cancer in an Egyptian mummy is one step along the way. Despite the fact that other explanations, such as inadequate techniques of disease diagnosis, cannot be ruled out, the rarity of malignancies in antiquity is strongly suggested by the available palaeopathological and literary evidence. This might be related to the prevalence of carcinogens in modern societies.

A. Rosalie David is at the KNH Centre of Biomedical Egyptology, The University of Manchester, 3.614 Stopford Building, Oxford Road, Manchester M13 9PT, UK.

Michael R. Zimmerman is at the Villanova University, 800 Lancaster Avenue, Villanova, Pennsylvania 19085, USA.

e-mails: rosalie.david@manchester.ac.uk; michael.r.zimmerman@villanova.edu

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