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Principles of clinical epidemiology

Annette C. Moll, Michiel R. de Boer and Lex M. Bouter

INTRODUCTION

During the last decade evidence-based medicine (EBM) became a dominant approach in many medical fields, including ophthalmology.^{1,2} Clinical epidemiologic studies provide evidence that can aid the decision-making process. The aim of this chapter is to provide the reader with some basic knowledge to allow them to judge the value of clinical epidemiological papers. Examples from ocular oncology will be used to illustrate the methodological principles.

RESEARCH QUESTION

A clinical epidemiological study should always start with a well-defined research question. Similarly, when reading a paper, one should always keep in mind the question(s) the authors wish to address (Fig. 1.1). Research questions can be aimed at explanation or description and are often categorized as etiologic, diagnostic or prognostic (Table 1.1). For example, an explanatory research question related to etiology in the field of ocular oncology is: are children born after in vitro fertilization at higher risk of developing retinoblastoma than children born after natural conception?³ A correct explanatory research question should contain information on the patients, interventions, contrast and outcomes (PICO).

OUTCOME MEASURES

Traditionally, prevalence, incidence and mortality (survival) have been the outcome measures in clinical cancer epidemiology studies. More recently, quality of life has become increasingly popular. In ophthalmic oncology, visual acuity is an important outcome measure.

Prevalence refers to the proportion of the population with the condition of interest. Usually prevalence is given for a specific moment in time (point prevalence), but sometimes it is estimated for a period of time (e.g. 1-year or lifetime prevalences). For example, the lifetime prevalence of uveal melanoma in a white population with ocular (dermal) melanocytosis is estimated to be 0.26%.⁴

Incidence Whereas prevalence relates to existing cases, incidence relates to the proportion of new cases in a certain population. It is important that the population under investigation is at risk of developing the condition. For example, persons with bilateral enucleation are no longer at risk of developing uveal melanoma. There are two different measures of incidence: cumulative incidence (CI) and incidence density (ID). CI is the proportion of new cases in a population at risk over a specified period. For example, the cumulative incidence of

second malignant neoplasms in hereditary retinoblastoma patients is 17% at the age of 35 years.⁵ ID refers to the rate of developing the condition during follow-up, usually expressed as a proportion of person-years at risk.

Mortality refers to the incidence of death. The mortality rate can be all-cause, indicating all deaths, or disease specific, for instance mortality caused by melanoma or retinoblastoma. Case fatality rate refers to the proportion of patients with a given disease who will die from that disease, and thus reflects the seriousness of the condition. More formally put, it concerns the cumulative incidence of death among the diseased. Often the survival rate is presented. For example, the 2-year survival rate after breast cancer metastases to the choroid is 30%.⁶ This means that of all the patients diagnosed with choroidal metastases from breast cancer, 30% are still alive 2 years after diagnosis. It is important to realize that these mortality figures are highly dependent on certain characteristics of the population, such as age, stage of cancer, and comorbidity.

Quality of life With the increasing survival rate and severe side effects of some treatment modalities, quality-of-life measures have become increasingly important in ophthalmic oncology. These measures encompass symptoms as well as physical, social and psychological functioning from the patient's perspective. Usually quality of life is assessed with a structured questionnaire and scores are summarized assuming an interval scale. Several questionnaires have recently been developed for patients with ocular diseases, such as the measure of outcome in ocular disease (MOOD).⁷

MEASURES OF ASSOCIATION

In epidemiological research we are usually interested in associations between certain interventions or exposures and their respective outcomes, e.g. is there an association between paternal age and retinoblastoma in the offspring?⁸ There are several statistical approaches that can be used to quantify associations, either as a ratio or as a difference, depending on the study design and statistical method used (Table 1.2).

Relative risk The ratio of cumulative incidence between a group of exposed and unexposed individuals or treated and untreated patients is the relative risk (RR). For example, in The Netherlands the RR of retinoblastoma in children conceived by in vitro fertilization is between 4.9 and 7.2. This implies that the risk of developing retinoblastoma is

Fig. 1.1 Steps in designing clinical epidemiological research.

Table 1.1 Types of epidemiological research

Type of research	Purpose	Example
Etiology (including prevention)	To examine possible etiological factors for the occurrence of a disease	Association between ultraviolet radiation and uveal melanoma
Diagnosis	To examine the usefulness of diagnostic tests for the disease	Accuracy of magnetic resonance imaging in determining choroidal invasion of retinoblastoma
Prognosis (including interventions)	To examine possible prognostic factors for the disease	Association between external beam therapy for retinoblastoma and the incidence of second malignant neoplasms

between 4.9 and 7.2 times higher for children conceived after IVF than for naturally conceived children.

Hazard ratio The ratio of incidence density between a group of unexposed and exposed patients is the hazard ratio (HR), which has a similar interpretation to the RR. This measure is often used in relation to mortality, because we are generally interested not only in the proportion of patients that die, but also in the time from baseline (diagnosis or start treatment) until death. A special application of the HR is the ratio of the observed to the expected number of cases (O/E ratio). In this case the observed ID is calculated for the study population and this is compared to the expected ID derived from a population registry (e.g. cancer registration). For example, in a study of lifetime risks of common cancers among hereditary retinoblastoma survivors ($n = 144$), 41 cancer deaths were observed, whereas only 7.58 deaths due to cancer were expected. These data can be expressed as a standardized mortality ratio of 5.41.⁹

Odds ratio The odds ratio (OR) is the most commonly reported measure of association in the literature, because this is the statistic that can be derived from popular logistic regression analysis. The OR is the ratio of the odds of outcome of interest between the exposed and the unexposed.

Differences in risk are preferably reported as the outcome of randomized controlled trials. The risk difference (RD) is easy to interpret and can be used to calculate the number of patients needed to treat (NNT) to prevent one extra event (e.g. death) compared to the standard treatment or placebo. The NNT can be calculated as inverse of RD ($1/RD$).

Differences in mean score For scores on interval scales, such as quality of life, differences in mean score between exposed and unexposed participants are the only measure of interest.

Table 1.2 The relation between outcome, measures of association, study design, and statistical methods

Outcome	Measure of association	Computation	Study design	Statistical method
Prevalence	Prevalence rate	P_1/P_2	Cross-sectional	χ^2 test Logistic regression analysis
Odds of exposure	Prevalence difference	$P_1 - P_2$	Cross-sectional	χ^2 test
	Odds ratio	Odds of exposure group 1/odds of exposure group 2	Case control study (cohort study, RCT)	χ^2 test Logistic regression
Cumulative incidence (CI)	Relative risk	CI_1/CI_2	Cohort study/RCT	χ^2 test
	Risk difference	$CI_1 - CI_2$	RCT	
Incidence density (ID)	Hazard ratio	ID_1/ID_2	Cohort study/RCT	Kaplan–Meier Cox regression
	Risk difference	$ID_1 - ID_2$	RCT	Kaplan–Meier
	O/E ratio	Observed ID/expected ID in general population	Cohort study/registry study	
Quality of life	Difference in mean score	$\chi_1 - \chi_2$	Cohort study/RCT	Independent <i>t</i> -test Linear regression analyses

P_1 , prevalence group 1; P_2 , prevalence group 2; CI = cumulative incidence; CI_1 , CI group 1; CI_2 , CI group 2; ID, incidence density; ID_1 , ID group 1; ID_2 , ID group 2; O/E ratio, observed to expected ratio; RCT, randomized controlled trial; χ_1 , mean score group 1; χ_2 , mean score group 2.

PRECISION OF THE ESTIMATE

When interpreting an outcome, we want to know not only the numerical value of the point estimate, but also the precision with which it has been estimated. In other words, can we be confident that the observation is not just a chance finding? The usual standard for accepting an outcome beyond chance is P (probability) < 0.05 . A more informative description is provided by the 95% confidence interval (CI). The rough interpretation of the 95% CI is that there is a 95% chance that the real value lies within the span of the confidence interval.

Statistical significance is strongly dependent on the sample size of a study. This means that in very large samples an only marginally elevated association can be statistically significant. In contrast, in small samples, strong associations are sometimes not statistically significant. The associations, although statistically significant, need not be clinically important. Therefore, the interpretation of findings should not rely solely on statistical significance.

BIAS

An estimate can be very precise, but still not be accurate because of bias. Three main sources of bias exist: confounding, selection, and information bias.

Confounding occurs when the association between exposure and outcome is influenced by a third variable that is related to both the exposure and the outcome (Fig. 1.2). A recent study found an association between cooking (as occupation) and the incidence of ocular melanoma.¹⁰ It could be argued that as many cooks work at night it is possible that they could have relatively high exposures to sunlight, as their leisure activities take place during the day, compared to people who work during the day. It is implied that the association between cooking and ocular melanoma could potentially (in part) be explained by a higher exposure of cooks to sunlight.

Selection bias may occur when the chance of being included in the study population is not random for all members of the source

Fig. 1.2 Schematic representation of confounding.

population. For example, patients with an advanced tumor stage are more likely to be referred to a special cancer center than are patients with a less advanced stage. This is called referral bias. Selection bias could also be introduced in a study by choosing the wrong control group, especially if controls are selected from hospital patients.

Information bias occurs when outcome or exposure variables are not accurately assessed. This is especially problematic when this occurs differently for exposed versus non-exposed cases, or for cases versus controls. A well known type of information bias is recall bias. This refers to the phenomenon that patients tend to remember more details about exposures that are possibly related to their disease than do controls. For example, patients with uveal melanoma are probably more aware of the fact that their disease could be related to sunlight exposure. This can lead to an underestimation of exposure in controls and hence an overestimation of the association with sunlight exposure.

STUDY DESIGNS

There are several research designs, such as case series, cross-sectional, cohort, randomized control trial, and case-control study, that can be adopted to address the research question. Each design has its advantages and disadvantages (Table 1.3).

Table 1.3 Advantages and disadvantages of study designs

Considerations		Type of study			
Methodological		Cross-sectional	Cohort	RCT	Case-control
	Confounding	–	–	+	–
	Selection bias	–	+/-	+/-	–
	Information bias	+/-	+/-	+/-	–
	Prior exposure	–	+	+	–
	Incident cases	–	+	+	+
Practical	Length of study	+	–	+/-	+
	Organization	+	+/-	–	+/-
	Expenses	+	–	–	+

Negative score (–) indicates disadvantage compared to other study designs.
 Positive score (+) indicates advantage compared to other study designs.
 Equivocal score (+/-) indicates neither advantage nor disadvantage compared to other study designs.
 RCT, randomized controlled trial.

Case series In a case series the authors present the clinical data regarding a group of patients, e.g. the response of tumors to chemotherapy combined with diode laser in retinoblastoma patients. The disadvantage is that this kind of study is not randomized and does not have a comparative design, and does not permit an answer to a question such as 'there is a good response, but compared to what?'¹¹

Cross-sectional study In a cross-sectional study the outcome (and exposure) are assessed at one point in time. In addition, outcome between exposed and unexposed study participants can be compared in order to explore etiological questions. In a cross-sectional study on the association between iris color and posterior uveal melanoma, melanoma patients ($n = 65$) with a light iris color were significantly more likely to have darker choroidal pigmentation than controls ($n = 218$) ($P = 0.005$). In addition, darker choroidal pigmentation was associated histologically with an increased density of choroidal melanocytes ($P = 0.005$). The authors concluded that increased choroidal pigmentation, as a result of an increase in the density of pigmented choroidal melanocytes, is not protective but may actually be a risk factor for the development of posterior uveal melanoma in white patients.¹²

The cross-sectional study design has the advantage that it is relatively easy to plan, only one measurement is needed, and it is inexpensive and quick to perform. As both exposure and outcome are measured at the same time, we cannot be sure that the exposure preceded the outcome (the most important criterion for causality). Moreover, the associations found in a cross-sectional study might not be applicable to incident cases.

Cohort study Some of the problems listed above can be overcome by conducting a cohort study. At baseline, one starts with a cohort of people free from disease and the exposure(s) of interest being assessed at baseline. During or at the end of follow-up, incident cases in both the unexposed and the exposed group are identified and RRs or HRs can be calculated. Despite the theoretical advantages of a cohort design, there are some practical disadvantages. The cohort studies are often expensive because they need large sample sizes and/or long follow-up to accumulate enough incident cases for meaningful analysis.

Moreover, the potential bias of (residual) confounding can never be totally excluded.

Randomized controlled trial is a specific type of cohort study. At the start of the study, participants are randomly assigned to the intervention group (treatment under investigation) or a control group (no treatment, placebo, or standard treatment). After the start of a treatment patients often get better. This may be due to the treatment or to other circumstances, such as spontaneous resolution, effective co-interventions, and placebo effects. The best comparison is often between the new treatment and the best available one, not the sham treatment.¹³ The randomization, if successful, ensures that confounding factors are evenly distributed between the intervention and control groups.

For clinicians interested in evidence pertaining most directly to a particular class of patient, subgroup analysis can be very informative. The strength of evidence for subgroup effects depends on whether hypotheses have been defined prior to analysis, whether potential problems regarding multiple comparisons have been considered, and whether the effects found are biologically plausible. Using these guidelines, the reader of a trial report should be able to decide whether the presented subgroup effects are of clinical importance or if the overall result is a better estimate of treatment effect.¹⁴

Case-control study In contrast to cohort studies, the starting point in case-control is to assess not the exposure status, but the disease status. People with the disease of interest are selected and a control group of people without the disease is subsequently recruited. The control group should include people from the same source population as the cases, implying that if any of the controls had developed the disease, they would have been eligible for inclusion in the study as a case.

The selection of a valid control group is important in case-control studies. It is possible to select population controls, hospital controls, friends or relatives of patients, or any variant of these.¹⁵ Case-control studies have the advantage of being relatively quick and inexpensive to conduct, and are especially appealing in rare diseases. A disadvantage is the large potential for selection bias, especially in the recruitment of controls. In addition there is also a real danger of information (recall) bias.

Pilot study A pilot study is often performed before the start of a large study. Its aim is to improve the methodological quality and evaluate the feasibility of the study. The results of a pilot study are often used to gain an impression of the efficacy of an intervention, which should then be tested in a larger study. The inclusion of pilot study results in a later cumulative meta-analysis may lead to sufficient power to assess the efficacy of an experimental intervention.¹⁶

Systematic review In a systematic review all the available evidence (literature) on a certain topic is reviewed in a systematic, transparent, and reproducible manner. These studies can be especially useful when results from single studies are contradictory and/or have large confidence intervals because of small sample sizes. When the studies in a systematic review are reasonably homogeneous, their results can be pooled in a meta-analysis. This results in one effect size for all the studies together, with a much smaller confidence interval than for the individual studies. An example is a systematic review on

the survival of patients with uveal melanoma treated with brachytherapy. The result of this meta-analysis showed that the 5-year melanoma-related mortality rate was 6% for small and medium tumors, and 26% for large tumors.¹⁷

CONCLUSIONS

In general, ophthalmic tumors are rare compared to other ophthalmic diseases. Therefore, it is difficult to conduct large studies with enough power to obtain statistically significant and clinically relevant results. Several studies are published each year, most of them descriptive and concerning retrospective patient series. To conduct a randomized clinical trial international collaboration is necessary, so as to include enough patients in the different treatment arms of the study. Furthermore, uniform definitions and study methodologies are very important so that the different studies in the literature can be compared and systematic reviews and meta-analyses performed.

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