Review of *Observational Studies Analyzed Like Randomized Experiments: An Application to Postmenopausal Hormone Therapy and Coronary Heart Disease*

Grace Yi Chen

The motivation of this study is that Women's Health Initiative (WHI) randomized trial found larger coronary heart disease (CHD) risk in women treated with hormone therapy than those treated with placebo, but previous observational studies suggested reduced CHD risk in hormone users. The authors decided to reanalyze the Nurses' Health Study (NHS) observational data in a way that is comparable with the WHI randomized trial to find the reason for this difference. The authors used observational analog intention to treat (ITT) principle and adjusted covariates in the Cox model to get the hazard ratio of CHD. In addition, the authors used inverse probability weighting (IPW) analysis to get adherence-adjusted effect estimates since the ITT effect would vary with different adherence proportions. The authors discovered that much of the apparent WHI and NHS ITT estimate difference is because the two studies include patients with different time since menopause at hormone therapy initiation and length of follow-up. Also, the reanalysis of NHS data suggested that hormone therapy may increase the long-term CHD risk only in women who started hormone therapy at 10 or more years after menopause.

I think this article did a good job reanalyzing observational data in a way that is comparable to a randomized trial using reliable statistical analysis methods. It not only answers the question why there is a difference between observational and clinical trial results, but also gets new insights from the observational data. CHD is a complicated disease and have many risk factors. Also, it is sometimes hard to insist using hormone therapy for a long time. These create a lot of problems both in the observational studies and clinical trials. The original NHS studies might not be comparable to the clinical trials because of these reasons. In addition, the original NHS studies were more of an adherence adjusted analysis since they updated treatment status at the return of each questionnaire without knowing what happened within the time intervals. Although clinical trial designs are able to draw causal inference, they are usually expensive to be implemented. Thus, we need to utilize observational studies in complementary to clinical trials by using robust and innovative statistical methods. Moreover, I learnt a lot from the 3 commentaries and the authors' response. I think the discussants' views are related to their personal background since the discussant with negative response is an epidemiologist and was involved in the previous NHS studies. He might think the statistically method which is different from what he used in his paper is too complicated to be understood. In the future, I hope there will be more novel and robust statistical methods being recognized in epidemiological studies.

Questions:

1. How should clinical trials deal with large non-adherence rate?
2. Why there are a lot of new statistical methods analyzing observational data but they are barely used in scientific research?