Estrogen Use and All-Cause Mortality

Preliminary Results From the Lipid Research Clinics Program Follow-up Study

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• **The association of exogenous estrogen use and hysterectomy status with all-cause mortality was examined in 2,269 white women, aged 40 to 69 years, who had been followed up for an average of 5.6 years in the Lipid Research Clinics Program Follow-up Study. A total of 72 deaths occurred during this period. The relative risk of death in estrogen users compared with nonusers was 0.54 in gynecologically intact women, 0.34 in hysterectomized women, and 0.12 in bilaterally oophorectomized women. The risk of death in estrogen users, irrespective of hysterectomy status, was 0.37 times that in nonusers (3.4/1,000 *v* 9.3/1,000). The significant negative association of estrogen use with mortality persisted after multivariate adjustment for confounding factors. Hysterectomy status alone was not a significant predictor of death. Some, but not all, of the lower risk of mortality in estrogen users can be accounted for by increased levels of high-density lipoprotein cholesterol.**

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THE WELL-ESTABLISHED female advantage in total mortality is poorly understood and not explained by sex differences in behavior or known risk factors.[1] Several investigators have suggested a protective effect of endogenous estrogens, a possibility supported by reports that women with bilateral oophorectomy have an increased risk of coronary heart disease (CHD).[2-4] In addition, some studies have reported a reduced risk of total mortality[5,6] and of death due to heart disease[7] in postmenopausal women taking exogenous estrogens.

To our knowledge, no previous study has systematically investigated the interrelationship among hysterectomy status, estrogen use or nonuse, and all-cause mortality. We report herein an analysis of prospectively collected data in which the association of both estrogen use and hysterectomy status with total mortality was examined in a free-living population.

METHODS

Participants were examined as part of the Lipid Research Clinics (LRC) Prevalence Study of cardiovascular disease, conducted between 1971 and 1976 by ten North American clinics. Details of the study design and data collection have been previously described.[8] Briefly, defined populations were selected by sampling households, schools, businesses, and one prepaid medical practice. A two-stage screening procedure was utilized. A total of 81,926 persons were eligible for the visit 1 screening, and 60,502 (74%) of those invited did participate. Demographic data and fasting plasma lipid levels were obtained at this first screening.

A 15% random sample of visit 1 participants (N=9,107) and additional persons with elevated lipid levels (N=6,882) or who were taking lipid-lowering medications (N=346) were then invited to a second screening (visit 2). Almost 85% (N=13,852) of those invited to visit 2 participated. The visit 2 screening involved a physical examination that included BP and anthropometric measures, graded and resting ECGs, eight nonlipid chemistry analyses, a 24-hour dietary recall, fasting lipid and lipoprotein level determinations, and a questionnaire concerning personal habits, menstrual history, and medication use.

All 8,260 men and women who were 30 years of age or older at the visit 2 screening were included in an ongoing mortality follow-up study. Vital status is determined annually by means of a mailed questionnaire. Ascertainment has been 99% complete. When a participant is identified as deceased, the death certificate is forwarded to the LRC Central Patient Registry, where it is coded by a nosologist according to the eighth revision of the *International Classification of Diseases.* The present analyses were initially restricted to the 2,389 white women aged 40 to 69 years at baseline.

Ascertainment of current medication

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consumption, including exogenous estrogen use, was done during the visit 2 interview. Women were asked if they had taken oral contraceptives or estrogens within the two weeks before visit 2 and were requested, for purposes of validation, to bring samples and drug containers with them to the interview. Color illustrations of medications and telephone calls to physicians and pharmacists were used to aid in identifying specific drugs. The trade or generic name of each medication was recorded. All women who were identified as oral contraceptive users were excluded from these analyses. Self-reported exogenous estrogen use was validated in 95% of women included as estrogen users in this study and in all deaths among users. More than two thirds of the women reporting estrogen use were using natural, conjugated estrogens (Premarin).

Hysterectomy status was determined by asking women who reported cessation of menses whether they had reached natural menopause or had had a hysterectomy. Women who reported a hysterectomy were asked whether their uterus and *both* ovaries were removed or whether only the uterus was removed. No distinction was made between hysterectomy (uterus only removed) and hysterectomy with unilateral oophorectomy. For this study, women were categorized into three hysterectomy-status groups: gynecologically intact, hysterectomy (uterus only or uterus and one ovary removed), and oophorectomy (uterus and both ovaries removed).

Excluded from these analyses were women who had missing data or who were uncertain as to hysterectomy or oophorectomy status (N=28), women who had missing data on estrogen use (N=1), as well as oral contraceptive users (N=91). These exclusions resulted in a final sample size of 2,269 women.

All-cause mortality rates were based on age at death and person-years of observation. Participants were followed up for an average of 5.6 years; thus, women aged 60 to 69 years at baseline could contribute person-years of observation or deaths in the 70- to 79-year age category. Rates were age adjusted by the indirect method, using the 1976 US white female population[9,10] as the standard. Ninety-five percent confidence limits (CL) on these age-adjusted rates were calculated.[11,12] The proportional hazards model[13] was used to assess the contribution of estrogen use and hysterectomy status to total mortality after adjustment for potentially confounding variables. Ninety-five percent CL on the relative risks were calculated using the method of Ederer and Mantel.[14]

RESULTS

Age-specific death rates and total number of women in each hysterectomy and estrogen use group are given in Table 1. With the exception of hysterectomized women aged 50 to 59 years and intact women aged 70 to 79 years, estrogen users had lower mortality rates than nonusers. The largest differences in age-specific death rates between estrogen users and nonusers were observed in oophorectomized women.

Table 1.—Age-Specific All-Cause Mortality Rates (per 1,000 per Year) by Hysterectomy Status and Estrogen Use

	Hysterectomy Status/Estrogen Use						
	Intact		Hysterectomy		Oophorectomy		
Age at Risk	Nonuser (N=1,295)*	User (N=267)	Nonuser (N=200)	User (N=141)	Nonuser (N=181)	User (N=185)	Total (N=2,269)
40-49	1.3 (3/2,298)†	0.0 (0/226)	3.1 (1/319)	0.0 (0/106)	15.3 (2/131)	0.0 (0/271)	1.8 (6/3,351)
50-59	3.9 (11/2,811)	2.6 (2/769)	5.0 (2/400)	6.0 (2/336)	11.5 (4/348)	0.0 (0/463)	4.1 (21/5,128)
60-69	13.1 (24/1,832)	2.2 (1/454)	9.7 (3/308)	0.0 (0/314)	2.5 (1/396)	0.0 (0/239)	8.2 (29/3,543)
70-79	19.4 (7/360)	31.9 (3/94)	11.9 (1/84)	0.0 (0/61)	40.8 (4/98)	14.9 (1/67)	20.9 (16/764)
Total	6.2 (45/7,301)	3.9 (6/1,544)	6.3 (7/1,112)	2.4 (2/817)	11.3 (11/973)	1.0 (1/1,040)	5.6 (72/12,786)‡

*Total number of women in hysterectomy status/estrogen use category.
†Number of deaths per person-years of observation.
‡Discrepancy in totals is due to rounding.

Table 2.—Age-Adjusted All-Cause Mortality Rates (per 1,000 per Year) by Hysterectomy Status and Estrogen Use

	Estrogen Use		
Hysterectomy Status	Nonuser	User	Total
Intact	9.0 (6.5-12.0)*	4.9 (1.8-10.7)	8.2 (6.1-10.8)
Hysterectomy	8.2 (3.3-16.8)	2.8 (0.3-10.0)	5.7 (2.6-10.8)
Oophorectomy	11.8 (5.9-21.2)	1.4 (0.0-7.6)	7.2 (3.7-12.6)
Total	9.3 (7.2-11.9)	3.4 (1.5-6.4)	...

*Ninety-five percent confidence limits on rate.

Age-adjusted mortality rates by hysterectomy status and estrogen use are shown in Table 2. In each hysterectomy category—intact, hysterectomy, and oophorectomy—estrogen users had a lower mortality rate than nonusers. Differences between users and nonusers were larger in hysterectomized and oophorectomized women. The mortality rate in estrogen users, irrespective of hysterectomy status, was 0.37 times (CL, 0.17 to 0.79) that in nonusers (3.4/1,000 *v* 9.3/1,000).

After adjustment for age, smoking, body mass, alcohol intake, education, systolic BP, and low-density lipoprotein cholesterol (LDL-C) level in the multivariate model, estrogen use remained inversely and significantly related to total mortality (β=−.83, P=.02). When high-density lipoprotein cholesterol (HDL-C) level was included in the same model, the effect of estrogen use was diminished but not eliminated (β=−.67, P=.07).

In the absence of exogenous estrogens, there was little difference in the mortality rates between intact women and those reporting gynecological surgery, although oophorectomized women had a somewhat higher death rate. Among estrogen users, the relative risk of death in participants with a history of gynecological surgery was 0.57 (CL, 0.06 to 3.52) to 0.29 (CL, 0.01 to 2.04) times that in intact women.

Because estrogen use may have been avoided in women already at a high risk of death, three additional analyses were done to assess potential selection bias. First, age-adjusted mortality rates were recalculated after excluding the 17 deaths due to gynecological cancers (breast, ovary, uterus). The resulting relative risk in users compared with nonusers was

0.37 (CL, 0.15 to 0.89). Second, if a selection effect were producing the difference in mortality, the difference would be expected to diminish with time. When analyses were restricted to the 54 deaths that occurred later in the follow-up period (two years or more after baseline), the relative risk in users was 0.38 (CL, 0.16 to 0.91) that in nonusers. Finally, if estrogen use was simply a "marker" for women who were healthier at baseline, the frequency of use of other prescription medications and the prevalence of cardiovascular morbidity would be expected to be lower in estrogen users. There were no significant differences, however, between estrogen users and nonusers in reported use of antihypertensive agents (16% *v* 12%, respectively), angina medications (2% *v* 1%), diuretics (15% *v* 10%), anticoagulants (1% *v* 1%), or antiarrhythmic drugs (2% *v* 1%). In fact, estrogen users were taking more of these selected medications than estrogen nonusers. In addition, the prevalence of CHD (Rose questionnaire angina, or resting ECG with major Q-wave abnormality or ST-segment depression) was slightly higher in estrogen users (11%) than in nonusers (8%). Finally, the proportion of women selected into the study because of hyperlipidemia was essentially the same in estrogen users (42%) as in nonusers (39%).

COMMENT

In this study and in previous reports,[5,6] exogenous estrogen use was associated with a lower risk of all-cause mortality, although this has not been a consistent finding.[4] Endogenous estrogens have long been cited as an explanation of the female mortality advantage, primarily by reducing the occurrence of cardiovascular disease.[15] In addition, several recent studies suggest that exogenous estrogen use in postmenopausal women may be protective for heart disease,[7,16] although conflicting results have been observed.[4] In this preliminary report, small numbers of deaths precluded cause-specific analyses.

Removal of the ovaries, the primary source of premenopausal estrogens, has been reported to increase the risk of cardiovascular disease,[2,3] although, to our knowledge, the relationship between oophorectomy and all-cause mortality has not been previously assessed. In this study, oophorectomized women had a slightly higher risk of death than intact or hysterectomized women only if they were not using estrogens. Hysterectomy status alone was not significantly associated with mortality, although the relative risk of death associated with estrogen use varied by hysterectomy status. The inverse association of estrogen use and mortality was strongest in women who reported oophorectomy (relative risk, 0.12; CL, 0.00 to 0.59).

Confounding and selection bias for estrogen use were examined as possible explanations for the lower risk of death in users. The higher risk of death observed in estrogen nonusers could not be accounted for by differences in age, education, smoking habits, alcohol consumption, body mass, systolic BP, or LDL-C level. It is possible that estrogen was either not prescribed or was discontinued in women with preexisting illness, resulting in an apparent excess mortality in nonusers of estrogen. However, neither exclusion of deaths due to cancers of selected sites (breast, ovary, uterus) nor restriction of analysis to deaths occurring after the first two years of follow-up altered the relative mortality advantage in estrogen users. Although there were no significant differences between users and nonusers in consumption of selected medications, estrogen users were more rather than less likely to be using these cardiovascular drugs. In addition, the baseline prevalence of CHD morbidity was somewhat higher in users than nonusers, suggesting that estrogens were not avoided in women with cardiovascular disease.

Comparisons of standardized mortality ratios (SMRs) based on 1976 US mortality rates showed an SMR close to 1.0 for estrogen nonusers (SMR, 0.8). An SMR slightly less than 1.0 is compatible with the "healthy participant" effect frequency observed in population studies. Among estrogen users, the SMR was significantly less than 1.0 (SMR, 0.3), suggesting that the difference in mortality between users and nonusers was not because of unusually high death rates in nonusers but because of low death rates in estrogen users.

Because of the design and purpose of the LRC studies, we do not have complete information on the pharmacologic composition of the estrogens used or information on dosage or duration of estrogen use. This lack of additional information limits our understanding of the results, in that we cannot assess whether a dose-response relationship between estrogen use and mortality exists, or whether duration of use is associated with lower death rates.

In this study, estrogen use was ascertained at only one point in time (visit 2), and nonusers (by our definition) may have used estrogens either before or after visit 2. Likewise, users may have discontinued estrogen consumption during the follow-up interval. The effect of these potential misclassifications or changes in exposure status should bias our relative risks toward one.[17] Assuming that estrogen use is "truly" associated with a lower death rate, then inclusion of past or subsequent users in the nonuser group would tend to *reduce* the death rate in the nonusers. That is, the "true" death rate in nonusers would be higher than that observed. Classifying women who subsequently stopped taking estrogens as users would tend to *increase* the death rate seen in the user group. Thus, the "true" difference in mortality between estrogen users and nonusers would be even larger than we observed. If we assume that estrogen use has no relationship with mortality, then changes in exposure category would have no effect on the results.

In this study, we have attempted, without success, to explain the lower risk of mortality in estrogen users by statistically controlling for potential confounders, by considering possible selection biases, and by critically examining the effect of misclassification of estrogen use. Another alternative explanation for our results is that estrogen users have health-oriented behaviors that are different from those of nonusers and that may favorably influence mortality. This issue, however, cannot be addressed with these data.

The inverse association of estrogen use and risk of death seen in this study provides evidence for an apparent protective effect of exogenous estrogen use. Such a protective effect is biologically plausible, as exogenous

estrogens have been shown to increase HDL-C levels,[18] high values of which are associated with reduced risk of CHD,[19,20] the major cause of death in postmenopausal women. In the present study, however, HDL-C level accounted for some but not all of the lower risk of death in estrogen users. Thus, other mechanisms for reducing risk of death may also be operating.

In light of these results from our observational study, and because of the relatively high frequency of estrogen use in the general population, additional studies of the complex relationship of estrogen use to risk of morbidity and mortality are needed. Given the limitations of observational studies, it would be particularly useful to have more controlled, experimental investigations. Pending the completion of additional studies, it would be premature to alter current estrogen prescribing practices.

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