

The Prevalence of Cancer in Britain Before Industrialization

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BACKGROUND: To plan for cancer services in the future, the long view of cancer prevalence is essential. It might be suspected that cancer prevalence before tobacco and industrial revolution pollutants was quite different to today. **METHODS:** To quantify the degree to which cancer prevalence may be changing over time, the authors analyzed 143 skeletons from 6 cemeteries from the Cambridge area (6th-16th centuries). Visual inspection coupled with screening using both plain radiographs and computed tomography scans was used to detect malignant lesions. **RESULTS:** A total of 3.5% of individuals showed evidence for metastases. Factoring in modern data for the proportion of those with cancer that die with bone metastases, this suggests a minimum prevalence of all cancers at the time of death in medieval Britain to be approximately 9% to 14% of adults. **CONCLUSIONS:** This figure compares with a 40% to 50% prevalence of cancer at the time of death for modern Britain. The difference may be explained by the effects of modern carcinogens, the spread of viruses that trigger malignancy, industrial pollutants, and longer life expectancy. *Cancer* 2021;0:1-6. © 2021 The Authors. *Cancer* published by Wiley Periodicals LLC on behalf of American Cancer Society. This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

LAY SUMMARY:

- Until now, no one has been able to work out how common cancer was before the time people were exposed to tumor-inducing chemicals from tobacco and industrial factories.
- In this novel study, the authors have determined the percentage of people living in medieval Britain who had cancer metastases to bone at the time of their death and then compared that with modern data.
- It was found that cancer was approximately 25% as common in medieval times as it is today.
- This article suggests cancer was much more widespread in medieval times than was previously realized.

KEYWORDS: bone malignancy, computed tomography (CT) imaging, epidemiology, medieval, metastases, oncology.

INTRODUCTION

It is important that we understand how the prevalence of cancer is changing over time. Such knowledge helps both clinicians and politicians to know whether cancer incidence has changed over time and helps them in planning for the future. It also helps anthropologists and archaeologists to better understand the lives of people who lived in the past, by developing a more accurate disease profile for past societies.¹ It has been found that the lifetime risk of developing cancer for those born in 1930 in Britain was 38.5% in men and 36.7% in women. In contrast, the risk for those born in 1960 was 53.5% in men and 47.5% in women.² Clearly, cancer as a whole became more common during this period. There is also evidence to suggest that, over time, some types of cancer are becoming more common, whereas others less so.¹ There are many potential reasons for these changes, including increasing life expectancy enabling cancers to develop in older people and changing environmental exposure to risk factors. Cancers may be triggered by carcinogenic compounds, infectious microorganisms (such as viruses, bacteria, and parasites), environmental sources of radiation, as well as random gene mutations.³⁻⁷ Cancers are also more common in people with predisposing oncogenes in their genome.^{8,9} Although the impact of some of these factors can be estimated by comparing cancer risk in groups who have been exposed to a particular agent with those who have not (eg, smokers), this is not always an easy task (eg, when we consider the effects of passive smoking).

One key question that remains unanswered is to what extent the effects of tobacco smoking and the toxins and pollutants from industrialization have had on the risk of developing cancer. The best way we have to answer

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The plain radiographs were performed by Reveal Imaging.

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this question would be to study data from before the Industrial Revolution of the 1700s and 1800s and before tobacco became available in Britain following the transatlantic settlement of the Americas by Europeans in the 1500s.¹⁰ Although historic texts do mention cancer in this time period, just the most advanced cases of malignancy would have been apparent to early medical practitioners, and their understanding of cancer only partially overlaps with modern views of this group of diseases.^{11,12} Because some diseases were associated with stigma in the past, the recorded cause of death in registers often reflected the preference of relatives rather than a physician's diagnosis following a postmortem examination. This means prevalence data from medieval or early modern period written sources is just not comparable with modern data.¹³ In consequence, an archaeological approach is the only one where we can apply modern diagnostic concepts to past populations. There have been a number of attempts to do this, some for distinct populations and some by pooling data from different populations where excavated human remains show lesions compatible with cancer.^{1,14-18} However, such an approach would suggest cancer was rare in the past, affecting less than 1% of the population. This is because such data only include individuals where lesions from cancer can be seen on the surface of the skeleton and it misses those with metastases located within bones.

To improve our estimates of the prevalence of cancer in pre-industrial societies, what is needed is a study that uses not only the visual analysis of human skeletal remains for lesions, but also screening for cancers within bone using radiological imaging.¹⁹ This would detect a much higher proportion of the cancers that were originally present in the population. Here, we present the first such study where plain radiographs and computed tomography (CT) scanning have been systematically applied to estimate the prevalence of cancer in Britain before the introduction of smoking and industrial revolution pollutants. The novel data acquired provide a key piece of missing information that enables the long view to understanding change in cancer prevalence over time.

MATERIALS AND METHODS

We analyzed 143 adult skeletons from 6 medieval cemeteries from the Cambridge area (see Supporting Appendix). They came from the cemeteries at Edix Hill (6th-7th century AD), Gamblingay (10th-11th century), Cherry Hinton (10th-12th century), All Saints

by the Castle parish church (10th-14th century), the Augustinian friary (13th-early 16th century), and the Hospital of St John the Evangelist (13th-early 16th century). Very few excavated burials have perfect preservation of the whole skeleton; thus, the minimum inclusion criteria for the study were individuals with intact spinal column, pelvis, and femora because these have been shown to be most likely to contain metastases in individuals with cancer.^{20,21} Children were not included in the study because their bones are not fully developed, and cancer is much less common in this stage of life. In total, 96 males, 46 females, and 1 of indeterminate sex met the criteria for inclusion in the study (see Supporting Appendix). The biological sex of each adult skeleton was estimated by examining the sexually dimorphic characteristics of the pelvis and cranium and through ancient DNA analysis when available (53 individuals).^{22,23} Age at death was estimated by examining the pubic symphysis, auricular surface of the pelvis, and sternal ends of the ribs following standard guidelines.²⁴

The bones of each individual were cleaned of soil and visually inspected for lesions compatible with primary or metastatic tumors, be they osteolytic, blastic, or mixed. We paid special attention to the spine, pelvis, and both femora because these bones have been shown to most commonly contain metastases when malignancy is present.^{20,21,25} The femora, pelvis, and vertebrae were then imaged using plain radiographs (x-rays) and CT scans to detect malignant lesions that may not be apparent on the bone surface and to aid in the diagnosis of suspicious lesions. CT was performed using a Nikon XT H 225 ST microCT scanner (140 kV, 100 μ A, 708 ms integration, 125 μ m). The criteria we used to identify metastases on imaging included rounded or oval destruction of trabeculae and the inner surface of adjacent cortical bone with ill-defined margins for osteolytic metastases; and nodular, rounded, or oval lesions with thickened coarse trabeculae for sclerotic metastases. Lesions with mixed lytic and sclerotic characteristics should show sclerotic change with areas of osteolysis.²¹ The imaging was assessed by 2 medically qualified clinicians. Initially, the entire set of imaging was reviewed by a consultant orthopedic surgeon with 25 years of experience working with excavated human skeletal remains in an archaeology department (P.D.M.). Images of all suspicious lesions were then reviewed by a consultant musculoskeletal radiologist (A.L.), and a positive diagnosis of malignancy was only made if the second opinion agreed with the initial interpretation.

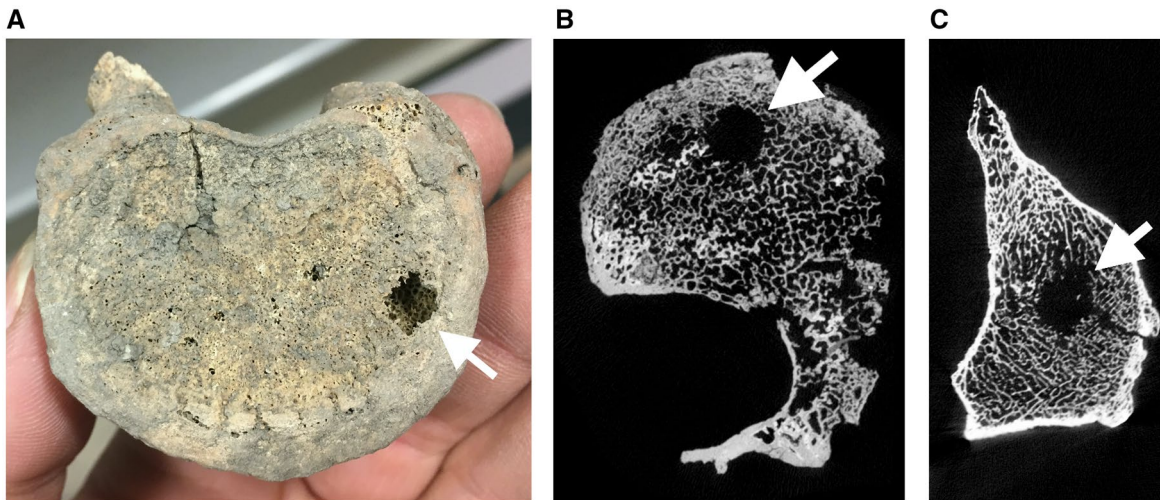


Figure 1. (A) Photograph of a lytic lesion from metastasis in the vertebral body of PSN796, a middle-aged to elderly male. (B) Computed tomography (CT) showing a round lytic lesion from metastasis in the body of a thoracic vertebra of PSN599, a male with likely multiple myeloma. (C) CT showing a round lytic lesion from metastasis in the pelvis of PSN737, an elderly male.

RESULTS

In the 143 individuals in the study, 5 showed evidence for malignancy (Fig. 1). One probable middle-aged male from Edix Hill (PSN599) showed small lytic lesions throughout the skeleton suggestive of multiple myeloma. One elderly male from Gamblingay (PSN 807) had a lytic metastasis in the right iliac wing. Two individuals from the parish cemetery of All Saints by the Castle showed evidence for lytic metastases of variable sizes. One elderly male had lytic metastases in the iliac wings of the pelvis (PSN737), and a middle-aged to elderly male had multiple lytic lesions of the vertebrae, ribs, and pelvis (PSN796). A middle-aged adult male from the hospital of St John the Evangelist was noted to have lytic metastases to the iliac wings and ischium of the pelvis (PSN160).

Estimating Cancer Prevalence in This Population

We identified lesions suggestive of malignancy in 5 of the 143 individuals, indicating a minimum prevalence of 3.5%. Clinical studies have shown that CT has approximately 75% sensitivity for detecting bone metastases.²¹ If the same applies to pre-industrial populations (which seems plausible), then the minimum true prevalence of bone involvement could be approximately one-third higher, in the region of 4.7%. Approximately one-third to one-half of modern people who die with cancer have metastases to bone.^{26,27} This might therefore suggest a minimum prevalence of all cancers at the time of death in medieval Britain to have been approximately 9% to 14% of adults.

DISCUSSION

In this study, we have screened the skeletal remains of 143 medieval individuals for cancer by visual inspection of their bones coupled with imaging of the femora, pelvis, and vertebrae. In this way, we have been able to detect cases of malignancy that were not visible on the external aspect of the bones. Although plain radiographs have been used in skeletal remains from the 1900s as a screening tool in one published study,¹⁹ research on patients with cancer has shown CT to be much more sensitive than plain radiographs alone. That is because CT will pick up metastases within the medulla of bone, whereas destruction of cortical bone is required before the lesions become visible on plain radiographs.²¹ Other imaging modalities that have even higher sensitivity for detecting metastases in live patients, such as positron emission tomography, magnetic resonance imaging, and single-photon emission computed tomography,²¹ cannot be used in excavated human skeletal remains because they require the presence of bone marrow and an intact cardiovascular system. Therefore, CT appears to be the gold-standard approach in archaeological bone. This is the first ever study to apply CT scanning to apparently normal archaeological bones to assess where metastases may be present within. In consequence, we found more cases of cancer than have past studies that relied on visual diagnosis alone.

We have used data from the oncology literature to estimate the true number of adults with cancer in the population by factoring in the sensitivity of CT scans in detecting metastases in bone and the percentage of people

with cancer who develop skeletal metastases. This suggests a minimum prevalence of all forms of cancer at the time of death in the medieval population in the area of Cambridge to have been in the region of 9% to 14% of adults. This compares with modern data indicating 40% to 50% prevalence of cancer at the time of death for modern Britain.²

The estimated cancer prevalence of 9% to 14% of adults in these pre-industrial populations is much higher than was previously thought. This shows that malignancy would have contributed to the disease burden of past populations in a much greater way than has been realized. Nevertheless, the figure of 9% to 14% is lower than prevalence in the 20th century and fits with the known increase in cancer prevalence noted over time.² It seems likely that the pre-industrial prevalence was lower because tobacco had not been introduced to Britain from the Americas, and the pollutants from the industrial revolution did not yet exist. It is also possible that some of the viruses that can trigger cancer may also have been less widespread in medieval Britain than they are in modern times now that long distance travel that can spread these organisms has become so much easier. When these factors are coupled with the longer life expectancy of modern populations because of improved hygiene, vaccination, and other health care improvements in recent times, the increase in cancer lifetime risk becomes understandable.

If we look at the types of cancer we identified, we see that one type had the appearance of multiple myeloma and the other four types were lytic metastases compatible with other soft tissue organ malignancies. It can be highly challenging to determine the organ of origin for a cancer merely from the appearance of the skeletal lesions. In modern populations, 80% of skeletal metastases originate in cancer of the breast, lung, prostate, kidney, and thyroid.²⁰ The incidence of metastatic bone disease varies considerably in different cancers, being roughly 95% to 100% in myeloma, 65% to 75% in breast and prostate cancers, 60% in thyroid cancer, 30% to 40% in lung cancer, 20% to 25% in renal cancer, and 14% to 45% in melanoma.²⁸ Although some metastases are predominantly osteolytic (such as myeloma and breast cancer) and others are osteoblastic (such as prostate cancer), many others have both osteolytic and osteoblastic elements.²⁶ Because the metastases we identified were all lytic, this makes prostate cancer unlikely. Because the 5 individuals we identified with metastases were all males and the vast majority of those with breast cancer today are females, this might suggest breast malignancy was unlikely to be the cause. This leaves tumors of other tissues the most

likely sources of origin, such as myeloma, lung, kidney, and thyroid.

Limitations of the Study

There will always be challenges facing studies that have to compare data calculated using different methods. Although we have tried to make allowances for the way the archaeological and clinical data have been acquired, there remains potential for these nonmatching data sources to have hidden errors compared with studies with matching data sources. For these reasons, we have given a plausible range (9%-14%) for the minimum true prevalence of cancer in our medieval samples, without claiming undue accuracy.

In ideal circumstances, cancer prevalence is determined using as large a sample size as possible. Unlike modern studies where thousands of individuals are often included, we were limited to 143 medieval individuals because of the need for good preservation in the spine, pelvis, and femora of the available skeletons. Smaller sample sizes will inevitably lead to a larger margin of error.

Diagnosing cancer in excavated human skeletal remains is more challenging than diagnosis in modern patients who can describe their symptoms, undergo physical examination, be assessed using a range of different types of imaging, have blood tests, and undergo biopsy and histology. Other diseases during life can cause changes in bone that may mimic the lesions made by metastases, and the decomposition process (taphonomic change) can lead to destructive processes affecting bone after death. To give just 2 examples, bacterial infectious diseases may cause cavity formation within bone, whereas burrowing insects or tree roots could mimic destructive change from malignancy.^{29,30} For these reasons, we only included cases where all the evidence (visual appearance and imaging) indicated malignancy as the most likely diagnosis. Having the diagnosis made with duplicate osteologists expert in diagnosing pathology in human skeletal remains (P.D.M. and J.D.) as well as the imaging undergoing duplicate reporting by clinicians who regularly deal with patients with cancer (P.D.M. and A.L.) should optimize our accuracy. This means the true prevalence of cancer in the medieval sample could have been higher than our estimate because some of the equivocal cases we excluded could have been genuine malignancy.

Bone containing lytic metastases may be more prone to decomposition in the soil than otherwise healthy bone that will be stronger. Therefore, it is possible that individuals with multiple lytic metastases may be underrepresented in the archaeological record because of failure of preservation. This could again lead us to underestimate the true prevalence of cancer in the past.

By chance, there were a larger number of males included in the study than females (96 males, 46 females, 1 indeterminate sex). This is purely because we studied all the remains that were available to us that met the study criteria. This ratio helps to explain why the cases of cancer we did find were in males. For this reason, we should not extrapolate from our data that cancer may have been more common in males than females in the past.

We have estimated the likely prevalence for all cancers in our medieval samples based on modern data for the proportion of different cancers that metastasize to bone. It is possible that the proportion of cancers from different organs may have been different in the past to that found today. If so, then the proportion of individuals with cancer who went on to develop bony metastases could also be different in the medieval period compared with today. This could mean that the true prevalence for all cancers in the medieval period could have been a little lower or higher than our estimate, without us being aware of this error. Variation in true prevalence may well also have differed across other regions of the world (eg, depending on which infectious diseases that induce cancer were endemic in the past).

In this study, we focused on the analysis of adults from the medieval period. We were unable to include medieval data for children who may have suffered from hematological malignancies such as leukemia because untreated children with these conditions often die too rapidly for skeletal changes to develop. Although archaeological cases of leukemia in children are occasionally identified,^{16,31,32} this challenge in identifying leukemia in human skeletal remains means this could have impacted our data for lifetime risk of developing cancer. However, in modern times, leukemia in children is extremely rare compared with most malignancies affecting adults,³³ thus we do not anticipate it would have had a major impact on our prevalence results.

Concentrating our imaging on femur, pelvis, and spine does mean that individuals with cancer who only had metastases elsewhere would have been missed. However, only a small proportion of individuals fall into this category.¹⁹ If we had imaged the entire skeleton, the time available for the study would only have allowed us to include a small number of individuals, which would have made the study unviable.

Future Potential to Investigate Ancient Cancer Gene Mutations

As the ability to extract ancient DNA from the skeletal remains of past individuals improves, the potential arises for us to investigate past cancer genetics.³⁴ One approach would be to analyze the human genome of skeletal remains

to look for those genes that are known to be predisposed to the development of malignancy.^{8,9} To date, only 1 case study has been successful in doing this. Colonic tissue from an 18th century Hungarian mummy has revealed a mutation (E1317Q) in the adenomatous polyposis coli tumor suppressor gene, although the individual did not actually have colon cancer.³⁵ If good-sized studies of the human genome could be undertaken in excavated human skeletal remains and predisposition gene prevalence were found to change over time, this could contribute to our understanding of the increasing prevalence of cancer noted in modern times. Another approach would be to compare the normal human genome in skeletal remains with that of the cancer from the same individual, following biopsy of cancer lesions identified in bones using imaging. Differences between the 2 would, in all probability, represent the mutations within the cancer that were responsible for its malignant behavior.³⁶ A 15th century Italian mummy was noted to have adenocarcinoma of the colon, and biopsy enabled identification of a mutation of the *K-ras* gene commonly associated with this malignancy.³⁷ However, mummies are much less common than human skeletal remains, so if we are to investigate cancer in past populations, we will need to be able to do so using techniques that are effective in human skeletal remains to obtain sufficient sample size. This has the potential to show if there has been a change over time in the types of gene mutation that are triggering cancers and help us to plan for changing trends in mutations in the future.

Conclusion

This is the first ever study to use radiographs and CT imaging to create a plausible estimate of the prevalence of cancer in pre-industrial populations. Our results show cancer to have been much more common in medieval Britain than was previously thought. At an estimated minimum prevalence of 9% to 14% of adults, this shows cancer would have made a significant contribution to the disease burden of medieval societies.

The proportion of skeletal remains with visually apparent malignant lesions was in line with past publications on the topic, at approximately 1%. The reasons we have been able to show cancer was more common than previously thought is first due to our use of imaging to detect lesions not visible on the bone surface, and second from our use of clinical data showing how the proportion of those with metastases relates to the entire body of individuals who develop cancer.

Diagnosing cancer in individuals who died hundreds of years ago is clearly a challenge. To minimize the risk of

error, we have carefully considered the differential diagnosis for each case, rejected those equivocal cases where diagnosis is possible but not secure, and double reported all skeletons and all imaging to optimize reliability. Such a stringent approach had probably led to us underestimating the true prevalence.

Our comparison of the medieval data with the prevalence of cancer during the 20th century indicates that cancer prevalence increased during the intervening period. If it has changed from 9% to 14% of adults in the medieval period to 40% to 50% in modern times, this raises the question as to whether it will continue to increase in prevalence in the future. Only time will tell.

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CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

AUTHOR CONTRIBUTIONS

Piers D. Mitchell: Conceptualization, methodology, investigation, data curation, formal analysis, funding acquisition, writing—original draft, and writing—review and editing. **Jenna M. Dittmar:** Methodology, resources, investigation, data curation, visualization, writing, and review and editing. **Bram Mulder:** Investigation, data curation, and writing—review and editing. **Sarah Inskip:** Resources and writing—review and editing. **Alastair Littlewood:** Investigation and validation. **Craig Cessford:** Resources, writing—original draft, and writing—review and editing. **John E. Robb:** Funding acquisition, project administration, and writing—review and editing.

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