

REVIEW

Methodological problems in the epidemiological study of osteoarthritis

Tim D Spector, Marc C Hochberg

Osteoarthritis (OA), also referred to as osteoarthrosis or degenerative joint disease, is the most common form of arthritis in developed countries.¹ One of the methods of studying the aetiology and course of a chronic disease such as OA is the application of epidemiological methods. Epidemiology can broadly be defined as a study of the distribution and determinants of disease in human populations. The epidemiology of OA has been reviewed elsewhere.² This paper will focus on potential methodological pitfalls in studies of the epidemiology of OA in the areas of (a) case definition, (b) determining and validating exposures to putative aetiological risk factors, especially in case-control studies, (c) assessing development and progression of the disease in longitudinal cohort studies and (d) controlling for comorbid disorders and OA related disability in clinical epidemiological studies.

Case definition

Epidemiological studies require a clear, concise, valid, and reliable case definition which can be measured in the general population and in the clinic. There is little consensus, however, on how to define OA. Classically, epidemiological studies have relied on characteristic radiographic changes described originally by Kellgren and Lawrence.³ This is basically a global score with grades between 0 and 4 where 0 = completely normal, 1 = questionable disease, 2 = definite but mild disease usually associated with the presence of small osteophytes, 3 = moderate disease typically with osteophytes and joint space narrowing, and 4 = severe disease with all characteristics of OA being present, including subchondral sclerosis, cysts, large spurs, and marked joint space narrowing. Most studies have used the presence of grade 2 changes to indicate a case. This has potential problems as grade 2 disease, which is defined as 'osteophytes only, without any obvious alteration in joint space, is believed by some workers to be a natural phenomenon of age related bone and joint remodelling.

Further problems arise when joint space narrowing occurs without any obvious osteophytes. This event may produce a normal score and potential misclassification. Additional problems in the misclassification of normal subjects results when studies have grouped together those with grade 0 and grade 1 changes. Although there is no clear consensus of whether grade 1 subjects are cases or

controls, we feel that this is at present best dealt with by separating grade 1 subjects from cases and controls either by excluding them from the basic analysis or alternatively by presenting them as a separate subgroup.

Several workers have prepared radiographic atlases for the hand and knee based on individual features such as the presence of osteophytes, joint space narrowing on a 0-3 scale, and sclerosis, cyst formation, and deformity on a 0, 1 scale.⁴⁻⁶ This allows the presence of these features to be scored independently or summated by computer algorithms into a global grade.

Another approach to case definition used by the American College of Rheumatology's Subcommittee on osteoarthritis is the development of classification criteria for symptomatic OA of the hand, hip, and knee.⁷ These criteria require that subjects have specific current joint pain on most days for at least one month, and are designed to be most useful for clinical trials of symptomatic patients. Their use in populations, however, has not been properly tested; studies suggest that they lack sensitivity, producing extremely low prevalence rates and are therefore likely to be of limited use in the population.⁸ Another approach might be to combine radiographic features with a less rigorous definition of joint pain. Epidemiological studies are in progress using definitions such as 'ever pain lasting more than a month' plus the presence of radiographic features and 'pain on most days for one month within the last year'.

Whether or not symptoms are taken into consideration in the classification of OA is important as several studies have shown differences in the outcome and demographic features of subjects with and without joint pain who all have the radiographic features of OA. Nevertheless, asymptomatic radiographic disease cannot be ignored as subjects are more disabled and have decreased survival with respect to radiologically normal subjects.⁹

Case-control studies

Case-control studies are one study design used in testing hypotheses about putative aetiological factors for a disease. First, cases with the disease and controls without the disease are identified. Data on exposure to the putative risk factors are then determined through either interview, self administered questionnaires, review of medical records, or direct examinations. Finally, the proportion of cases with

Department of
Rheumatology,
St Thomas's Hospital,
London SE1 7EH,
UK

T D Spector

Departments of
Medicine and
Epidemiology and
Preventive Medicine,
University of Maryland
School of Medicine,
419 West Redwood
Street,
Baltimore,
Maryland, USA
M C Hochberg

Correspondence to:
Dr Spector.

the exposure is compared with that of controls, and an odds ratio to measure the association of exposure and case status is calculated.

Several potential problems may limit the design and conduct of case-control studies of OA. (1) The correct definition of cases and controls and avoidance of misclassification particularly of controls. This is discussed in some detail in the preceding section. (2) The choice of control group is important and difficult. Controls should be representative of the population being studied and also matched for potential confounding variables such as age and sociodemographic status. Either a hospital based or population based control group can be used, though both have inherent biases. Wherever possible two sources of controls should be used for comparisons. (3) Determination of the temporal sequence of exposure and disease. It is important to ensure that exposure was before, and not a consequence of, the disease. This requires that some estimation of the onset of OA is made. This is often problematic as radiographic changes of OA may be present without symptoms. (4) Validating self reported data on exposures or medical history. This should usually be done on a subgroup and checked against medical records from the hospital or general practice. (5) Sufficient adjustment for potential confounders in the analysis which have a strong effect on OA. The best example of this is if cases and controls are not perfectly matched for age. Adjustment for age in the subsequent analysis should always be performed.

Cohort studies

There are two major forms of cohort study used in OA: retrospective cohort studies and prospective cohort studies. The differences between the two are that the former is currently investigating a group of subjects who were part of a cohort in the past, say 10 years ago, and are only now evaluated for the presence or absence of OA to identify cases. A prospective cohort study, on the other hand, identifies a cohort currently and then follows them up from that point of time into the future when new cases will be identified as they occur.

Problems with the retrospective cohort design include (a) that subjects may not have been free from disease at entry to the cohort as radiographs may not have been performed at study entry; (b) selection bias may have occurred, altering the make up of the population that is seen subsequently on follow up; (c) difficulties in obtaining reliable data on timing and type of exposure in all subjects—data may not be available on exposures of current interest if they were not obtained at the original inception of the cohort; (d) a retrospective cohort was often brought together for the study of another problem or disease unrelated to that which is currently under study; (e) the timing of when the disease began, as it may have been any time up to the present examination. These problems often limit the ability to use more sophisticated types of analysis which allow for the timing of disease

onset, such as life table or survival analysis. The advantages, however, are that these studies are easier and quicker to perform and may not be excessively expensive, often allowing them to be completed within the time specified by most project grants. A representative example of such a study design is the Framingham OA study.¹⁰

Prospective longitudinal studies have the benefit of defining the protocol initially to include all exposures of interest in a group of subjects free of disease and who are appropriate and generalisable to study. These subjects can then be assessed prospectively for the development of disease. The study design enables the investigator to examine close relations between exposure and onset of disease and include analysis of time dependent variables. In theory therefore this study design is the most powerful epidemiological tool. In practice, however, there are some problems. Cohorts need to be large, especially if the rate of development of new cases is small and the cohort may have to be studied over a long period of time to obtain sufficient new cases for statistical analysis. Cohort studies are expensive to set up and require long term commitment in staffing and funding. Another problem with long term studies is that drop outs are a major problem for a variety of reasons. If this drop out rate is too high the validity of the study is likely to be severely impaired. It is for these reasons that relatively few prospective studies are performed and we have little data on the incidence of OA. One rare example is the Baltimore longitudinal study of ageing.^{5 11}

Another similar approach is to perform sequential surveys in the populations whereby an initial population survey is followed up, say five or 10 years later, on a subgroup of the original sample and new cases identified. Examples of this include the NHANES 1 and the subsequent follow up known as the NHANES epidemiologic follow up study (NHEFS),⁹ and the Tecumseh community health survey.¹²

Epidemiological studies assessing course and prognosis

These studies usually involve a form of cohort study but using clinic derived cases rather than population based subjects. Similar problems arise in this form of study to that of the prospective studies with regard to measurement of baseline parameters, including potential confounders such as obesity, trauma, or other comorbid disorders. The other major problem is maintaining the status of the patient cohort and trying to minimise losses to drop outs. This is the most difficult, given the fact that most clinic patients are elderly and are likely to have a number of other diseases. One representative study retrospectively followed up 169 patients for 13 years and obtained complete data on only 63.¹³

Choosing the outcome measure is also a major difficulty. Choices include disability or functional status, symptoms, joint surgery, and

finally the ultimate outcome mortality. A number of specifically designed functional indices (for example, WOMAC, Lequesne, Health Assessment Questionnaire, Arthritis Impact Measurement Scale) have been devised for OA, though there is no clear consensus as to which is the most appropriate. There are also a number of performance based functional tests applicable for the different joint groups—grip strength, timed walk, timed sitting/standing. The other major problem in assessing follow up is how long a time period is needed to assess outcome as there is little data on which to base expectations. Radiographs are another way of assessing progression, though the original classification system of Kellgren and Lawrence³ was never designed to look longitudinally at change. Indeed, this may be the major use of the new individual feature scales. There is some evidence that radiographic change is extremely slow using traditional techniques; the Baltimore longitudinal study of ageing has shown that it may take 10 years on average to progress one grade on the Kellgren and Lawrence scale for OA of the hands.⁵ Other studies of OA of the knee have shown that even over 10 year periods most clinic patients may not actually alter grade at all, with only a minority deteriorating.^{13 14}

Genetic epidemiological studies

Assessing the genetic component of any chronic disease is an essential part of epidemiology. There are two main ways of doing this: (a) twin studies and (b) family studies. Twin studies are generally considered to be the most powerful whereby concordance of disease is compared between identical and non-identical twins who are assumed to share the same environmental factors. The concordance rate in the identical twins therefore reflects the maximum amount of genetic influence on the disease. These studies also enable environmental factors to be studied in discordant twin pairs. To date there are no good twin studies that have been performed on OA, though a small, highly selected sample of twins did show high concordance rates.¹⁵ A large population based twin study is currently in progress.

Family linkage studies, where several generations within a family are examined, can provide useful data, particularly on assessing the type of inheritance. A major problem with family studies involves case definition and the fact that it is difficult to call relatives unaffected when the disease onset may be late in life or occur in other joints. For this reason OA is difficult to study in families as there may be only a short time between the expression of the disease and death. In these family studies it is important to either have control pedigrees to look at for the prevalence or incidence of OA or, alternatively, have sufficiently accurate data from the population so that estimates of the numbers of expected OA cases can be made. Linkage studies can also be performed and a small number of large pedigree families have been identified which have shown linkage with

the collagen type II gene (COL 2AI).¹⁶ These families have, however, also had chondrodysplasia and the results have not been confirmed in families with idiopathic OA.

Migration studies

Migration studies are also a potentially powerful tool for separating genetic and environmental contributions to a disease. Examples where these have been useful include the study of Japanese immigrants to the USA over successive generations. They have shown decreasing rates of gastric and increasing rates of breast carcinoma, suggesting a powerful environmental effect on these diseases. To our knowledge no studies have yet been performed in OA. Possible opportunities include the study of Chinese immigrants to the USA, looking at possible changes in the incidence of osteoarthritis of the hip—a disorder rare in Hong Kong Chinese subjects.¹⁷ Other examples include studying Afro-Caribbean or West Indian populations who have migrated to the United Kingdom to look for changes in the prevalence of OA at different sites.

Summary

In conclusion, though there are numerous opportunities and different approaches to studying the epidemiology of OA, we have concentrated on some of the methodological problems and difficulties inherent in these methods. We think it is important that researchers are aware of these problems before undertaking such studies. In addition, readers of published studies need to be aware of these potential pitfalls before being able to make valid judgements on research papers. We hope, however, that stressing these problems does not dissuade present and future investigators from participating in this area of research. Despite difficulties inherent in the epidemiology of chronic diseases and OA in particular, studies may uncover modifiable risk factors for the development and progression of OA which could lead to important preventive strategies.¹⁸

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