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Ancient cancers and infection-induced oncogenesis

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ABSTRACT

Cancers have been reported in bone and soft tissue of ancient agricultural populations. Fossilized bones from prehistoric periods provide evidence of tumors but only one example of cancer. Difficulties in diagnosing the causes of lesions in mummified tissue and fossilized bone, and in interpreting the prevalence of cancers from remains, draw attention to the need for complementary approaches to assess the occurrence of cancer in ancient populations. This paper integrates current knowledge about pathogen induction of cancer with phylogenetic analyses of oncogenic pathogens, and concludes that pathogen-induced cancers were probably generally present in ancient historic and prehistoric human populations. Consideration of cancers in extant human populations and wildlife lends credence to this conclusion, with the caveat that the presence of cancers may depend on population-specific exposures to oncogenic parasites and carcinogens.

1. Introduction

Over the past half century, the central theory for explaining cancer has relied on accumulation of mutations that dysregulate control over cellular reproduction and invasion. This mutation accumulation theory was first proposed during the middle of the 20th century (Armitage and Doll, 1954; Nordling 1953) but became the dominant conceptual principle when mutated genes were found that directly enhanced cellular proliferation in cancerous cells. This emphasis focused attention on the causes of mutations—particularly radiation and carcinogenic chemicals—as contributors to cancer (Tomasetti et al., 2017), and generated compelling explanations for environmental causes of cancer, such as tobacco smoking for lung cancer and ultraviolet radiation for skin cancer, as well as inherited genetic vulnerabilities, such as the mutations in BRCA alleles for breast cancer (Pfeifer et al., 2002; Pomerantz and Freedman, 2011; Narayanan et al., 2010).

Arguments based on the mutation accumulation theory suggest that the apparent rarity of cancer in wildlife and human populations living in ancient settings could result from the absence of modern exposures to carcinogens (David and Zimmerman, 2010; McAloose and Newton, 2009). This reasoning emphasizes the evolutionary novelty of recent exposures to chemical mutagens (e.g., in tobacco smoke and industrial chemicals) and unnaturally high levels of radioactive materials. A similar argument can be applied to natural causes of cancer when humans move into environments that differ from ancestral environments. Skin cancer, for example, can be attributed to light-skinned people moving from ancestral regions with low insolation (e.g., northern Europe) to areas with higher insolation intensities (e.g., the southern United States) (Del Bino and Bernerd, 2013).

The rarity of cancer in ancient human remains has been interpreted as evidence that cancer was rare in ancient populations (Binder et al., 2014; David and Zimmerman, 2010). This conclusion can be challenged on the basis of two arguments: (i) cancer may not be present in ancient remains even if it was relatively common, and (ii) the mutational theory of cancer is, by itself, insufficient as a general explanation of oncogenesis.

One problem with inferring cancer from bone evidence is the ambiguity associated with differential diagnosis (Brothwell, 2016; Phelan et al., 2007). A key distinction between cancer and benign tumors is metastasis, but pathological alterations of bone are less distinct in metastases (Brothwell, 2016). They are therefore difficult to distinguish from inflammatory effects and post-mortem damage, particularly in fossilized bones, which may have been exposed to post-mortem damage from erosion, decomposition of soft-tissue cancers that obfuscate associated bone lesions, geochemical alteration, and scavenging (Brothwell, 2016).

Another confounding factor is that individuals with cancer in prehistoric times may have been particularly vulnerable to predation. Predators may have reduced the time over which a cancer could affect bone, obscured the evidence of cancer on bones, or destroyed the bones altogether. This effect of predators can be cast in the context of the "osteological paradox" (Wood et al., 1992), with "selective mortality" due to predation in pre-agricultural times biasing the fossil record by reducing the frequency of bones with unambiguous manifestations of

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cancer.

The apparent prevalence in the fossil record also can be biased by the immediate environment of bones after death (Assis et al., 2015). If the presence of cancer influenced the microenvironment of the bones (e.g., as a result of vulnerability to predation or through effects on burial) or the action of the microenvironment on the bones (e.g., through facilitation of erosion), the apparent prevalence of cancer could be less than the actual prevalence.

In mummified remains from ancient urban populations, where remains were protected from bone damaging predation and erosion, one would expect to see frequencies of cancer manifestations in bone that are similar to those in recent centuries. Comparisons of bone cancers from ancient Egyptian mummies and relatively modern populations accord with this expectation (Nerlich et al., 2006; Zink et al., 1999). Five cases of malignant tumors affecting the skeleton were identified in 905 skeletons from Egyptian populations living from 3200 to 500 BCE. This frequency was not significantly different from those found in a German population buried between 1400 and 1800 CE (13 cancers in 2547 individuals), or a comparison group of skeletons in England buried during 1901–1905 (Nerlich et al., 2006; Zink et al., 1999).

Another problem with inferences about ancient cancer from bone evidence is that bone cancer was probably less common in ancient populations than other forms of cancer, if current incidences are any indication. Today, primary bone cancers are relatively rare (Macedo et al., 2017). Most bone cancers arise through metastasis from primary cancers in the lung, prostate, and breast (Guise, 2010; Macedo et al., 2017). These types of cancer were probably particularly uncommon in prehistoric millennia. Lung cancer is mainly a modern disease associated with smoking tobacco (Hecht 1999). Prostate cancer tends to occur in old age groups (Li et al., 2012), which were probably much less common than today because of reduced longevity (Gurven and Kaplan, 2007). Breast cancer also tends to occur in older age groups (Verdial et al., 2017; Youlden et al., 2014); on this basis and its rarity in hunter-forager populations, it is thought to have been rare in prehistoric populations (Eaton et al., 1994).

These considerations indicate that bone cancer is expected to be less common in ancient remains, particularly in fossils, relative to non-cancerous tumors and contemporary prevalences of bone cancer. Noncancerous neoplasms have been found in prehistoric hominins suggesting a potential for the existence of cancer (Randolph-Quinney et al., 2016); however, Brothwell (2016) concluded that none of the bone lesions found on hominin fossils could be unambiguously attributed to cancer. Since his review, an osteosarcoma has been reported in an early *Homo* metatarsal bone dated to about 1.7 million years ago (Odes et al., 2016). The paucity of fossilized remains, the low proportion of cancers leaving unambiguous evidence on fossilized bones, and shorter lifespans of prehistoric populations all may contribute to the rarity of evidence documenting hominin cancer during prehistoric periods (Randolph-Quinney et al., 2016).

Inferences about the prevalence of ancient cancers in soft tissues are constrained by the paucity of ancient populations from which soft tissues have been preserved, and by the particular tissues that have been preserved. A few cases of cancer have been documented in mummified soft tissue (Fornaciari and Giuffra, 2012). The low number has been attributed to shorter lifespans in the study populations, scarcity of remains studied, and technical difficulties associated with diagnoses (Fornaciari and Giuffra, 2012).

The limitations associated with use of ancient remains draw attention to the need for additional perspectives that might shed light on the presence of cancer in ancient populations. This paper integrates three complementary perspectives that pertain to infection-induced cancers. The first uses knowledge about molecular mechanisms by which parasites induce cancer and evolutionary histories of parasites to gain insight into the presence of parasite-induced cancers in ancient human populations. The second perspective considers variation in cancer and oncogenic agents among extant human populations, including hunter-foragers, to suggest how cancer rates in ancient populations could compare with each other and modern populations. The third perspective considers cancer in ancient environments in the context of cancers in wildlife, while addressing the need to assess exposure of wildlife to man-made carcinogens and oncogenic parasites.

2. Infection-induced oncogenesis

Although oncogenesis has been explained mainly through the accumulation of oncogenic mutations, there has been increasing recognition that cancers can be caused by parasites, defined broadly to include multicellular, cellular, and subcellular replicative agents that live in or on a host organism and negatively affect the evolutionary fitness of the host. It is now generally accepted that parasites play a role in causing about 20% of all human cancer (zur Hausen and de Villiers, 2015). When parasites were first causally linked to human cancer about 50 years ago, their contribution was explained largely by mutagenic effects of cellular proliferation and reactive compounds generated during infection. If the oncogenic effects of infection were limited to these mechanisms the contributions of parasites to oncogenesis would not challenge the idea that cancer is largely a recent problem generated by increases in mutagenic environmental factors. Parasites would be just one more initiator of cancer-generating mutations. The increasingly detailed understanding of the mechanisms by which parasites contribute to cancer, however, has led to a different conclusion, one that restricts the explanatory scope of mutation accumulation. In particular, each of the accepted infectious causes of cancer encodes proteins that directly interfere with at least two and usually all four of the most important cellular barriers to cancer: cell cycle arrest, apoptosis, telomerase regulation, and cell adhesion [Table 1; see Ewald and Swain Ewald (2013) for a discussion of barriers to cancer]. By abrogating barriers, viruses push infected cells substantially toward cancer immediately after infection. Mutations complete the transition to cancer by transforming cells that are in this precancerous state.

The broadening acceptance of infectious causes of cancer results largely from the increased recognition of the oncogenicity of human viruses. Molecular evidence shows that each of the viruses that have been accepted as causes of cancer compromises major barriers to oncogenesis by manipulating cellular biochemistry (Table 1). All four barriers are known to be compromised by six of the seven viruses (Table 1). The least studied virus, Merkel cell polyomavirus, is known to compromise three barriers and may compromise all four (see footnote c in Table 1).

These mechanisms of viral oncogenicity are related to modes of transmission. Each tumor virus is transmitted largely or entirely by routes that are associated with relatively infrequent opportunities for transmission: through sexual contact, intimate salivary exchange and/or breast milk (Table 1). When transmission opportunities are infrequent, natural selection should strongly favor persistence within infected hosts, because such persistence allows pathogens to be successfully transmitted through suquential contacts with new hosts. Human T-lymphotropic virus type 1 (HTLV-1), for example, is transmitted to babies through breast milk and through sexual contact (Verdonck et al., 2007). When a baby is infected through milk, the virus generally must persist within that individual until reproductive maturity before it can be transmitted to that person's baby or sexual partner. Persistence beyond that time is also favored to allow for transmission to subsequent babies or sexual partners. Sexual transmission depends on the formation of new sexual partnerships, which requires more time than transmission that depends, for example, on coughing. Because natural selection will favor those pathogen variants that are transmitted to more rather than fewer new hosts, sexual transmission favors persistence within infected hosts through time periods that span multiple sexual partnerships. A similar argument applies to transmission by intimate kissing.

Favoring persistence within a host, natural selection is, in many