

The epidemiology of Paget's disease of bone

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Summary

Paget's Disease of Bone (PDB), first described by James Paget in 1877, is characterized by rapid bone remodeling and the formation of bone that is structurally abnormal. The aetiology is unknown, although both genetic and environmental factors have been implicated. PDB is more prevalent among men than women, and prevalence increases progressively with age, reaching around 15% in elderly men in Britain. In this article, we review the patterns of occurrence of Paget's disease according to age, gender, ethnic group, and geographical location. We also discuss recent work documenting mortality rates and secular trends for the disorder over the last two decades, and discuss the aetiological implications of the epidemiological data.

KEY WORDS: *Paget's disease of bone, epidemiology.*

Introduction

James Paget originally described "osteitis deformans" in an elderly man with progressive skeletal deformities in 1877 (1). The condition subsequently became known as Paget's Disease of Bone (PDB), and is characterized by rapid bone remodeling and the formation of bone that is structurally abnormal. The aetiology is unknown, although both genetic and environmental factors have been implicated. Postmortem and radiographic series have confirmed that the disease is more prevalent among men than women, and that prevalence increases progressively with age, reaching around 15% in elderly men in Britain (2, 3). In this article, we review the patterns of occurrence of Paget's disease according to age, gender, ethnic group, and geographical location. Moreover, we discuss recent work documenting mortality rates and secular trends for the disorder over the last two decades, and discuss the aetiological implications of the epidemiological data.

Prevalence of Paget's disease by age and gender

The most comprehensive available data on the prevalence of Paget's disease by age and gender were provided from surveys of abdominal radiographs from stored films within a group of British hospitals, conducted during 1970-1977 (4, 5). As part of these studies, around 30,000 radiographs of men and women aged ≥ 55 years were evaluated in 31 towns throughout the Country. In each town, samples were taken from the stored films within X-ray Departments of the Serving General Hospitals. The selected films showed the entire pelvis and sacrum, both femoral heads, and all lumbar vertebrae. Ninety five percent of patients with Paget's disease demonstrate radiographic abnormalities of the disorder at one of these sites (5). The films included those taken specifically to show the skeleton, as well as those taken during intravenous pyelography, barium studies, and plain abdominal radiographs. Samples of about 1000 radiographs were drawn for each of the towns studied (500 male and 500 female).

The films were initially classified by a trained observer into three groups: positive (unequivocal signs of Paget's disease); doubtful; and negative. A second observer (a consultant radiologist) then examined all the positive and doubtful films and a one in ten sample of the negative ones. The doubtful group made up about 3-4% of the total films examined, and all were subsequently classified as either positive or negative. Standardized criteria for the radiological diagnosis of Paget's disease (Table 1) were established in a pilot study and were derived from those of Murray and Jacobson (6) and Campbell-Goulding (7). Figure 1 shows the prevalence of radiographically apparent Paget's disease according to age and gender in this study. The overall prevalence of the disorder was 5% (men 6.2%, women 3.9% after age and gender standardization). There was a steep increase in the frequency of Paget's disease with advancing age in both genders. Thus, prevalence rose from around 2% in men aged 55-59 years to 20% in those aged 85+ years; in women of comparable ages, the prevalence rose from 1% to around 7%.

Geographic variation in prevalence

Prevalence in Britain

This large British survey (4), performed 20 years ago, revealed marked geographic variation in prevalence within the Country. Age/gender-standardized prevalence rates above 6%, were

Table 1 - Radiographic criteria for the diagnosis of Paget's disease.

- Increase in bone density/areas of increased lucency
- Increase in bone size
- Bone deformity
- Cortical thinning
- Enhanced trabecular pattern

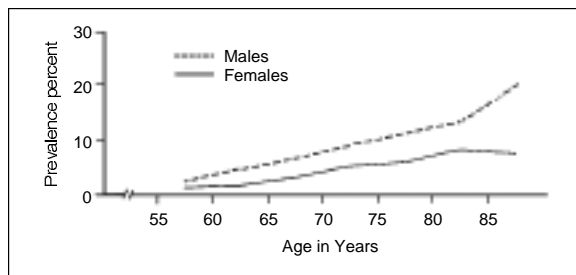


Figure 1 - Prevalence of PDB in England and Wales, by age and sex, based on a radiographic survey performed in 1974 (5).

only found in a cluster of six Lancashire towns: Lancaster (8.3%); Preston (7.5%); Bolton (7.1%); Wigan (6.8%); Burnley (6.5%); and Blackburn (6.3%). Outside this small area of high prevalence, the rates fell sharply, with the bordering towns having rates of around the average for all other towns. This striking geographic variation is illustrated in Figure 2. It was apparent for subjects undergoing radiography for skeletal and non-skeletal indications.

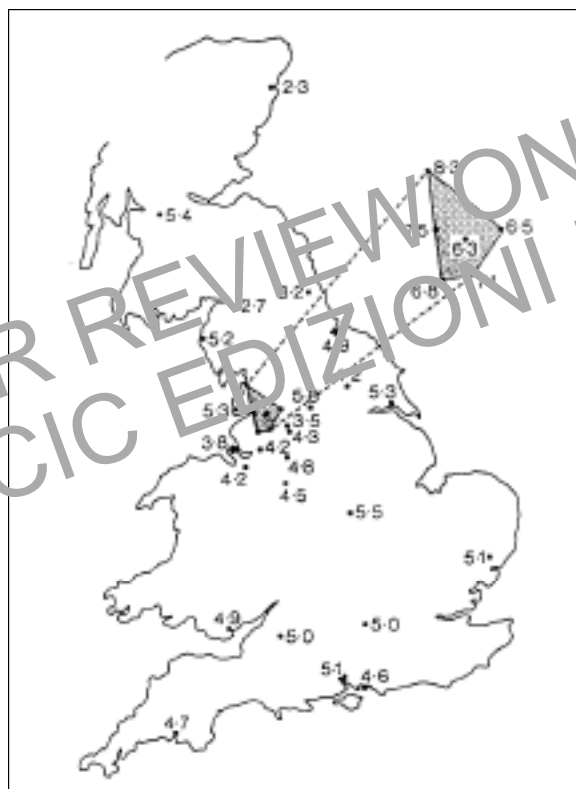


Figure 2 - Age- and sex-standardised prevalence rate (%) of PDB among men and women aged 55 years in 31 British towns surveyed in 1974 (4).

Prevalence in Europe

Extension of this radiographic survey to Western Europe (8), revealed that rates in Britain were substantially higher than for

most other countries of Western Europe. Outside Britain, the highest prevalences (2.0% to 2.7%) were found in three French towns (Bordeaux, Rennes, and Nancy). These prevalences were lower than the overall prevalence of 4.6% in Britain, but were comparable with the lowest values recorded in individual British towns (2.7% in Carlisle and 2.3% in Aberdeen). In the remaining European towns, the prevalence rates ranged from 1.7% in Dublin (Ireland) and 1.3% in Valencia (Spain), to 0.5% in Palermo (Italy) and 0.4% in Malmö (Sweden). This geographic variation was concordant with a questionnaire survey of radiologists in these countries of Western Europe, which enquired about the frequency with which Paget's disease was seen as either the principal abnormality, or as an incidental abnormality, on radiographs.

However, in a more recent case control study, nested within the Rotterdam Study (The Netherlands), a higher overall prevalence of 3.6% was ascertained (9). The Rotterdam Study is a well-characterized cohort of 7983 men and women 55 years old, recruited in the early 1990s for the study of chronic diseases. Those subjects with a raised serum alkaline phosphatase were matched with controls, and radiographs of the hands, thoracolumbar spine, pelvis and knees were taken. The relative risk of PDB in subjects with a raised alkaline phosphatase was 10.9 (95% CI, 4.8-24.9). When diagnoses of PDB based on radiographic localizations not included in previous studies were excluded, the prevalence dropped to 2.4%. The only previous study in The Netherlands was a small hospital based survey of abdominal radiographs, which found a prevalence of 0.6%. This may reflect differences in the populations studied (community vs hospital), and the small numbers included in the earlier study.

Prevalence in North America, Australia, and New Zealand

Within the USA, comparison of a northern city, New York, with a southern city, Atlanta, revealed a marked difference in prevalence rates, with a rate of 3.9% in New York and only 0.9% in Atlanta (10). Markedly lower rates in the southern city were also seen among blacks than whites. This accords with the observation that Paget's disease is rare in Africa. It also parallels findings in Perth, Australia (11), where the prevalence among British-born immigrants (4%) was intermediate between the British rate (5%) and that among native-born Australians (3.2%) (Table II). These two sets of observations among communities that have migrated point strongly to the influence of environment in the etiology of the disease.

Table II - Migrant studies of Paget's disease (11).

Birth	Prevalence (%)*			
	Residence	Men	Women	All
Australia	Australia	3.5	2.8	3.2
UK	Australia	5.7	2.3	4.0
UK	UK	6.2	3.9	5.0

* Prevalence adjusted for age.

Incidence by age and gender in Britain

The General Practice Research Database (GPRD) contains computerized patient records from 683 GP practices in England and Wales, covering 6% of the registered population. In-

formation recorded in the database includes diagnosis and treatment. The dataset was used in a retrospective cohort study to assess the incidence of PDB over the period 1988 to 1999 (12): 2465 patients with PDB were identified after exclusion of those with Paget's disease of the breast, out of the 5 million subjects 18 years old. The validity of diagnostic recording was assessed by questionnaire to individual general practitioners (GPs) in 150 patients; the diagnosis was confirmed in 93.8% of responders. The mean age of patients with Paget's disease was 75 years and 51% were men. Incidence rates for clinically diagnosed Paget's disease rose steeply with age thus the rate was 0.3 per 10,000 person-years for women aged 55-59 years, rising to 5.4 per 10,000 person years at age 85 years. The corresponding figures for men were 0.5 and 7.6 per 10,000 person-years respectively. Figure 3 shows the influence of age on incidence on PDB in men and women.

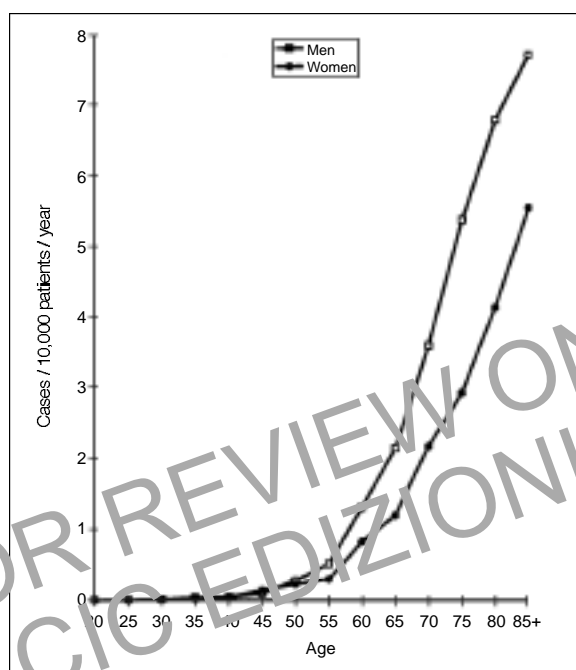


Figure 3 - Age- and sex-specific incidence rate of PDB among 5 million men and women registered on the GPRD (1988-1999) (12).

Morbidity and mortality

PDB is associated with increased morbidity through bone pain, fracture, deafness and increased risk of osteoarthritic change in an adjacent joint, and malignant change to an osteosarcoma. The GPRD study (12) explored these factors by comparing subjects with PDB to three controls matched by age, gender, and general practice. Cases had a greater risk of back pain (relative risk [RR], 2.1; 95% CI, 1.9-2.3), osteoarthritis (RR, 1.7; 95% CI, 1.5-1.9), hip arthroplasty (RR, 3.1; 95% CI, 2.4-4.1), knee arthroplasty (RR, 1.6; 95% CI, 1.0-2.6), fracture (RR, 1.2; 95% CI, 1.0-1.5), and hearing loss (RR, 1.6; 95% CI, 1.3-1.9). Seven patients with Paget's disease developed a malignant bone neoplasm (0.3%). Using life table methodology, the estimated number of people who died within 5 years of follow-up was 32.7% among the patients with Paget's disease, and 28.0% among the control patients. Figure 4 shows the Kaplan-

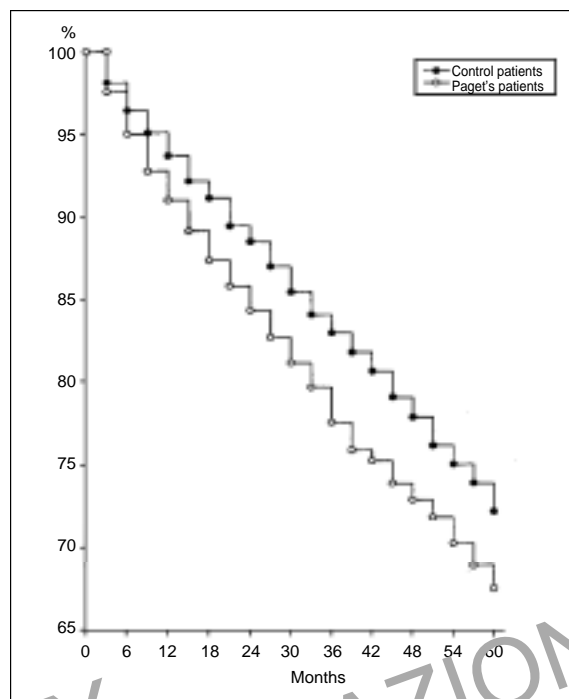


Figure 4 - Survival over 5 years after clinical diagnosis among 2465 patients with PDB and 730 control patients registered in the GPRD (12).

Meier survival plot for subjects and controls over time.

Time trends in mortality, prevalence, and severity

There is much circumstantial evidence pointing to a decline in the frequency of Paget's disease in recent years. Table III reveals mortality rates attributable to (a) Paget's disease and (b) malignant tumors of bone between 1951 and 1970. Throughout Great Britain there has been a gradual decline in mortality from both causes over the 20 year period studied (13,14). Furthermore, when mortality is analyzed in relation to year of birth, successive British birth cohorts have had progressively lower death rates from Paget's disease; the highest death rates have been observed in cohorts born during the 1880s, with progressively lower rates thereafter. Analyses of mortality from Paget's disease among whites in the USA appear to show a similar pattern of decline, although death rates in the USA are somewhat lower. Recent data on temporal trends in the prevalence of Paget's disease have emerged from a follow-up prevalence survey in ten British towns during 1993-1995 (15), utilizing identical methods to those of the original surveys of 1970-1977. The results of this follow-up study suggest that the age/gender-standardized prevalence of Paget's disease has fallen sharply between 1974 and 1994. Indeed the overall prevalence in the follow-up was 40% of that in the initial study. The overall age-adjusted prevalence rate in the ten towns in 1994 was 2.5% (95% CI, 2.1%-3.0%) for men and 1.6% (95% CI, 1.3-1.9) for women, compared with 6.2% and 3.9% respectively observed during 1974. The prevalence rate had decreased among both men and women, and was most marked in those towns with the highest prevalence in the original study.

Other clinical surveys also point to a decrease in the prevalence and severity of Paget's disease. The GPRD study (12) was able to observe changes in incidence over the period

1988 to 1999. Over the 11-year period of the study, the age- and sex-adjusted incidence rate of clinically diagnosed Paget's disease declined from 1.1 per 10,000 person-years to 0.7 per 10,000 person-years (Figure 5). Additionally, observation of temporal trends in the radiographic and biochemical severity of Paget's disease at diagnosis in a New Zealand hospital service (16) suggests a progressive decline in both serum alkaline phosphatase and scintigraphic grade at presentation, between 1973 and 1993. These data suggest that both the prevalence and severity of the disorder have been declining in recent years.

Table III - Mortality rates from PDB and malignant tumours of bone among men and women aged 55 years in UK (1951-1970) (14).

Annual mortality rate (per 10 ⁶)	England / Wales	Scotland
Paget's disease		
1951-55	3.7	2.9
1956-60	3.6	2.4
1961-65	3.4	2.2
1966-70	3.2	1.4
Malignant tumours of bone		
1951-55	48.2	82.4
1956-60	39.7	57.6
1961-65	32.6	41.2
1966-70	23.2	31.7

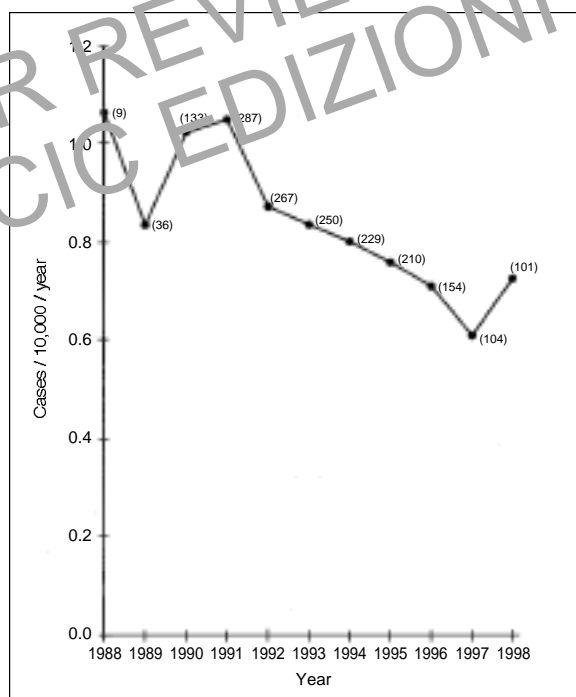


Figure 5 - Decline in age- and sex-standardised incidence rates of PDB in GPRD population (1988-1998) (12).

Aetiology

These epidemiological observations have implications for our understanding of aetiology of PDB. A strong familial aggregation has been observed for PDB, and recent molecular studies have proposed genetic markers for susceptibility among affected members of multicase families. However, in one study only 4-5% of patients with PDB had a strong family history (17), and it seems unlikely that an exclusively genetic predisposition will account for a large proportion of PDB in the general population. Other investigators have suggested an infectious etiology for PDB. Focus has been directed at the role of viral infection, but attempts to identify a specific causative agent have yielded inconsistent results.

The dramatic decline in the prevalence of Paget's disease, coupled with the marked geographic variations and cohort effects in mortality, strongly support an environmental contribution to its etiology. Recent work, using 202 subjects in the New England Registry for Paget's Disease of Bone (18), found that those cases with a positive family history of PDB had an earlier age of onset (51 years vs 59 years, $p < 0.05$), and trend to a higher incidence of bone deformity (49% vs 33%, $p < 0.1$), and an increased fracture rate (27% vs 11%, $p < 0.05$). Environmental factors were further explored, and the Authors found that a history of measles infection, childhood exposure to pets, milk ingestion, year of immigration to the USA, birth order, level of education, and functional status, were not significantly differentiate between those with a family history of PDB and those without. Interestingly, in this cohort the proportion of patients with a positive family history was 30%, but, as families share environmental as well as genetic factors, this figure does not reflect the purely genetic component of aetiology.

Conclusions

Descriptive epidemiological studies suggest that Paget's disease shows an increasing frequency of occurrence with age in Western populations, and is more frequent among men than women. There is marked geographic variation in the prevalence of disease throughout Western Nations, with the highest rates reported during the 1970s in Britain. Heterogeneity in prevalence is also found within Britain, with foci of high rates in the Northwestern region of the Country. Recent studies of the secular trends in Paget's disease suggest declining rates in both prevalence and severity at diagnosis. The epidemiological data suggest a substantial environmental role in the aetiology of PDB, in addition to a genetic component. Further studies should be directed at characterizing the nature of environmental risk factors and exploring the means whereby genetic and environmental risk factors might interact.

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The epidemiology of Paget's disease of bone

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