ICMR Centenary 1911-2011: National Institute of Medical Statistics Foundation Day Oration, 28 Sep 2011.

The Case for Case-Control Studies in Medical Research.

Prasanta Mahapatra[1]

Respected Dr. Katoch, Secretary to Governemnt of India & DG ICMR Dr. Pande, Director, National Institute of Medical Statistics, doyens of biostatistics on the dais. Firstly, I would like to thank the ICMR, and its leadership for this opportunity to share with you my thoughts.

While preparing for this day, I have pondered, how can medical statistics help improve the state of medical care? The potential for better medical care is dependent on the scientific temper of our medical profession. The question is how can we improve the scientific temper? The search for evidence is fundamental to the practice of modern day medicine. There is now a movement towards evidence based medicine. But evidence does not come neatly. How do we get past the veil of perception, and how do we tease out reality from illusion? Random noise is a fact of life. We do not have access to all aspects of any experience. Our cognitive stance affects what we perceive and how we process those inputs. Hence, in general, we like to start with skepticism, and look for evidence to improve our understanding. The search for a criterion of truth and knowledge prompted Descartes to start with a system of doubt. Our search for explanations and the quest for knowledge uses strategies, commonly referred to as scientific method. Four key elements of the scientific method are; (a) descriptive, (b) analytic, (c) deductive, and (d) experimental.

Inevitably, we have to make do with shades of evidence. Consequently, various classifications of the levels of evidence exist in the field of medicine. For example; the United States Preventive Services Task Force, categorises evidence into three levels. Properly conducted randomised controlled trials are at the top, rated as level-I evidence. Level-II evidences are further stratified into three sub classes. Evidence from well designed cohort and case control studies are rated at level-II-2. Level-III evidences are clinical experience, professional opinion, expert committee reports and other descriptive studies. Many classifications, however, place case-control studies a notch below cohort studies. For example; (a) the United States department of Health and Human Services, rates prospective studies at level-2, and case-control studies at level-3; (b) the Oxford Centre for Evidence Based Medicine, lists cohort studies at

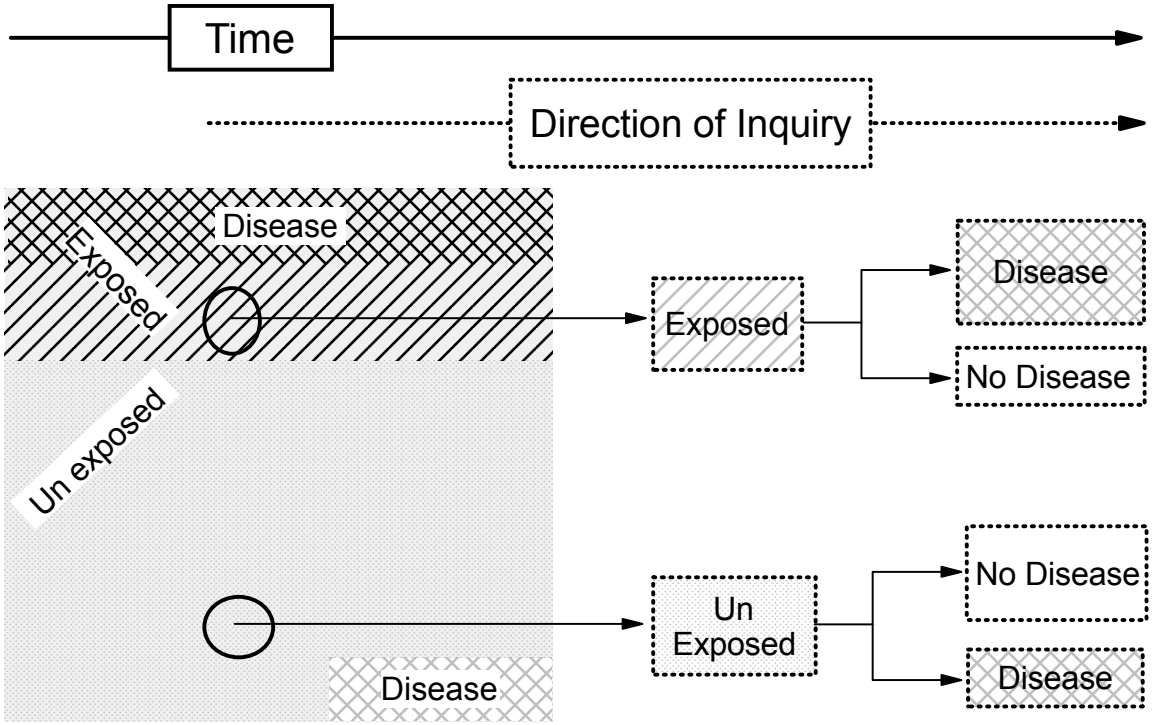
[1] Principal Secretary, Irrigation & Command Area Development Department, Government of Andhra Pradesh, Director & Vice Chancellor, Nizam's Institute of Medical Sciences, and Hon. President, Institute of Health Systems, Hyderabad.

level-2 and case-control studies at level-3. Sackett et al. also consider the evidence from cohort studies higher at level-2, and that from case-control studies at level-3.

Obviously, the cohort study happens to be the preferred design to establish causative relationship between exposures to potential risk factors and disease. In its simplest form, two groups of disease free persons, one exposed and the other unexposed, to the risk factor of interest, are followed-up over a period of time, to observe the incidence of adverse events. The incidence of disease development in the exposed group is compared with that of the unexposed group, to estimate the relative risk of disease.

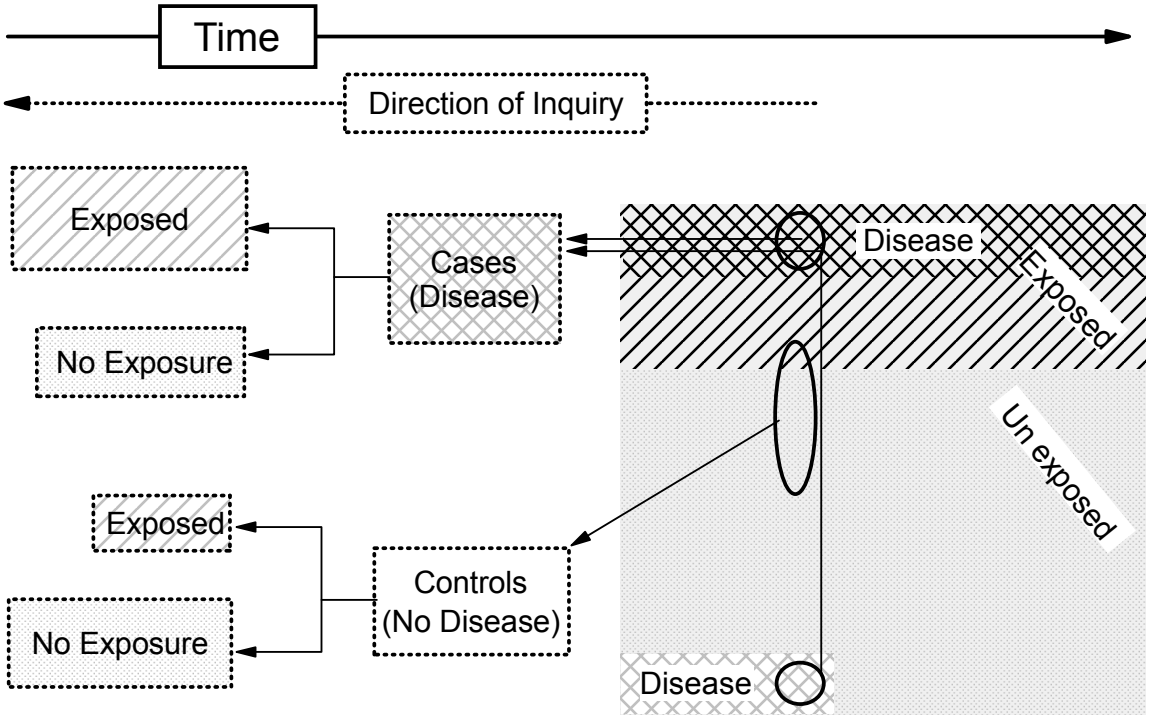
Examples of landmark cohort studies are; (a) the Framingham Heart Study, (b) the British Physicians Study on the effect of smoking, (c) the Nurses Health Study on diet and disease, and (d) the Multi center AIDS cohort study.

Figure-1: Schematic representation of cohort study design.



Case control studies start with cases and controls and look for history of exposure. Recall that subjects in all groups of cohort studies are disease free to start with. Both the exposed and unexposed group are followed-up to count events of interest. On the other hand, case control studies starts with a sample of people with the disease of interest, namely the cases, and another group without that disease, namely the controls. The direction of inquiry in case control studies is focussed backwards, looking for history of exposure.

Figure-2: Schematic representation of case - control studies.



Here I stop for an interesting aside...

The two study designs differ in the way we measure the probability of an event. Cohort studies yield straight forward probabilities, which is a proportion ranging between 0 and 1. Case control studies rely on odds of exposure, which is an alternate measure of chance. The probability measure is denominated on the total probability of all events. The odds of an event is denominated on the probability of the complement event(s). Thus odds of an event with respect to its complement can range from 0 to infinity. For probabilities up to about 0.1, the odds and probability values are close together. As the probability of an event increases, the odds value diverges and blows up into a large number. Our mind handles differences between large numbers more easily than equivalent differences in small numbers. The strategy is some what similar to embedding of tissue into paraffin, to cut fine slices for microscopy. That explains gamblers preference for odds as a measure of chance.

Cohort studies yield estimates of cumulative incidence, and incidence rates, allowing for computation of relative risks as well as rate ratios. The odds ratio from a well designed case control study happens to be an unbiased estimate of the relative risk.

As the case-control study developed during the first half of the twentieth century, there were doubts about the comparability of the odds ratio obtained from these studies, with relative risk derived from cohort studies. In 1951, Cornfield showed that the odds ratio approximates the relative risk, if the disease is rare, and the cases and controls are representative. Subsequently,

Miettinen (1976) showed that the rare disease assumption can be relaxed. The odds ratio happens to be an unbiased estimator of the relative risk, provided the case-control study recruits incident cases, controls are representative of the population, and selection of cases and controls are independent of exposure status.

Case control studies are vulnerable to biases in selection of cases as well as the controls. For example, Horwitz and Feinstein (1979) have catalogued about twelve methodological standards to minimise potential biases of case control studies. The text book of epidemiology by Hennekens and Burring (1987) lists out biases in selection of cases or controls, and differential reporting of exposure information between cases and controls as the most important pitfalls of case control studies.

Cohort studies are time consuming and expensive. They require strong organisation, long term collaborations, and effective mechanisms of recruitment of new scientists, for effective follow-up. The number of medical professionals, participating in cohort studies is constrained by resources. Naturally cohort studies are not easily handled by small groups and solo researchers working in clinical settings. On the other hand, case control studies are well suited for research in standard clinical settings. Most of our medical professionals are hospital based. Case-control studies provide them an opportunity to engage in research. Even partial engagement in research, by at least a subgroup of medical professionals in any hospital or health care setting substantially changes the professional discourse towards, medical discoveries, and evidence based medicine. At present India needs both. We carry a large part of the world population. We can not expect to provide the best medical care to our people, without developing a scientific temper and continuously reinforcing the evidence base of our clinical practice.

I think the National Institute of Medical Statistics, can play a vital role to inculcate scientific temper among our physicians. The potential for biases in case-control studies can be minimised by cultivated expertise. The NIMS could consider to develop expertise in statistical methods for analysis of case control data. Organise a massive program to develop physician capacity for case control studies. Launch a national program of ad-hoc research grants for case control studies. Get the participating researchers to publish their findings. In the process we would have engaged thousands of doctors to create a culture of medical research, generated hundreds of hypotheses for further study, and improved the evidence base of medical practice in our country.

Please note that, I am not arguing for case-control over cohort studies. I prefer cohort over case-control study design, as a more elegant means to test hypotheses on causative relationships and measure the effect of risk factors. I

think the ICMR should conceive well designed cohort studies, and sustain them over long periods of half a century or more.

I am arguing for exploitation of the case-control design as a means to secure the massive engagement of a large number of medical professionals. This engagement will help advance evidence based medicine and harness the creative energies of the large body of medical professionals. Hundreds of hypotheses, generated in this process, can fuel further medical research. That, I think, will help position India at the fore front of medical discoveries. We have a large body of doctors. Our people are known to have the intellect for knowledge creation. The medical and health is founded on the twin pillars of knowledge base and high skill. The dream is to harness this energy for India's good and in the process we will also be able to help others in the world.

Can we do it? I think we can! All we need is a few determined women and men, fired with the zeal and inspired to lead by ground breaking medical discoveries, and path breaking health system development.

As Patanjali, the great author of Yoga Sutras, said;

'When you are inspired by some great purpose,

some extraordinary project,

all your thoughts break their bonds;

Your mind transcends limitations,

your consciousness expands in every direction, and

you find yourself in a new, great and wonderful world.

Dormant forces, faculties and talents become alive,

and you discover yourself to be a great person

by far than you ever dreamed yourself to be.'

I wish you all health and happiness, and once again thank you for this opportunity.

Jai Hind.

References:

1. Evidence Based Medicine Working Group. Evidence Based Medicine. A new approach to teaching the practice of medicine. Journal of American Medical Association. 1992 Nov 4; 268(17):2420-2425.

2. Sackett DL. Evidence based medicine: what it is and what it isnt' Br Med J. 1996; 312: 71-72.

3. Sackett, DL, Straus, SE, Richardson, WS, et al. Evidence-based medicine. How to practice and teach EBM, 2nd edition, Churchill Livingstone, Edinburgh 2000.

4. Dawber TR. The Framingham Heart Study: the epidemiology of atherosclerotic disease. Cambridge, MA: Harvard University Press, 1980.

5. Doll R, Peto R, Wheatley K, et al. Mortality in relation to smoking: 40 years observation on male British doctors. BMJ 1994; 309:901-11.

6. Colditz GA, Willett WC, Hunter DJ, et al. Family History, age, and risk of breast cancer: prospective data from the Nurses' Health Study. JAMA, 1993; 270: 338-43.

7. Polk BF, Fox R, Brookmeyer R, et al. Predictors of the acquired immunodeficiency syndrome developing in a cohort of seropositive homosexual men. N Engl J Med 1987; 316:61-6.

8. Cornfield Jerome. A method of estimating comparative rates from clinical data. Applications to cancer of the lung, breast and cervix. Journal of the National Cancer Institute. 1951.

9. Miettinen Olli S. Estimability and Estimation in case-referent studies. American Journal of Epidemiology. 1976; 103(2):226-235.

10. Horwitz Ralph I. and Feinstein Alvan R. Methodologic standards and contradicotry results in case-control studies. The American Journal of Medicine. 1979; 66:556-564.