Brief Report

Postmenopausal Estrogen and Prevention Bias

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In the last decade many investigators reported that postmenopausal women taking estrogen were at reduced risk for cardiovascular disease compared with women not taking estrogen (1). Many clinicians in the United States now believe that replacement estrogen prevents heart disease. The results are fairly consistent and biologically plausible. Replacement estrogen lowers low-density lipoprotein (LDL) cholesterol and raises high-density lipoprotein (HDL) cholesterol (2) and may also lower blood pressure, blood glucose, and plasma insulin (3). If estrogen does prevent heart disease, the quantitative benefit would far exceed any known or postulated adverse events, including cancer (4).

Observational studies suffer from several types of bias. Postmenopausal women treated with estrogen tend to be upper middle class and relatively well educated, factors that offer significant protection from heart disease. Women prescribed estrogen are often healthier before treatment in terms of blood pressure and other risk factors (5, 6). In addition, women who take elective estrogen for prolonged periods are, by definition, compliant. In clinical trials (7, 8), good drug adherence carries a significantly reduced risk for cardiovascular disease compared with poor adherence, even when the prescribed medication is placebo (7, 8).

Finally, behaviors and preventive measures may differ by estrogen use, possibly because women who are prescribed estrogen must see their physician regularly for follow-up and prescription renewal. Investigators in Sweden, for example, who reported an increased risk for breast cancer in all women treated with a noncontraceptive estrogen (9) also reported that estrogen-associated breast cancer carried a significantly better prognosis than breast cancer occurring in the absence of estrogen (10). One plausible explanation is that breast cancer was diagnosed earlier in the estrogen-treated women. If this analogy holds, then some of the benefits or "protection" attributed to estrogen may in fact be due to better behaviors, including use of the health care system.

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Methods

From 1984 through 1987, 1057 postmenopausal women aged 50 to 79 years who were residents of a socioeconomically upper-middle-class California community participated in a clinic evaluation that ascertained current and past use of replacement estrogen (1). All subjects were white and most were in social classes I through III (Hollingshead Index). In 1989, an average of 4.4 years later, 1008 (95%) of these women responded to a mailed health survey questionnaire. Subjects were asked if they had increased, decreased, or not changed their amount of dietary fat, salt, and exercise; they were also asked an open-ended question about other changes in life-style designed to promote health. They were asked whether, in the past 12 months, they had seen a physician for any reason, had their cholesterol or blood pressure checked, had a stool examination for blood, had a rectal examination, mammogram, or Papanicolaou smear, or done anything else specifically recommended to prevent disease.

These behaviors and preventive services were compared by never, past, and current estrogen use as reported from 1984 to 1987, when hormone use was validated by prescriptions brought to the clinic for that purpose. Hormone use reported on the mailed questionnaire showed nearly identical associations. Data are presented only for validated estrogen use. (Current users were nearly 4 years younger than never-users but age adjustment did not significantly alter the results and only unadjusted data are shown.) Comparisons were made using the Mantel extension test for trend.

Results

Among the 1008 respondents, 238 reported never using estrogen, 461 reported past use, and 309 reported current use. As previously reported, most women used or had used an oral unopposed conjugated estrogen (6). Women in every estrogen-use group were, on average, more than 70 years of age at the time they answered the questionnaire.

As shown in Table 1, there was a statistically significant trend to more reported exercise and other life-style changes (answers to this open-ended question included weight loss; increased dietary fiber, potassium, or calcium; and stress reduction) among users of estrogen. Reduced dietary fat and salt were reported by over 70% of all women in this educated cohort and did not vary significantly by hormone use. Less than 15% of these women smoked cigarettes at baseline, a behavior that did not differ by estrogen use status.

Over 90% of the cohort had visited a physician at

Table 1. Percentage of 1008 Postmenopausal Women with Reported Health-related Behaviors and Preventive Health Care by Estrogen Replacement Therapy

Variable	Estrogen Use			*P* Value*
	Never (n = 238)	Past (n = 461)	Current (n = 309)	
	← % →			
Behavior change				
Decreased dietary fat	72.9	75.5	78.0	> 0.05
Decreased dietary salt	72.5	71.3	72.8	> 0.05
Increased daily exercise	28.9	30.9	38.0	< 0.05
Other life-style changes	30.3	38.7	44.7	< 0.001
Preventive health care				
Physician visit	93.1	91.9	97.0	> 0.05
Cholesterol check	75.2	80.9	86.4	< 0.01
Blood pressure check	93.3	93.3	97.1	> 0.05
Stool test for occult blood	43.6	50.5	56.3	< 0.01
Rectal examination	41.2	47.3	57.1	< 0.001
Mammogram	45.3	51.7	69.8	< 0.001
Papanicolaou smear	49.8	56.0	76.6	< 0.001
Other preventive measures	29.8	36.4	41.1	< 0.05

* Mantel extension test for trend.

least once during the past year. Nevertheless, several tests, including blood cholesterol measurement, stool examination for occult blood, rectal examination, mammogram, Papanicolaou smear, and other medically recommended preventive measures, showed a significant gradient by hormone-use status. Screening and case-finding were least common in never-users and most common in current users of estrogen, with past users holding an intermediate position (Table 1). Only blood pressure checks, which closely paralleled physician visits, did not differ significantly by estrogen use.

Discussion

In this upper-middle-class older cohort, improved health behavior and use of screening services were high, and nearly all of these women had seen a physician for some reason at least once during the preceding year. Nevertheless, women who never used estrogen generally had implemented the fewest healthy behavior changes and were least likely to have had screening evaluations.

This study did not determine whether physician contacts related to prescription of hormone replacement led to preventive measures or whether women interested in prevention also request and continue hormone replacement therapy. It does show that, even within a socioeconomically homogeneous cohort with ready access to medical care, women taking estrogen are quite different from nonusers with regard to health promotion and disease prevention measures. These differences may determine their probability of early diagnosis and treatment of both cancer and heart disease. Studies that report a lower risk for death or cardiovascular disease or a higher risk for cancer must consider the extent to which biases of self-selection, prevention, and ascertainment can explain some or all of the observed differences. Despite considerable current enthusiasm for estrogen replacement therapy as a panacea, only a randomized clinical trial can adequately address these biases and resolve this question.

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