

The New England Journal of Medicine

© Copyright, 1997, by the Massachusetts Medical Society

VOLUME 336

JUNE 19, 1997

NUMBER 25



POSTMENOPAUSAL HORMONE THERAPY AND MORTALITY

FRANCINE GRODSTEIN, Sc.D., MEIR J. STAMPFER, M.D., GRAHAM A. COLDITZ, M.B., B.S., WALTER C. WILLETT, M.D.,
JOANN E. MANSON, M.D., MARSHALL JOFFE, M.D., BERNARD ROSNER, M.D., CHARLES FUCHS, M.D.,
SUSAN E. HANKINSON, Sc.D., DAVID J. HUNTER, M.B., B.S., CHARLES H. HENNEKENS, M.D.,
AND FRANK E. SPEIZER, M.D.

ABSTRACT

Background Postmenopausal hormone therapy has both benefits and hazards, including decreased risks of osteoporosis and cardiovascular disease and an increased risk of breast cancer.

Methods We examined the relation between the use of postmenopausal hormones and mortality among participants in the Nurses' Health Study, who were 30 to 55 years of age at base line in 1976. Data were collected by biennial questionnaires beginning in 1976 and continuing through 1992. We documented 3637 deaths from 1976 to 1994. Each participant who died was matched with 10 controls alive at the time of her death. For each death, we defined the subject's hormone status according to the last biennial questionnaire before her death or before the diagnosis of the fatal disease; this reduced bias caused by the discontinuation of hormone use between the time of diagnosis of a potentially fatal disease and death.

Results After adjustment for confounding variables, current hormone users had a lower risk of death (relative risk, 0.63; 95 percent confidence interval, 0.56 to 0.70) than subjects who had never taken hormones; however, the apparent benefit decreased with long-term use (relative risk, 0.80; 0.67 to 0.96, after 10 or more years) because of an increase in mortality from breast cancer among long-term hormone users. Current hormone users with coronary risk factors (69 percent of the women) had the largest reduction in mortality (relative risk, 0.51; 95 percent confidence interval, 0.45 to 0.57), with substantially less benefit for those at low risk (13 percent of the women; relative risk, 0.89; 95 percent confidence interval, 0.62 to 1.28).

Conclusions On average, mortality among women who use postmenopausal hormones is lower than among nonusers; however, the survival benefit diminishes with longer duration of use and is lower for women at low risk for coronary disease. (N Engl J Med 1997;336:1769-75.)

©1997, Massachusetts Medical Society.

WHETHER to take postmenopausal hormones is a difficult decision. Hormone use carries many benefits, including decreased risks of osteoporosis¹ and cardiovascular disease,² as well as hazards, especially an increase in the risks of breast and endometrial cancers.¹ Observational studies have reported reduced mortality among women taking hormones,³⁻⁹ but many of the studies have had methodologic flaws that limit firm conclusions. Specifically, women for whom estrogens are prescribed are often healthier initially, and those who continue to take hormones tend to be free of disease (for example, women in whom cancer is diagnosed often stop taking hormones).^{8,10,11} Thus, lower mortality among hormone users may be attributed erroneously to the hormone itself. In addition, studies that combine current and past use into an "ever" category may underestimate the benefits of postmenopausal hormones, since the decrease in cardiovascular disease appears to be limited largely to current users.¹²

In this prospective study, we addressed these issues and examined the relation between postmenopausal hormones and mortality to provide a balanced assessment of the risks and benefits of hormone use. Moreover, because of the increase in the incidence of breast cancer with long-term hormone use and the decrease in heart disease previously observed in this cohort,^{12,13} we also examined the relation be-

From Channing Laboratory (F.G., M.J.S., G.A.C., W.C.W., J.E.M., B.R., C.F., S.E.H., D.J.H., F.E.S.) and the Division of Preventive Medicine (J.E.M., C.H.H.), the Departments of Medicine and of Ambulatory Care and Prevention (C.H.H.), Brigham and Women's Hospital and Harvard Medical School; and the Departments of Epidemiology (F.G., M.J.S., G.A.C., W.C.W., J.E.M., S.E.H., D.J.H., C.H.H.), Nutrition (M.J.S., W.C.W.), and Biostatistics (M.J., B.R.), Harvard School of Public Health — all in Boston. Address reprint requests to Dr. Grodstein, Channing Laboratory, 181 Longwood Ave., Boston, MA 02115.

tween hormones and mortality among women at high risk and those at low risk for these diseases.

METHODS

The Nurses' Health Study Cohort

The Nurses' Health Study began in 1976 when 121,700 female registered nurses, 30 to 55 years of age, completed a mailed questionnaire concerning their medical history, including information on menopause, cardiovascular disease, and cancer. We also obtained information on risk factors for cardiovascular disease and cancer and on the use of postmenopausal hormones. Biennial follow-up questionnaires were mailed to update information on risk factors and identify newly diagnosed cases of major illnesses.

Population for Analysis

Women who reported a history of cardiovascular disease (stroke, myocardial infarction, angina, or coronary revascularization) or cancer (except nonmelanoma skin cancer) on the 1976 questionnaire were excluded from the study. We classified women as postmenopausal from the time they reported having a natural menopause or hysterectomy with bilateral oophorectomy. Women who underwent hysterectomy without bilateral oophorectomy were considered postmenopausal when they reached the age at which natural menopause had occurred in 90 percent of the cohort (54 years for smokers and 56 for nonsmokers).¹⁴ Women were eligible for the analysis when they became postmenopausal; those in whom cardiovascular disease or cancer was diagnosed before menopause were excluded, because this might have influenced their subsequent use of hormones and risk of death.

Identification of Case and Control Subjects

We included deaths that occurred after the completion of the 1976 questionnaire and before June 1, 1994. Most deaths were reported by the participants' families. We searched the National Death Index to identify deaths among nonrespondents; mortality follow-up was more than 98 percent complete.¹⁵ For all deaths, we sought death certificates and, when appropriate, requested permission from the next of kin (subject to state regulations) to review medical records. The underlying cause of death was assigned according to the *International Classification of Diseases, Eighth Revision* (ICD-8).¹⁶ The primary end point was death from any cause, but we also examined mortality from coronary heart disease (ICD-8 codes 410 to 414), stroke (codes 430 to 438), and cancer (codes 140 to 207). We identified 3637 deaths among women who provided information about postmenopausal hormones.

For each case subject, 10 controls were chosen at random, without replacement, from among women alive either at the time of the case subject's death or, where relevant, at the time of the diagnosis of the disease leading to death. The control pool consisted of all the women who met the same criteria as the case subjects (that is, they were postmenopausal and free of cancer and cardiovascular disease at base line or before menopause) and did not include women who died during follow-up. Controls were chosen for each case subject, beginning with the earliest deaths and proceeding systematically through the end of follow-up. Controls were matched to case subjects for age (within one year), age at menopause (within one year), and type of menopause (natural, bilateral oophorectomy, or hysterectomy or other), and the period of the case patient's death (two-year time period). For 50 case subjects, we were unable to identify 10 controls who met these criteria, and thus fewer than 10 were chosen; in all, 36,097 controls were selected, of whom 34,625 provided information about hormone use for the relevant questionnaire cycle and were included in this analysis. Since our focus was mortality, women who acquired major illnesses during follow-up but did not die of their diseases were eligible to be controls. However, only 3.2 percent of the controls had confirmed cardiovascular disease or cancer.

Ascertainment of Hormone Use

In 1976, women were asked about hormone therapy after menopause and about the duration of their hormone use. Subsequent biennial questionnaires, from 1978 to 1992, collected information on the types of hormones used and updated information about current use.

For each death, we defined the woman's hormone status according to the report on the last questionnaire completed before her death or before diagnosis of the disease that led to her death (e.g., if breast cancer was diagnosed in 1983 in a participant who died of the disease in 1988, hormone use was defined according to her 1982 questionnaire report). We thereby reduced bias caused by the discontinuation of hormone use between the diagnosis of a potentially fatal disease and subsequent death. For 71 percent of the case subjects, we used the last questionnaire completed before death (i.e., no change was made in the assignment of exposure); for 11 percent, we used the questionnaire completed two time periods before death; for 8 percent, three time periods before death; and for the remaining 10 percent, more than three time periods before death. Each control's hormone use was identified on the basis of her report on the same questionnaire as that of the matched case subject, thereby taking account of the increasing trend toward prescribing hormones during the course of the study.

Statistical Analysis

The standard prospective analysis used for incident diseases in this cohort¹²⁻¹⁴ would have been inappropriate to use for mortality. Because of the need to establish hormone use at the time of diagnosis of the fatal disease rather than uniformly at death, we would have thereby truncated follow-up for case subjects but not for other subjects in a prospective analysis, thus exaggerating any apparent benefit of estrogen. In our nested case-control analysis, we could end follow-up simultaneously for each case subject and her matched controls. This analysis has been used previously in examining mortality in the Nurses' Health Study.¹³

We used analytic techniques for matched data, including conditional logistic regression¹⁷ to estimate the relative risks, calculated as odds ratios, of death associated with hormone use, and the corresponding 95 percent confidence intervals. Relative risks were adjusted for the following risk factors: body-mass index (quintiles of the weight in kilograms divided by the square of the height in meters), cigarette smoking (never a smoker, past smoker, or current smoker [1 to 14, 15 to 24, 25 to 34, or 35 or more cigarettes per day]), hypertension (yes, no), high cholesterol (yes, no), diabetes (yes, no), parental myocardial infarction before the age of 60 (yes, no), history of breast cancer in mother or sister (yes, no), previous use of oral contraceptives (yes, no), parity (no children, one or more), and menarche before 13 years of age (yes, no). In some analyses, we further adjusted for quintiles of saturated-fat and alcohol intake; use of multivitamins (yes, no), vitamin E (yes, no), and aspirin (none, 1 to 6 aspirin tablets per week, daily); and regular exercise (yes, no). These analyses included only case subjects and matched controls from 1980 to 1994, because data on these variables were not available until 1980. In subgroup analyses limited to women with specific risk factors, we used unconditional logistic regression¹⁷ and controlled for the matching factors.

RESULTS

We included in the analysis 3637 deaths that occurred between 1976 and 1994 among postmenopausal women; 461 of the women died of coronary heart disease, 167 of stroke, and 1985 of cancer. Of the women who died of cancer, 425 died of breast cancer and 58 (of whom 5 were hormone users) of endometrial cancer. Among all the case subjects,

TABLE 1. RISK OF DEATH AMONG ALL POSTMENOPAUSAL HORMONE USERS IN THE NURSES' HEALTH STUDY, 1976 TO 1994.*

CAUSE OF DEATH	HORMONE USE		
	NEVER	CURRENT	PAST
All causes			
No. of cases	2051	574	1012
Relative risk (95% CI)			
Crude	1.0	0.58 (0.52-0.64)	1.00 (0.92-1.08)
Adjusted	1.0	0.63 (0.56-0.70)	1.03 (0.94-1.12)
Coronary heart disease			
No. of cases	289	43	129
Relative risk (95% CI)			
Crude	1.0	0.35 (0.25-0.49)	0.84 (0.67-1.05)
Adjusted	1.0	0.47 (0.32-0.69)	0.99 (0.75-1.30)
Stroke			
No. of cases	91	28	48
Relative risk (95% CI)			
Crude	1.0	0.56 (0.35-0.89)	1.00 (0.68-1.47)
Adjusted	1.0	0.68 (0.39-1.16)	1.07 (0.68-1.69)
All cancer			
No. of cases	1103	353	529
Relative risk (95% CI)			
Crude	1.0	0.67 (0.59-0.76)	1.01 (0.90-1.13)
Adjusted	1.0	0.71 (0.62-0.81)	1.04 (0.92-1.17)
Breast cancer			
No. of cases	246	85	94
Relative risk (95% CI)			
Crude	1.0	0.77 (0.59-1.00)	0.80 (0.62-1.03)
Adjusted	1.0	0.76 (0.56-1.02)	0.83 (0.63-1.09)

*CI denotes confidence interval. Values are adjusted for age, age at menopause, type of menopause, body-mass index (quintiles), diabetes (yes, no), high blood pressure (yes, no), high cholesterol (yes, no), smoking (never, past, or current [1 to 14, 15 to 24, 25 to 34, or 35 or more cigarettes per day]) past oral-contraceptive use (yes, no), family history of myocardial infarction (yes, no), family history of breast cancer (yes, no), parity (no children or at least one), age at menarche (<13 years or ≥13), and time period (eight two-year periods).

15.8 percent reported current hormone use on the last questionnaire completed before death or before the diagnosis of fatal disease, 27.8 percent were past users, and 56.4 percent had never used hormones. Among the controls, 24.5 percent reported current use on the same questionnaire as their matched case subjects, 24.9 percent reported past use, and 50.6 percent reported that they had never used hormones.

Overall, we found an inverse association between current hormone use and death from all causes (crude relative risk, 0.58; 95 percent confidence interval, 0.52 to 0.64) (Table 1). Adjustment for a wide variety of risk factors attenuated this estimate slightly, primarily because fewer hormone users than nonusers smoked cigarettes; after adjustment, we observed a 37 percent decrease in the risk of death for current hormone users as compared with those who had never used hormones (relative risk, 0.63; 95 percent confidence interval, 0.56 to 0.70). Additional adjustment for dietary factors, alcohol intake, vitamin or aspirin use, and exercise did not materially affect the relative risk (0.67; 95 percent confidence interval, 0.59 to 0.76). Because adjustment for these additional variables had little effect on the findings but would limit the population to those alive in 1980,

when we began collecting these data, subsequent estimates are not adjusted for these factors. There was no apparent survival benefit for past hormone users (relative risk, 1.03; 95 percent confidence interval, 0.94 to 1.12).

Among specific causes of death, as expected, the most marked reduction was in death due to coronary heart disease (relative risk, 0.47; 95 percent confidence interval, 0.32 to 0.69 for current users) (Table 1). The apparent decrease in mortality due to stroke among current hormone users was less certain because of the small number of deaths from stroke (relative risk, 0.68; 95 percent confidence interval, 0.39 to 1.16). Mortality due to cancer was also lower in current hormone users (relative risk, 0.71; 95 percent confidence interval, 0.62 to 0.81). Additional adjustment for diet, alcohol intake, vitamin or aspirin use, and exercise did not materially affect these cause-specific results.

The survival benefit was attenuated among long-term hormone users (relative risk for 10 or more years of current use, 0.80; 95 percent confidence interval, 0.67 to 0.96) (Table 2). This attenuation was primarily attributable to a 43 percent increase in death due to breast cancer (relative risk, 1.43; 95 percent confidence interval, 0.82 to 2.48) with

TABLE 2. RISK OF DEATH FROM ALL CAUSES AMONG CURRENT USERS AS COMPARED WITH THOSE WHO NEVER USED POSTMENOPAUSAL HORMONES, ACCORDING TO THE DURATION OF USE, 1976 TO 1994.*

DEATH FROM ALL CAUSES	HORMONE USE			
	NEVER	CURRENT		
		<5 yr	5-9 yr	≥10 yr
No. of cases	2051	215	163	181
Relative risk (95% CI)†				
Crude	1.0	0.54 (0.47-0.63)	0.54 (0.45-0.63)	0.69 (0.59-0.81)
Adjusted‡	1.0	0.56 (0.48-0.65)	0.60 (0.50-0.72)	0.80 (0.67-0.96)

*Information about the duration of current hormone use was missing for 15 case subjects.

†CI denotes confidence interval.

‡Values are adjusted for age, age at menopause, type of menopause, body-mass index (quintiles), diabetes (yes, no), high blood pressure (yes, no), high cholesterol (yes, no), smoking (never, past, or current [1 to 14, 15 to 24, 25 to 34, or 35 or more cigarettes per day]), past oral-contraceptive use (yes, no), family history of myocardial infarction (yes, no), family history of breast cancer (yes, no), parity (no children or at least one), age at menarche (<13 years or ≥13), and time period (eight two-year periods).

TABLE 3. RISK OF DEATH FROM ALL CAUSES AMONG PAST USERS AS COMPARED WITH THOSE WHO NEVER USED POSTMENOPAUSAL HORMONES, ACCORDING TO THE LENGTH OF TIME SINCE THE LAST USE, 1976 TO 1994.*

DEATH FROM ALL CAUSES	HORMONE USE			
	NEVER	LAST USE (YR BEFORE DEATH)		
		<3	3 to 4.9	≥5
No. of cases	2051	173	115	618
Relative risk (95% CI)†				
Crude	1.0	0.74 (0.62-0.87)	0.77 (0.63-0.94)	1.16 (1.06-1.28)
Adjusted‡	1.0	0.78 (0.66-0.92)	0.81 (0.66-0.99)	1.16 (1.04-1.29)

*Information about the length of time since the last use of hormones was missing for 106 case subjects.

†CI denotes confidence interval.

‡Values are adjusted for age, age at menopause, type of menopause, body-mass index (quintiles), diabetes (yes, no), high blood pressure (yes, no), high cholesterol (yes, no), smoking (never, past, or current [1 to 14, 15 to 24, 25 to 34, or 35 or more cigarettes per day]), past oral-contraceptive use (yes, no), family history of myocardial infarction (yes, no), family history of breast cancer (yes, no), parity (no children or at least one), age at menarche (<13 years or ≥13), and time period (eight two-year periods).

long-term use (data on hormone use and breast cancer have been detailed elsewhere^{13,18}). Past hormone use, regardless of duration, was not related to mortality.

Among past users, women who had stopped using hormones less than three years in the past had a 22 percent decrease in the risk of death from all causes (Table 3) (relative risk, 0.78; 95 percent confidence interval, 0.66 to 0.92); this decrease in risk was maintained for three to four years after the discontinuation of hormone use, but the risk was slightly elevated after five years.

We also examined the effect of estrogen, both alone and combined with progestin (information was

available for 92 percent of the case subjects and 89 percent of the controls). The relative risk of death for current users of estrogen with progestin was 0.46 (95 percent confidence interval, 0.36 to 0.58); for users of estrogen alone it was 0.69 (95 percent confidence interval, 0.60 to 0.80).

Because the greatest apparent decrease in risk was for death from coronary heart disease, we repeated the analysis within strata defined by cardiovascular-risk status (Table 4). Among the 69 percent of the women who had at least one major cardiovascular risk factor (current smoking, high cholesterol levels, high blood pressure, diabetes, a parental history of premature myocardial infarction, or body-mass in-

TABLE 4. RISK OF DEATH FROM ALL CAUSES AMONG CURRENT USERS AS COMPARED WITH THOSE WHO NEVER USED POSTMENOPAUSAL HORMONES, ACCORDING TO RISK-FACTOR GROUP.

RISK-FACTOR GROUP	CURRENT HORMONE USE	
	NO. OF CASE SUBJECTS	ADJUSTED RELATIVE RISK (95% CI)*
Cardiovascular risk†		
High	419	0.51 (0.45–0.57)
Low	54	0.89 (0.62–1.28)
Breast cancer in mother or sister		
Yes	63	0.65 (0.47–0.90)
No	511	0.60 (0.54–0.68)
Age (yr)		
<50	56	1.05 (0.65–1.68)
50 to 59	260	0.63 (0.53–0.73)
60 to 73	258	0.58 (0.49–0.68)
Age at menopause (yr)‡		
<49	232	0.58 (0.48–0.70)
≥54	25	0.62 (0.39–0.97)
Smoking status		
Current smoker	169	0.55 (0.45–0.66)
Never a smoker	178	0.64 (0.53–0.77)
Type of menopause		
Bilateral oophorectomy	210	0.71 (0.55–0.93)
Natural	243	0.59 (0.51–0.68)
Body-mass index§		
<23.0	263	0.63 (0.53–0.74)
23.0–28.9	239	0.60 (0.50–0.70)
≥29.0	71	0.54 (0.41–0.72)
Weight change since age 18 (kg)		
<10	311	0.55 (0.48–0.64)
≥10	263	0.87 (0.74–1.03)

*Values are adjusted for age, age at menopause, type of menopause, body-mass index (quintiles), diabetes (yes, no), high blood pressure (yes, no), high cholesterol (yes, no), smoking (never, past, or current [1 to 14, 15 to 24, 25 to 34, or 35 or more cigarettes per day]), past oral-contraceptive use (yes, no), family history of myocardial infarction (yes, no), family history of breast cancer (yes, no), parity (no children or at least one), age at menarche (<13 years or ≥13), and time period (eight two-year periods); for the analyses of weight change since age 18, body-mass index at age 18 was included and current body-mass index was excluded. CI denotes confidence interval.

†High cardiovascular risk includes one or more of the following factors: current cigarette smoking, high cholesterol levels, high blood pressure, diabetes, parental history of premature myocardial infarction, and a body-mass index of 29 or greater. Low risk is defined as never having smoked; no high cholesterol, blood pressure, or diabetes; no parental history of premature myocardial infarction; and a body-mass index of less than 25.

‡The analysis according to strata of ages at menopause includes only women with natural menopause or bilateral oophorectomy.

§Body-mass index is the weight in kilograms divided by the square of the height in meters. Information about body-mass index was missing for one case subject.

dex of 29 or higher), we observed a 49 percent decrease in deaths from all causes for current hormone users as compared with those who had never used hormones (relative risk, 0.51; 95 percent confidence interval, 0.45 to 0.57). There was substantially less benefit among the 13 percent of the women who were at low risk for coronary heart disease (those who had never smoked cigarettes; did not have high cholesterol levels, high blood pressure, or diabetes; had no parental history of myocardial infarction; and

had a body-mass index of less than 25) (relative risk, 0.89; 95 percent confidence interval, 0.62 to 1.28).

We also examined the relation between current hormone use and mortality from all causes among women with a family history of breast cancer (mother or sister) (Table 4). In that group (11 percent of the population), the relative risk of all-cause mortality was 0.65 (95 percent confidence interval, 0.47 to 0.90) for current hormone users as compared with those who had never used hormones. We also explored the association between current use and mortality in the presence of several other risk factors (Table 4). For women with a body-mass index of 29 or more, the inverse relation between hormone use and mortality (relative risk, 0.54; 95 percent confidence interval, 0.41 to 0.72) was similar to that in the whole population. Among current hormone users 50 years of age or less, the relative risk of death was 1.05 (95 percent confidence interval, 0.65 to 1.68) as compared with those who had never used hormones; for women who had used hormones for 10 or more years, the relative risk was 1.16 (95 percent confidence interval, 0.39 to 3.47) (data not shown). For those 60 years of age or older, the relative risk was 0.58 (95 percent confidence interval, 0.49 to 0.68) for current hormone use; the relative risks were 0.49 (0.40 to 0.59) for less than 10 years of use and 0.79 (0.63 to 0.99) for 10 or more years of use.

DISCUSSION

In this large, prospective study, women who were currently taking postmenopausal hormones (i.e., as reported on the last questionnaire completed by the case subject before a diagnosis of fatal disease or death) had a lower mortality rate than women who had never used hormones, particularly for death due to coronary heart disease. This apparent benefit disappeared within five years after stopping use. Women with coronary risk factors had the greatest reduction in mortality with hormone use, and there was little decrease for women at low risk of heart disease.

We observed no increasing benefit of hormones with increasing duration of use; in contrast, the apparent benefits were attenuated after 10 or more years of current hormone use. Whereas lower rates of cardiovascular mortality were maintained for long-term users, the risk of breast cancer mortality in this population was elevated by 43 percent after 10 years of taking hormones. Thus, with additional years of use, expected mortality advantages were, in part, offset by the risk of breast cancer; this was true even for the oldest women in the cohort (those 60 to 73 years of age).

Information on hormone use was self-reported, perhaps leading to some misclassification. However, we believe the reports to be accurate, because participants were registered nurses with a demonstrated interest in medical research. Because the information

was gathered prospectively, any misclassification is likely to have been random and to have resulted in underestimation of the true association between hormone use and mortality. In addition, the causes of death were carefully documented.

The presence of a "healthy user" bias has been discussed in observational studies of postmenopausal hormones and mortality.¹⁸ Sturgeon et al.⁸ examined data from a prospective study that, like ours, regularly updated information on the use of hormones. They reported a higher mortality rate among women who had recently stopped taking estrogen than among those who had never taken or were currently taking estrogen. Sturgeon et al. hypothesized that women discontinue hormone use when symptoms of a fatal disease develop, so that healthy women are classified as current hormone users and diseased women as recent-past hormone users. The design of the present study addresses this problem by identifying hormone status among the case subjects on the last biennial questionnaire completed by each one before the diagnosis of the fatal disease rather than at death when relevant. Defining hormone use in this way, rather than in the way it was defined by Sturgeon et al., we found a decrease in the risk of total mortality from any cause among recent-past hormone users.

Posthuma et al.¹¹ reviewed studies of postmenopausal hormone use that reported data on cancer (primarily mortality from cancer). They found lower risks of cancer among hormone users and suggested that the decrease must reflect the selection of healthy women for estrogen therapy. Part of the decrease may be due to a causal relation between hormones and some cancers (e.g., recent studies, including our own, have found a strong inverse association between hormone use and colon cancer^{19,20}). In addition, most of the studies reviewed considered hormone use before death rather than before diagnosis, leading to the bias described above, which we attempted to avoid; notably, for three leading causes of death from cancer whose incidence is unrelated to estrogen use, we found no association with hormone use (ovarian: relative risk, 0.94; pancreatic: relative risk, 1.00; and brain: relative risk, 0.97).

General population surveys^{21,22} have found that women who take hormones are leaner and more likely to have screening tests. However, because variations in socioeconomic status and access to health care are smaller among the registered nurses in the study than in the general population,¹⁸ the corresponding health differences between the women who choose estrogen and those who do not are likely to be smaller than in the general population. The magnitude of such differences in the overall risk profile in our study can be gauged by comparing the crude relative risk (0.58) with the multivariate relative risk (0.63); the modest attenuation in apparent

benefit after adjustment for many risk factors shows that the degree of confounding is not large. Furthermore, most studies neither adjust for as many factors nor update information on confounding variables; thus, confounding in this study was more rigorously controlled.

Nonetheless, a potential "healthy user" effect cannot be completely eliminated in an observational study. Hormone users are more likely to have certain diseases diagnosed in earlier stages than nonusers and will be less likely to die of their diseases. In support of this concept, we found a relative risk of 0.65 for the incidence of colorectal cancer,¹⁹ and a relative risk of 0.46 for mortality from colorectal cancer among current hormone users. Similarly, the relative risk of death from breast cancer among current users was 0.76, whereas the relative risks of incident disease ranged from 1.09 to 1.47,²³ depending on the duration of use. Furthermore, for breast cancer, postmenopausal estrogen probably acts as a late-stage growth promoter; withdrawal of the hormone (that is, stopping its use after a diagnosis of cancer) could be particularly beneficial in cases due to exogenous hormone use, perhaps rendering the cancer less malignant (and less likely to be fatal) than that which arises in nonusers of hormones.

However, these phenomena are more plausible for cancer than for cardiovascular disease; for coronary heart disease, the relative risks of fatal and nonfatal disease are more similar (0.47 for mortality due to coronary disease and 0.58 for nonfatal coronary events). Thus, a better disease prognosis or other health characteristics in estrogen users can explain only part of the 37 percent decrease in mortality we observed among current hormone users, much of which was attributable to a 53 percent decrease in mortality due to heart disease.

The few other studies of mortality report an inverse association with postmenopausal hormone use, with most estimates of relative risk ranging from 0.4 to 0.8,³⁻⁹ although only two studies excluded prevalent cases of cancer and cardiovascular disease at base line.^{6,9} Since women with disease at base line are more likely to die during the study period and less likely to take hormones, their inclusion would exaggerate the protection provided by hormone use. Finally, most previous studies have not updated the information on hormone use. Because the benefit appears to be concentrated among current and recent users,^{2,12} failure to update data will tend to result in underestimation of the value of current use. Further evidence bearing on the relation between hormone use and mortality will emerge in the next decade from the Women's Health Initiative, a large, randomized trial.

In the population we studied, the largest reduction was for mortality due to coronary disease and for mortality due to any cause among women with

cardiovascular risk factors. However, our study population ranged in age from 30 to 73, with similar numbers of deaths due to heart disease and breast cancer; in the general population, heart disease is more prevalent. The balance of risks and benefits for mortality will be determined largely by the decreased risk of heart disease and the long-term increase in breast cancer among women taking hormones and thus will vary according to the distribution of causes of death in the population under study.

Nonetheless, we know many ways to lower the risk of coronary disease, but few to lower the risk of breast cancer. Furthermore, in the Nurses' Health Study, women taking hormones appear to be at a greater risk for the development of breast cancer¹³ than for death from the disease. The decision to use hormones will be based on many factors besides mortality, including quality of life and the possibility of living with breast cancer. On average, the survival benefits appear to outweigh the risks, but the risks and benefits vary depending on existing risk factors and the duration of hormone use and must be carefully considered for each woman.

Supported by research grants (CA 40356 and HL 34594) from the National Institutes of Health.

REFERENCES

1. Grady D, Rubin SM, Petitti DB, et al. Hormone therapy to prevent disease and prolong life in postmenopausal women. *Ann Intern Med* 1992; 117:1016-37.
2. Grodstein F, Stampfer MJ. The epidemiology of coronary heart disease and estrogen replacement in postmenopausal women. *Prog Cardiovasc Dis* 1995;38:199-210.
3. Bush TL, Cowan LD, Barrett-Connor E, et al. Estrogen use and all-cause mortality: preliminary results from the Lipid Research Clinics Program Follow-Up Study. *JAMA* 1983;249:903-6.
4. Henderson BE, Paganini-Hill A, Ross RK. Decreased mortality in users of estrogen replacement therapy. *Arch Intern Med* 1991;151:75-8.
5. Petitti DB, Perlman JA, Sidney S. Noncontraceptive estrogens and mortality: long-term follow-up of women in the Walnut Creek Study. *Obstet Gynecol* 1987;70:289-93.
6. Folsom AR, Mink PJ, Sellers TA, Hong CP, Zheng W, Potter JD. Hormonal replacement therapy and morbidity and mortality in a prospective study of postmenopausal women. *Am J Public Health* 1995;85:1128-32.
7. Criqui MH, Suarez L, Barrett-Connor E, McPhillips J, Wingard DL, Garland C. Postmenopausal estrogen use and mortality: results from a prospective study in a defined, homogeneous community. *Am J Epidemiol* 1988;128:606-14.
8. Sturgeon SR, Schairer C, Brinton LA, Pearson T, Hoover RN. Evidence of a healthy estrogen user survivor effect. *Epidemiology* 1995;6:227-31.
9. Ettinger B, Friedman GD, Bush T, Quesenberry CP Jr. Reduced mortality associated with long-term postmenopausal estrogen therapy. *Obstet Gynecol* 1996;87:6-12.
10. Vandenbroucke JP. How much of the cardioprotective effect of postmenopausal estrogens is real? *Epidemiology* 1995;6:207-8.
11. Posthuma WFM, Westendorp RGJ, Vandenbroucke JP. Cardioprotective effect of hormone replacement therapy in postmenopausal women: is the evidence biased? *BMJ* 1994;308:1268-9.
12. Grodstein F, Stampfer MJ, Manson JE, et al. Postmenopausal estrogen and progestin use and the risk of cardiovascular disease. *N Engl J Med* 1996;335:453-61. [Erratum, *N Engl J Med* 1996;335:1406.]
13. Colditz GA, Hankinson SE, Hunter DJ, et al. The use of estrogens and progestins and the risk of breast cancer in postmenopausal women. *N Engl J Med* 1995;332:1589-93.
14. Willett WC, Stampfer MJ, Bain C, et al. Cigarette smoking, relative weight, and menopause. *Am J Epidemiol* 1983;117:651-8.
15. Stampfer MJ, Willett WC, Speizer FE, et al. Test of the National Death Index. *Am J Epidemiol* 1984;119:837-9.
16. National Center for Health Statistics. International classification of diseases: adapted for use in the United States. 8th rev. ICDA. Vol. 1. Tabular list. Washington, D.C.: Government Printing Office, 1967. (DHEW publication no. (PHS) 1693.)
17. Hosmer DW JR, Lemeshow S. Applied logistic regression. New York: John Wiley, 1989.
18. Grodstein F. Can selection bias explain the cardiovascular benefits of estrogen replacement therapy? *Am J Epidemiol* 1996;143:979-82.
19. Grodstein F, Martinez ME, Giovannucci EL, et al. Postmenopausal hormone use and colorectal cancer in the Nurses' Health Study. *Am J Epidemiol* 1996;143:Suppl:S63. abstract.
20. Calle EE, Miracle-McMahill HL, Thun MJ, Heath CW Jr. Estrogen replacement therapy and risk of fatal colon cancer in a prospective cohort of postmenopausal women. *J Natl Cancer Inst* 1995;87:517-23.
21. Cauley JA, Cummings SR, Black DM, Mascioli SR, Seeley DG. Prevalence and determinants of estrogen replacement therapy in elderly women. *Am J Obstet Gynecol* 1990;163:1438-44.
22. Barrett-Connor E. Postmenopausal estrogen and prevention bias. *Ann Intern Med* 1991;115:455-6.
23. Colditz GA, Willett WC, Speizer FE. Breast cancer and hormone-replacement therapy. *N Engl J Med* 1995;333:1357-8.