ONLINE MATERIAL THAT ACCOMPANIES CHAPTER 8

Box 1. A case study in non-comparability: hormone treatment and cardiovascular disease

Women transitioning through menopause have been treated with synthetic forms of two hormones, estrogen and progesterone, for many decades. Estrogen and progesterone naturally circulate at varying levels in women's bodies throughout the menstrual cycle. When women undergo menopause, their levels of estrogen and progesterone precipitously drop and they experience physical symptoms that may include hot flashes, irritability, and anxiety. Treatment with synthetic estrogen and/or progesterone was commonly prescribed to treat these symptoms.

More than twenty studies and several meta-analyses were conducted in the 1970s and 1980s examining health outcomes among women who did vs. did not take hormone therapy (Barrett-Connor and Bush 1991). These were not randomized trials, rather observational studies in which women who were prescribed and chose to take hormone therapy were compared with women who were either not prescribed or chose not to take the therapy. The results of these observational studies were nearly unequivocal. Women using hormone therapy had a lower risk of many cardiovascular disease endpoints compared to women not using hormone therapy. Meta-analyses indicated that the reduction in risk among hormone users was almost 50% (Stampfer and Colditz 1991).

However, there were many reasons to believe that these groups were not comparable (Barrett-Connor 1991). Women using hormone therapy were more highly educated, had lower body mass indexes, were less likely to smoke and more likely to exercise, and were more likely to take multivitamins and make other efforts at preventative care. Thus, while many in the medical and research community recommended treatment of all post-menopausal women with estrogen treatment, others suggested that randomized trials were necessary before such wide-spread conclusions could be reached (Barrett-Connor 1995).

The Women's Health Initiative was the largest such clinical trial to be undertaken. More than 370,000 women were screened for inclusion and almost 17,000 were ultimately enrolled in a hormone replacement trial (Rossouw, Anderson et al. 2002). Those women were randomized to receive either a combined protocol of estrogen plus progesterone or a placebo protocol. In contrast to the observational studies, the two comparison groups had an equal distribution of age, race, body mass index, parity, blood pressure, and medical history. Women were followed for approximately five to seven years to examine cardiovascular disease, stroke, and cancer endpoints, among others.

Investigators not only found no evidence for a protective effect of hormone therapy on cardiovascular disease. On the contrary, women who were randomized to receive hormone therapy had higher rates of coronary heart disease, pulmonary embolism, and stroke compared to women randomized to placebo. These unexpected results underscore how important a careful assessment of confounding is in observational epidemiology. While there are important criticisms of the randomized trial, including a substantial proportion of women who stopped their protocol or switched protocols, a number of trials began to be published with consistent results, suggesting that hormone therapy is at least not protective against cardiovascular disease and is potentially harmful for cardiovascular disease.

Citations

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