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Increased longevity in older users of postmenopausal estrogen therapy: the Leisure World Cohort Study

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Abstract

Objective—To examine the effect of postmenopausal estrogen therapy (ET), including duration and recency of use, on all-cause mortality in older women.

Design—As part of a prospective cohort study of residents of a California retirement community begun in the early 1980s, Leisure World Cohort women (median age, 73 y) completed a postal health survey including details on ETuse and were followed up for 22 years (1981–2003). Age- and multivariate-adjusted risk ratios (RR) and 95% CIs were calculated using proportional hazard regression.

Results—Of the 8,801 women, 6,626 died during follow-up (median age, 88 y). ET users had an age-adjusted mortality rate of 52.9 per 1,000 person-years compared with 56.5 among lifetime nonusers (RR = 0.91; 95% CI, 0.87–0.96). Risk of death decreased with both increasing duration of ET and decreasing years since last use (*P* for trend <0.001). The risk was lowest among long-term (≥15 y) users (RR = 0.83; 95% CI, 0.74–0.93 for 15–19 y and RR = 0.87; 95% CI, 0.80–0.94 for 20+ y). For long-term users, the age-adjusted mortality rate was 50.4 per 1,000 person-years. Lower-dose users (≤0.625 mg) had a slightly better survival rate than higher-dose users (RR = 0.84; 95% CI, 0.78–0.91 vs RR = 0.91; 95% CI, 0.83–0.97). Risk did not differ by route of administration (*P* = 0.56). Further adjustment for potential confounders had little effect on the observed RRs for ET.

Conclusion—Long-term ET is associated with lower all-cause mortality in older women.

Keywords

Mortality; Longevity; Estrogen therapy; Risk factors

Results of recent clinical trials have raised concern about the long-term effects of postmenopausal estrogen therapy (ET). Two randomized trials of combined hormone therapy reported increased risk of coronary heart disease, stroke, and venous thromboembolic disease among women in the group assigned to conjugated equine estrogens plus medroxyprogesterone acetate.[1,2] Most recently, the Women's Health Initiative (WHI) trial of unopposed estrogen was terminated after finding that the risks exceeded benefits.[3] However, these studies were unable to answer questions regarding long-

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term use, and it is unlikely that randomized trials involving large numbers of women with follow-up of 15 or more years will be conducted.

In 1981, we undertook a prospective cohort study of 8,877 postmenopausal women with the aim of studying the risks and benefits of ET. This cohort has the advantages of large size, high frequency of ET use, and long follow-up. Also, many of the women had used ET for long periods. We report here the results of ET on all-cause mortality after 22 years of follow-up.

METHODS

We mailed a health survey to all residents who owned homes in Leisure World Laguna Hills, a California retirement community, on June 1, 1981. New residents moving into the community after this date were sent the survey in June 1982, June 1983, and October 1985. Of the 13,978 residents who returned the questionnaire and now constitute the Leisure World Cohort, 8,877 are women. The cohort, like the study population, is predominantly white, well-educated, and upper middle class.

The baseline health survey asked about demographic information (birth date, marital status, number of children, height, weight); brief medical history (hypertension, angina, heart attack, stroke, diabetes, rheumatoid arthritis, fractures after age 40 y, cancer, gallbladder surgery, glaucoma, cataract surgery); medication use (hypertensive medication, digitalis, nonprescription pain medication); personal habits (cigarette smoking, alcohol consumption, exercise, coffee and tea intake); use of vitamin supplements and usual frequencies of consumption of 58 foods (or food groups) that are common sources of dietary vitamins A and C; and, for women, menstrual history, including use of ET.

Women were classified as ever- or never-users of ET. Duration of ET was defined as the total number of years during which any type of ET was taken. Women taking oral conjugated estrogens were also asked to supply dose information; the dose reported here is the dose taken for the longest period.

Cohort members have been followed by periodic resurvey, review of local hospital admission/discharge records, and determination of vital status by search of national and commercial death indexes and ascertainment of death certificates. Participants were followed up to death or June 1, 2003, whichever came first. To date, 68 cohort members (58 women) have been lost to follow-up; search of death indices did not reveal that these individuals were deceased. Follow-up of these individuals was censored on June 1, 2003. Further details of the methods and validity of exposure and outcome data from this cohort have been reported elsewhere.[4–8]

Age-adjusted mortality rates, using seven age groups (≤69, 70–74, 75–79, 80–84, 85–89, 90–94, and 95+ y) were computed by direct standardization using an internal standard (ie, the person-years distribution of the total cohort under study).[9] Age-adjusted risk ratios (RRs) and two-sided *P* values were obtained using proportional hazard regression analysis.[10] To control for potential confounding factors previously found to be related to mortality in this cohort, we performed multiple proportional hazard regression analysis adjusting for age at entry (continuous), smoking (never, past, current), exercise (0, <1, ≥1 h/d), body mass index (tertiles), and history of hypertension, angina, heart attack, stroke, diabetes, rheumatoid arthritis, and cancer. For ordinal variables, a trend test was used to determine whether risk decreased or increased linearly. Statistical analyses were performed using SAS version 8.01 (SAS Institute Inc., Cary, NC). No adjustment in the *P* values was made for multiple comparisons.

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This study was approved by the Institutional Review Boards of the University of Southern California and the University of California, Irvine.

RESULTS

After eliminating 27 women who did not report their use of ET and 49 women with missing information on the other potential confounding variables, data from 8,801 women were analyzed. These women ranged in age from 44 to 101 years (median, 73 y). At study entry (completion of initial survey), 4,961 women (56%) reported having used ET. Estrogen users were on average younger than nonusers, and more estrogen users were past smokers, exercised daily, and had a history of angina and cancer, but fewer had a history of stroke and diabetes (Table 1). Among users, the median duration of ET was 8 years. Eighty-nine percent of estrogen users had used oral estrogen at least part of the time, and 61% had used only oral estrogen. Most estrogen use in this cohort was initiated in the immediate postmenopausal years and had been discontinued before entry into this study. Of those with a history of estrogen use, 1,298 (26%) had used ET within 1 year of study entry. The addition of progestogen to the treatment regimen is a recent phenomenon, and combination hormone therapy is uncommon in this cohort. In 1985, only 13% of estrogen users (1.6% of the cohort) were using progestogen. In 1992, these figures were 16% and 3.6%, respectively; in 1998, they were 18% and 5.8%.

By June 1, 2003, these 8,801 women had contributed 122,203 person-years of follow-up, and 6,626 had died. Age at death ranged from 59 to 110 years (median, 88 y). Ever use of ET was significantly related to increased longevity (RR = 0.91; 95% CI, 0.87–0.96; Table 2). Women who had used ET had an age-adjusted mortality rate of 52.8 per 1,000 person-years, compared with 56.4 per 1,000 person-years among lifetime nonusers (Table 3).

Risk of death decreased with increasing duration of ET (P for trend <0.001; Table 2). The lowest risks were observed among long-term (15+ y) users (RR = 0.83; 95% CI, 0.74–0.93 for 15–19 y and RR = 0.87; 95% CI, 0.80–0.94 for 20+ y compared with lifetime nonusers). The decreased risk among long-term users was evident within all age groups except those aged 95 years or older (Table 3). For long-term users, the age-adjusted mortality rate was 50.4 per 1,000 person-years.

Risk also decreased with increasing recency of use (P for trend <0.001; Table 2). The relative risk for women who had used ET within 1 year of baseline compared with nonusers was 0.86 (95% CI, 0.79–0.93). Users of both lower (≤0.625 mg) and higher (≥1.25 mg) doses had significantly decreased risks of death compared with nonusers (RR = 0.84; 95% CI, 0.78–0.91 and RR = 0.91; 95% CI, 0.84–0.97, respectively). Although lower-dose users seemed to have a better survival rate than higher-dose users, the relative risk of death for higher-dose users compared with lower-dose users was not significant (RR = 1.07; 95% CI, 0.99–1.17). Likewise, risk did not differ significantly by route of administration (P = 0.56).

Table 2 also shows the relation of the combined effect of duration and years since last use on mortality. Within each last use category, the lowest risk of death was observed for long-term users (15+ y). Long-term use significantly increased longevity in both recent users (within 4 y; RR = 0.85; 95% CI, 0.78–0.92) and in those who stopped using ET 5 to 14 years previously (RR = 0.86; 95% CI, 0.77–0.97). Long-term use also seemed to do so in those who stopped using ET 15 or more years previously (RR = 0.89; 95% CI, 0.71–1.11). However, the number of subjects in this category was small (n = 88), and the result was not significant. The largest risk and the only increased risk among estrogen users was in recent, short-term users (RR = 1.09; 95% CI, 0.86–1.38).

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Adjustment for potential confounders (smoking, exercise, body mass index, and history of hypertension, angina, heart attack, stroke, diabetes, rheumatoid arthritis, and cancer) had little effect on the observed RRs for ET (Table 2). The risk of death among ever-users of ET changed from 0.91 with only age adjustment to 0.90 with adjustment for all potential confounders. For long-term users (20+ y), the risk changed from 0.87 to 0.84.

DISCUSSION

Our study found that ET users, especially long-term users, had increased longevity compared with nonusers. Observational studies have consistently shown a 20% to 50% decrease in mortality among users of estrogens.[11–26] Table 4 summarizes the overall relative risk estimates for all-cause mortality among estrogen users compared with nonusers among prospective studies exploring this relation. Grady et al[27] calculated that the life expectancy for a 50-year-old woman choosing long-term ET was nearly a year greater than that of nonusers. Daly et al[28] estimated an increase in life expectancy of almost 2 years after 10 years of ET beginning at age 50 years.

Like most previous studies reporting on the association of ET and mortality, our investigation is an observational study, not a randomized trial. A major concern in such studies is the possibility that unrecognized confounders or bias account for the observed results. In general populations, women taking ET may have other health-promoting habits and may differ from nonusers in unmeasured ways that influence longevity—the healthy user effect.[29–31] However, the Leisure World Cohort is a relatively homogeneous group of mostly white, highly educated, upper-middle-class women with access to health care. Differences between hormone users and nonusers in this study are not great, and adjusting for other risk factors and potentially confounding factors in this group did not appreciably change the observed RR estimates for ET users. Although we could not control for educational level because this variable was not collected at baseline, on the 1992 follow-up questionnaire, approximately two thirds of the women reported having at least some college education. Furthermore, education was unrelated to mortality in this subgroup of women. Nonetheless, uncontrolled confounding cannot be ruled out in this or any observational study.

Recent clinical trials in postmenopausal women demonstrating that estrogen-progestin therapy does not prevent coronary heart disease and may actually increase early adverse events have raised doubts about its use to prevent these diseases. In the Heart and Estrogen/Progestin Replacement Study (HERS), 2,763 postmenopausal women with coronary heart disease were randomly assigned to receive 0.625 mg of conjugated equine estrogens plus 2.5 mg of medroxyprogesterone acetate or placebo daily.[2] Hormone therapy did not reduce mortality from any cause during the 4.1 years of follow-up (RR = 1.08; 95% CI, 0.84–1.38) but did increase the rate of thromboembolic events and gallbladder disease. Disease surveillance continued in HERS II for an additional 2.7 years, during which time many of the women assigned to hormones took open-label estrogen prescribed by their personal physicians, but only a few of those assigned to placebo did. During the 6.8 years of observation of HERS and HERS II combined, hormone therapy had no overall effect on death (RR = 1.10; 95% CI, 0.91–1.31).[32] Similarly, in the Women's Estrogen for Stroke Trial, a randomized, placebo-controlled trial of ET for the secondary prevention of cerebrovascular disease in 664 postmenopausal women, daily therapy with 1 mg of estradiol-17β for 3 years did not reduce the risk of death (RR = 1.2; 95% CI, 0.8–1.8).[33]

In 2002, the findings of the first randomized controlled primary prevention trial of estrogen-progestin were reported.[1] The WHI randomly assigned 16,608 women with an intact uterus to the same combined hormonal treatment given in HERS or placebo. After a mean of 5.2

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years of follow-up, the trial was stopped because of an increase in invasive breast cancer and a global index statistic supporting that early risks (increased incidence of coronary heart disease, stroke, venous thromboembolism) exceeded benefits (fewer hip fractures and cases of colorectal cancer). However, the numbers of overall deaths in the estrogen-progestin and placebo groups were statistically and clinically similar in this short-duration (5-year) study (RR = 0.98; 95% CI, 0.82–1.18).

Last year, the intervention phase of the second trial within the WHI of unopposed estrogen in 10,739 hysterectomized women was terminated.[3] Like the HERS and WHI trials of combined estrogen-progestin therapy, women in this trial assigned to unopposed conjugated equine estrogens had an increased risk of stroke. This was the only statistically significant adverse effect of estrogen alone, although the incidence of pulmonary embolism was also increased. Like combined therapy, unopposed estrogen decreased fractures. However, after an average follow-up of 6.8 years, overall death rates did not differ between the estrogen and placebo arms (RR = 1.04; 95% CI, 0.88–1.22).

In the WHI, the mean age of participants was in the mid-60s, raising concern that the results may not apply to treatment begun early in menopause. In fact, in the WHI estrogen-alone trial, women aged 50 to 59 years seemed to respond more favorably than older postmenopausal women with a period of low endogenous estrogen levels. In contrast, our cohort members initiated estrogen use primarily in the immediate postmenopausal years.

Although a clinical trial randomly assigning women to estrogen and placebo groups ensures that the estrogen, and not some characteristic of estrogen users, accounts for the beneficial effects observed among estrogen users, long-term treatment and follow-up in the setting of a randomized clinical trial is unlikely. The clinical trials to date could not determine the effect of long-term therapy. The Leisure World Cohort Study is currently in its 23rd year. It and other long-term observational studies will continue to contribute valuable data that complement those of clinical trials.

Our study does not address the issue of mortality in the immediate years of initiation of therapy. However, the only increased risk of death among estrogen users, although not statistically significant, was observed in recent, short-term users. Women who started using estrogen after the baseline survey were considered nonusers. Given the age of the women, the number of these women is probably small. However, if recent, short-term use increases risk of death, our study will underestimate this increased risk and overestimate benefits. In addition to the recent clinical trials,[1,2] three observational studies of women using hormone therapy showed increased risk of coronary heart disease in the first year.[26,34,35] This may reflect prothrombotic and proinflammatory effects of progestogens that outweigh any effects of estrogen on atherogenesis and vasodilation. Nonetheless, our study suggests that those women surviving the period of increased mortality immediately after initiation of therapy may experience increased survival with long-term use compared with nonusers.

Although our data on estrogen use were self-reported through the use of a mailed questionnaire, we have evidence to support their validity. We have demonstrated consistencies of results on the relation between estrogen use and various disease outcomes in this population using pharmacy, medical records, and self-reports.[36,37] We validated the self-reported estrogen-use histories on a sample of this cohort through use of medical records and demonstrated that those histories, which extended more than a few months, are accurately reported.[7]

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CONCLUSIONS

Long-term users of ET seem to have a lower death rate in the Leisure World population. The reduction in the risk of death from all causes was 15%. Considering only mortality as the index of therapeutic success or failure, these results suggest that long-term therapy may extend life. Our results add to the complexity of issues surrounding the risk-benefit equation of hormone therapy. However, with the results of recent clinical trials and other observational studies, our findings suggest that after an initial period of increased risk, use of ET may be without excess adverse effect.

In the post-WHI era, some women will continue to use hormone therapy and others will be started on hormones for menopause-related symptoms. It is especially important that the postmenopausal patient be fully informed of the current state of knowledge regarding these risks and benefits and fully participate with her doctor in decisions regarding choice of therapy.

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TABLE 1

Baseline characteristics of never vs ever users of estrogen therapy: the Leisure World Cohort Study, 1981–2003

	Never estrogen therapy	Ever estrogen therapy	*P* value[a]
Number	3,840	4,961	
Age (y)	75 ± 7.5	72 ± 7.0	<0.001
Body mass index (kg/m^2)	23.1 ± 3.6	23.2 ± 3.3	0.19
Smoker			<0.001
Never	60%	51%	
Past	28%	36%	
Current	12%	13%	
Exercise (h/d)			<0.001
0	23%	19%	
<1	39%	40%	
≥1	37%	40%	
Hypertension	40%	42%	0.06
Angina	8.5%	10%	<0.01
Heart attack	6.9%	6.4%	0.32
Stroke	4.3%	3.2%	<0.01
Diabetes	5.5%	4.6%	0.05
Rheumatoid arthritis	6.9%	6.7%	0.78
Cancer	12%	14%	0.05

Data are presented as mean ± SD or percent.

[a] *P* value for comparison of ever vs never users of estrogen therapy.

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TABLE 2

Risk ratio of dying by use of estrogen therapy: the Leisure World Cohort Study, 1981–2003

			Age-adjusted		Multivariate-adjusted[a]	
	No. of subjects[b]	No. of deaths	Risk ratio	95% CI	Risk ratio	95% CI
Ever ET						
No	3,840	3,110	1.00		1.00	
Yes	4,961	3,516	0.91	0.87–0.96	0.90	0.85–0.94
Duration (y)						
<2	928	708	0.95	0.87–1.03	0.98	0.90–1.06
2–4	761	528	0.90	0.82–0.98	0.89	0.81–0.98
5–9	864	577	0.89	0.82–0.98	0.88	0.80–0.96
10–14	745	500	0.94	0.85–1.03	0.90	0.81–0.99
15–19	570	365	0.83	0.74–0.93	0.82	0.74–0.92
20+	961	717	0.87[c]	0.80–0.94	0.84[c]	0.77–0.91
Years since last use						
20+	1,131	994	0.96	0.89–1.03	0.94	0.88–1.01
15–19	409	293	0.91	0.81–1.03	0.92	0.81–1.04
10–14	605	420	0.86	0.78–0.96	0.88	0.79–0.97
5–9	784	527	0.91	0.82–0.99	0.87	0.79–0.96
1–4	623	396	0.85	0.76–0.95	0.85	0.76–0.94
<1	1,298	783	0.86[c]	0.79–0.93	0.84[c]	0.78–0.92
Dose (mg)						
≤0.625	1,461	968	0.84	0.78–0.91	0.84	0.78–0.91
≥1.25	1,698	1,135	0.91	0.84–0.97	0.89	0.83–0.96
Route of administration						
Oral only	3,046	2,159	0.92	0.87–0.97	0.91	0.86–0.96
Oral and other	1,355	913	0.88	0.82–0.95	0.86	0.79–0.92
Injection, cream, or both	528	416	0.92	0.83–1.02	0.93	0.83–1.03
Years since last use and duration (y)						
15+ y ago						
<2	650	525	0.95	0.87–1.04	0.98	0.89–1.08

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			Age-adjusted		Multivariate-adjusted[a]	
	No. of subjects[b]	No. of deaths	Risk ratio	95% CI	Risk ratio	95% CI
2–14	790	670	0.96	0.88–1.04	0.92	0.84–0.99
15+	88	81	0.89	0.71–1.11	0.82	0.66–1.03
5–14 y ago						
<2	172	108	0.87	0.71–1.05	0.90	0.74–1.09
2–14	822	527	0.91	0.82–0.99	0.90	0.82–0.99
15+	390	309	0.86	0.77–0.97	0.83	0.74–0.94
0–4 y ago						
<2	99	69	1.09	0.86–1.38	1.07	0.84–1.36
2–14	756	406	0.83	0.74–0.92	0.83	0.74–0.92
15+	1,053	692	0.85	0.78–0.92	0.83	0.77–0.91

ET, estrogen therapy.

[a] Adjusted for age at entry, exercise, body mass index, smoking, and history of hypertension, angina, heart attack, stroke, diabetes, rheumatoid arthritis, and cancer.

[b] Number of women with missing information: duration = 132; years since last use = 111; dose = 1,802; route of administration = 32; and years since last use and duration = 141.

[c] P for trend <0.001.

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TABLE 3

Morality rate by age and use of estrogen therapy: the Leisure World Cohort Study, 1981–2003

	Never estrogen			Ever estrogen			Long-term (15+ y) estrogen		
Age (y)	**Person-years**	**No. of deaths**	**Mortality rate[a]**	**Person-years**	**No. of deaths**	**Mortality rate[a]**	**Person-years**	**No. of deaths**	**Mortality rate[a]**
≤69	3,976	40	10.1	8,703	60	6.9	2,189	15	6.9
70–74	5,866	93	15.9	11,764	190	16.2	3,639	44	12.1
75–79	9,829	251	25.5	16,360	364	22.2	5,301	120	22.6
80–84	11,881	597	50.2	17,011	684	40.2	5,544	201	36.3
85–89	9,999	766	76.6	12,260	934	76.2	4,117	294	71.4
90–94	5,509	866	157.2	5,601	859	153.4	1,860	277	149.0
95+	1,887	497	263.3	1,557	425	273.0	465	131	281.5
Age-adjusted	48,947	3,110	56.4	73,256	3,516	52.8	23,115	1,082	50.4

[a]Number of deaths per 1,000 person-years.

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TABLE 4

Prospective observational studies of the association of hormone therapy and all-cause mortality

Reference	Year	Group studied	RR	95% CI
Burch et al[11]	1974	Hysterectomized women, Nashville, TN	0.4	Not reported
Wilson et al[12]	1985	Framingham Study, MA	0.97	Not significant
Bush et al[13]	1987	Lipid Research Clinics Program Follow-up Study, North America	0.54	0.29–0.79
Petitti et al[14]	1987	Kaiser HMO, Walnut Creek, CA	0.8	0.6–1.1
Criqui et al[15]	1988	Rancho Bernardo, CA	0.69	0.55–0.87
Snowdon et al[16]	1989	Seventh Day Adventists, CA		
		Natural menopause	1.13	0.88–1.45
		Surgical menopause	0.80	0.56–1.14
Hunt et al[17]	1990	British menopausal clinics	0.56	0.47–0.66
Paganini-Hill[18]	1994	Leisure World Cohort Study, CA	0.82	$P < 0.01$
Sturgeon et al[19]	1995	Breast Cancer Demonstration Project, USA	0.7	0.7–0.8
Folsom et al[20]	1995	Iowa's Women's Health Study	0.73[a]	0.61–0.86
Ettinger et al[21]	1996	Kaiser HMO, San Francisco, CA	0.54	0.38–0.76
Schairer et al[22]	1997	Uppsala, Sweden	0.77	0.73–0.81
Goldstein et al[23]	1997	Nurses' Health Study, USA	0.58[a]	0.52–0.64
Cauley et al[24]	1997	Study of Osteoporotic Fractures	0.69[a]	0.54–0.87
Rodriguez et al[25]	2001	Cancer Prevention Study, USA	0.82	0.78–0.87
Alexander et al[26]	2001	Coumadin Aspirin Reinfarction Study	0.36	0.17–0.77

HMO, health maintenance organization; RR, risk ratio.

[a]Current users.