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THE INFLUENCE OF EXOGENOUS ESTROGEN USE ON SURVIVAL AFTER DIAGNOSIS OF ENDOMETRIAL CANCER

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For examination of the effect of prior exogenous estrogen use on survival after diagnosis of endometrial cancer, 244 endometrial cancer cases newly diagnosed at North Carolina Memorial Hospital, Chapel Hill, North Carolina, between 1970 and 1976 were followed until 1982. Estrogen users (n = 46) were younger, had less advanced disease, and were more likely to be nonobese and white than were nonusers (n = 198). The estimated probability of surviving (Kaplan-Meier) five years after diagnosis was 0.89 for users and 0.53 for nonusers. When adjusted for age, grade, stage, obesity, race, and treatment (using the Cox proportional hazards regression model), the survival probabilities throughout the period of observation for estrogen users continued to be higher. The adjusted hazard rate for a nonuser was 2.05 (95% confidence interval (CI) 0.96–4.39) times that for an estrogen user. The adjusted hazard rate from endometrial cancer only was 4.01 (95% CI 1.22–13.21) times greater among estrogen nonusers. The more frequent occurrence of endometrial cancer in an earlier stage and grade among estrogen users may not be the sole cause of their lower hazard rate from this disease.

estrogens, synthetic; mortality; uterine neoplasms

Although exogenous estrogen use increases the risk of endometrial cancer (1–4), endometrial cancer patients who have used exogenous estrogen are characterized by factors associated with better survival than those who have not used estrogen (2). The purpose of this analysis is to determine whether women who have used exogenous estrogen before a diagnosis of endometrial cancer actually have a survival advantage in addition to having known indicators of better survival from endometrial cancer. Of the five previous survival comparisons (6–10), three found a survival advantage for estrogen users (6, 8, 10), and two found none (7, 9). The negative results might be due to a sample of deaths too small to observe survival differences between estrogen users and nonusers.

To further evaluate the effects of exogenous estrogen use on the survival of patients with endometrial cancer, we analyzed probabilities of survival in a sample of endometrial cancer cases with a number of deaths larger than that in previously re-

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ported studies. For most statistics commonly used in survival analysis, the greater the number of deaths observed, the higher the statistical power (11). Therefore, this study had a better chance of detecting survival differences, if such differences exist, than did previous studies.

MATERIALS AND METHODS

The endometrial cancer cases in this study consisted of all 290 endometrial cancer patients initially treated at North Carolina Memorial Hospital between 1970 and 1976. These women were originally identified as participants in a case-control study, and their selection has been described elsewhere (1). Two internationally recognized outside pathologists reviewed the histologic material together with samples of normal tissue from gynecologic controls. After histologic review, 255 cases remained. Information on estrogen use (i.e., drug dosage, type, duration, and dates of first administration and discontinuation of use) and potentially confounding and effect modifying variables of the association between estrogen use and survival was collected from personal interviews with 88 per cent of the cases. Medical record data were abstracted from hospital patient files; the patient's usual source of medical care was visited, and her record was abstracted (73 per cent response). Additional physicians seen by the patient were mailed questionnaires requesting information on the case's history of estrogen use (83 per cent response).

Information on the case's vital status as of June 1982 was collected from 1) the underlying cause of death on the death certificate, 2) the gynecology records at North Carolina Memorial Hospital, and/or 3) the hospital cancer data base (a follow-up service based on physician letters), 4) letters from physicians, and 5) letters to the patient herself and to her relatives. One hundred per cent follow-up was achieved.

In keeping with the definition in the literature (7–9), estrogen use was given as estrogen consumption for at least six months. This definition was used so that only women who had taken a biologically relevant dose would be considered estrogen users. Furthermore, we observed that estrogen use among the women in our study who had taken estrogen for less than six months tended to be fragmentary and trivial. With this definition of estrogen use, 11 women were excluded from the analysis because of incomplete information on the duration of estrogen use.

Cox's proportional hazards regression model was used to estimate the hazard rate adjusted for confounding and effect modifying variables (12). The model is

$$\lambda(t) = \lambda_0(t)e^{\beta_1(x_1-\bar{x}_1)+\cdots+\beta_k(x_k-\bar{x}_k)},$$

where $\lambda(t)$ is the hazard rate (the death density or the instanteneous death rate) at time t. The hazard rate can be interpreted as the death rate in a small time interval, given survival to that interval. $\lambda_0(t)$ is the hazard rate when the independent variables are set to their average values. The β_i's (i going from 1 to k) are the regression coefficients to be estimated, and the x_i's (i going from 1 to k) are the values of the exposure variable, confounding variables, and effect modifying variables. The $\bar{x}_i$'s (i going from 1 to k) are the average values of the independent variables. Survival probabilities are presented for all causes of death combined, and cumulative hazard rates are shown for specific causes of death (13). The hazard ratios are the ratios of the hazard rates for values of a variable unfavorable to survival to values of that variable favorable to survival. To test the proportionality of the hazard rates for the different strata of each independent variable (an assumption on which the Cox model is based), we graphed the −log (−log) survival curves for deaths from all causes against the length of time, in days, since diagnosis for estrogen users and nonusers, and for each stratum of the potentially confounding and effect modifying variables (14). Plots were created with and without a preliminary set of confounding variables (age, stage, and grade). The survival curves were approximately

parallel, indicating that the proportionality assumption was met.

We modeled deaths due to all causes combined, deaths due to endometrial cancer, and deaths due to causes other than endometrial cancer separately, using a backward stepping procedure. First, potential effect modifiers (estrogen use × age, estrogen use × year, and estrogen use × obesity) were added to a basic model consisting of estrogen use (coded as a dichotomous variable), age in years, and histologic grade and stage (both coded as categorical variables). The basic model for deaths due to causes other than endometrial cancer included only estrogen use and age. The interaction terms were not significant and were excluded for the remainder of the analysis.

Second, all potentially confounding variables were added to the basic model (diabetes, hypertension, obesity, race, and year of diagnosis, coded as dichotomous variables, and treatment, coded as a categorical variable). The variable representing estrogen use was retained as were variables whose regression coefficients tested statistically different from zero at the 0.05 level. Estrogen use, age, grade, stage at diagnosis, obesity, race, and treatment were included in the final model for deaths from all causes. The same variables were retained in the model for deaths due to endometrial cancer only, and year of diagnosis was included. For deaths due to causes other than endometrial cancer, only the variables estrogen use, age, and diabetes were used in the final model.

Although we are aware of the pitfalls of backward stepping procedures (15), we know of no better method to reduce the number of independent variables when one's prior belief is that the potentially confounding variables are weakly associated with survival and are all equally likely to be confounding variables. However, to evaluate the sensitivity of the regression coefficient for estrogen use to changes in the methods of model selection, we examined the regression coefficient for estrogen use in the basic model and in models created through forward selection.

Information on the extent of invasion was missing for nine cases. After the final models were selected, we excluded these cases and examined the influence of the variable myometrial invasion (coded as a dichotomous variable) on the final models of deaths from all causes combined and deaths due to endometrial cancer.

RESULTS

The 244 subjects in this study were followed for a median length of 5.7 years, with a range of 1–13 years. Among the 46 estrogen users, the average length of observation was 7.8 years during which time eight died. One hundred and ninety-eight estrogen nonusers were observed for a median length of 5.3 years, and 107 deaths were reported. Eighty deaths were due to endometrial cancer (three among estrogen users), and 35 deaths were from other causes (five among estrogen users). Eighty-four per cent of the total deaths occurred within the first five years of observation (92 among nonusers and five among users).

Table 1 characterizes estrogen users and nonusers by a number of potentially confounding variables. Estrogen users were younger, had less advanced disease, were less likely to have had diabetes and hypertension, and were more likely to be white than were nonusers. Obesity was more common among women who did not use exogenous estrogen than among those who did. Estrogen users were more frequently treated with both radiation and surgery than were women who did not use exogenous estrogen.

The Kaplan-Meier estimates of the probabilities of surviving at least five years, shown in table 2, were higher for estrogen users than for nonusers for each level of each potentially confounding variable. These probabilities were not adjusted for other covariates and may differ because of the unequal distribution of confounding variables between estrogen users and nonusers. For most variables, estrogen users

TABLE 1

Per cent distribution of potentially confounding variables for estrogen users and nonusers diagnosed with endometrial cancer at North Carolina Memorial Hospital, Chapel Hill, NC, 1970–1976

Variable	Estrogen users (n = 46)	Estrogen nonusers (n = 198)
Age (years)		
30–49	6.5	16.2
50–59	63.0	22.7
60–69	26.1	34.9
70+	4.4	26.3
Histologic grade		
I	63.0	39.4
II	26.1	43.4
III	10.9	17.2
Stage		
I, IA	56.5	35.3
IB	8.7	21.2
II	30.4	25.8
III, IV	4.4	16.7
Missing	0.0	1.0
Diabetes mellitus		
No	91.3	75.8
Yes	8.7	24.2
Hypertension		
No	56.5	37.4
Yes	43.5	62.6
Obesity		
No (≤77.11 kg)	65.2	43.4
Yes (>77.11 kg)	34.8	56.6
Race		
Black	2.2	32.8
White	97.8	67.2
Treatment type		
Surgery only	6.5	8.5
Radiation only	8.6	29.8
Radiation and surgery	73.9	42.4
Other	10.8	19.2
Years of diagnosis		
1970–1973	45.7	50.5
1974–1976	54.4	49.5

predominate in those categories that have better survival. Obesity, however, which is less common among estrogen users (34.8 per cent) than among nonusers (56.6 per cent) (table 1), shows a small survival advantage. The five-year survival probability for obese nonusers was 0.63, while that for nonobese nonusers was 0.40.

Higher survival rates for estrogen users than for nonusers were found throughout the period of observation. Figure 1 shows that this trend persisted even after adjustment for the confounding variables shown in table 3, which shows the variables selected by the backward stepping procedure described above. The hazard rate for estrogen nonusers was 2.05 (95 per cent confidence interval (CI) 0.96–4.39) times that for users. Most of the adjusted hazard ratios are around 2 except that for the variable treatment, for which methods "other than radiation and surgery" has a hazards rate 3.89 times larger than the hazard rate for radiation and surgery combined. The different methods of modeling yielded similar hazard ratios for estrogen use: The model that contained all potentially confounding variables produced a hazard ratio of 1.97 (95 per cent CI 0.92–4.24), that resulting from forward selection yielded a value of 2.03 (95 per cent CI 0.95–4.32), and the basic model produced the highest hazard ratio, 2.26 (95 per cent CI 1.07–4.78).

TABLE 2

Percentage deceased and unadjusted five-year survival rates in 1982 for estrogen users and nonusers, by categories of potentially confounding variables among women diagnosed with endometrial cancer at North Carolina Memorial Hospital, Chapel Hill, NC, 1970–1976

Potentially confounding variable	Percentage deceased	Probability of surviving at least five years	
		Estrogen user	Estrogen nonuser
Overall	47	0.89	0.53
Age (years)			
≤61	30	0.94	0.64
>61	66	0.70	0.44
Histologic grade			
I	27	0.97	0.74
II	57	0.92	0.46
III	77	0.40	0.24
Stage			
I, IA	37	0.92	0.67
IB	30	No deaths	0.71
II	54	0.86	0.47
III, IV	83	0.50	0.13
Diabetes mellitus			
No	43	0.88	0.54
Yes	64	No deaths	0.50
Hypertension			
No	39	0.89	0.55
Yes	53	0.90	0.52
Obesity			
No (≤77.11 kg)	52	0.83	0.40
Yes (>77.11 kg)	43	0.94	0.63
Race			
Black	80	No deaths	0.28
White	37	0.89	0.65
Treatment type			
Surgery only	24	No deaths	0.70
Radiation only	76	0.50	0.29
Radiation and surgery	13	0.97	0.86
Other	72	No deaths	0.20
Years of diagnosis			
1970–1973	52	0.91	0.54
1974–1976	42	0.92	0.52

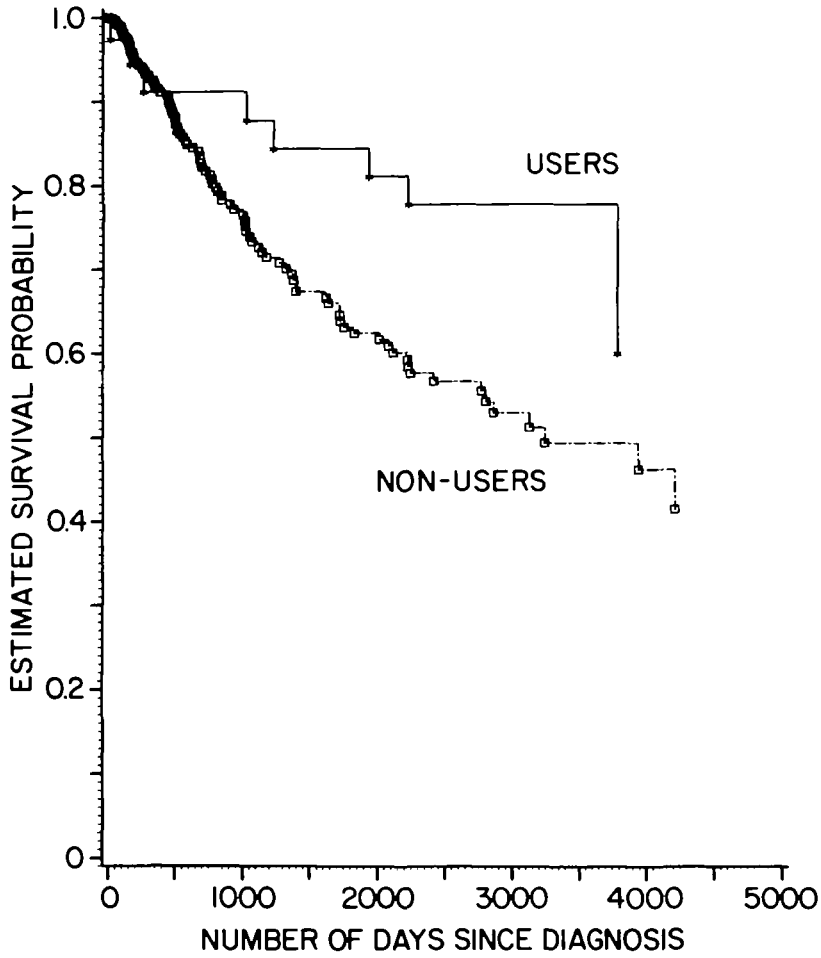

FIGURE 1. Adjusted survival probability from all causes of death in 1982, adjusted for age, grade, stage, obesity, race, and treatment. Study population consists of women who were diagnosed with endometrial cancer at North Carolina Memorial Hospital, Chapel Hill, NC, 1970–1976.

Figure 2 shows the adjusted cumulative hazard rates for estrogen nonusers and estrogen users for deaths from endometrial cancer only. The nonusers had higher death rates than the estrogen users. Table 4 shows the variables used to adjust the cumulative hazard rates in figure 2. The variables included in this model were the same as those included in the model for deaths due to all causes (table 3), with the addition of year of diagnosis, which was statistically significant. The hazard ratio for estrogen use was 4.01 (95 per cent CI 1.22–13.21), approximately twice as large as that observed for deaths from all causes (table 3). As in the previous model, the hazard ratio was similar for all the strategies of variable selection that we used. It was 3.95 (95 per cent CI 1.20–13.02) for the model that included all potentially confounding variables, 4.62 (95 per cent CI 1.43–15.13) for the basic model, and 4.63 (95 per cent CI 1.33–14.25) for the model created by forward selection. Most of the hazard ratios in table 4 are larger than those in table 3, suggesting that the effect of most of the variables on the hazard rates from all causes combined arises from their relation to death from endometrial cancer.

Excluding the nine cases with information missing on the extent of myometrial invasion produced no substantive change

TABLE 3

Influence of exogenous estrogen use and confounding variables on the hazard rate from all causes in 1982 among women diagnosed with endometrial cancer at North Carolina Memorial Hospital, Chapel Hill, NC, 1970–1976, using Cox's regression model

Variable	Regression coefficient	Standard error	Hazard ratio*	95% confidence interval
Estrogen use	−0.7182	0.3885	2.05	0.96–4.39
Age	0.0326	0.0101	1.53	1.18–1.98
Grade				
II	0.6178	0.2495	1.86	1.14–3.03
III	0.7059	0.3003	2.03	1.13–3.65
Stage				
IB	−0.8537	0.3323	2.35	1.22–4.50
II	0.0493	0.2510	1.05	0.64–1.72
III, IV	0.9805	0.2927	2.67	1.50–4.73
Obesity	−0.5307	0.2000	1.70	1.15–2.52
Race	−0.8100	0.2225	2.23	1.44–3.44
Treatment				
Surgery only	−0.9747	0.4356	2.65	1.13–6.22
Radiation only	−0.1529	0.2528	1.17	0.71–1.91
Radiation and surgery	−1.3593	0.2985	3.89	2.17–6.99

* Ratio of hazard rates for categories of each variable. The ratio contains the hazard rate for the "unfavorable to survival" category in the numerator and the "favorable to survival" category in the denominator. Unfavorable categories are no estrogen use; grades II and III; stages II, III, and IV, and stages I and IA, only when compared with stage IB; nonobese; black; and treatment other than surgery only, radiation only, and radiation and surgery. Favorable categories are estrogen use; grade I; stages I and IA, except when compared with stage IB (then stage IB is the favorable category); obese; white; surgery only, radiation only, and radiation and surgery. For the continuous variable, age at diagnosis, age 68 (the third quartile) is the value unfavorable to survival, and age 55 (the first quartile) is the value favorable to survival.

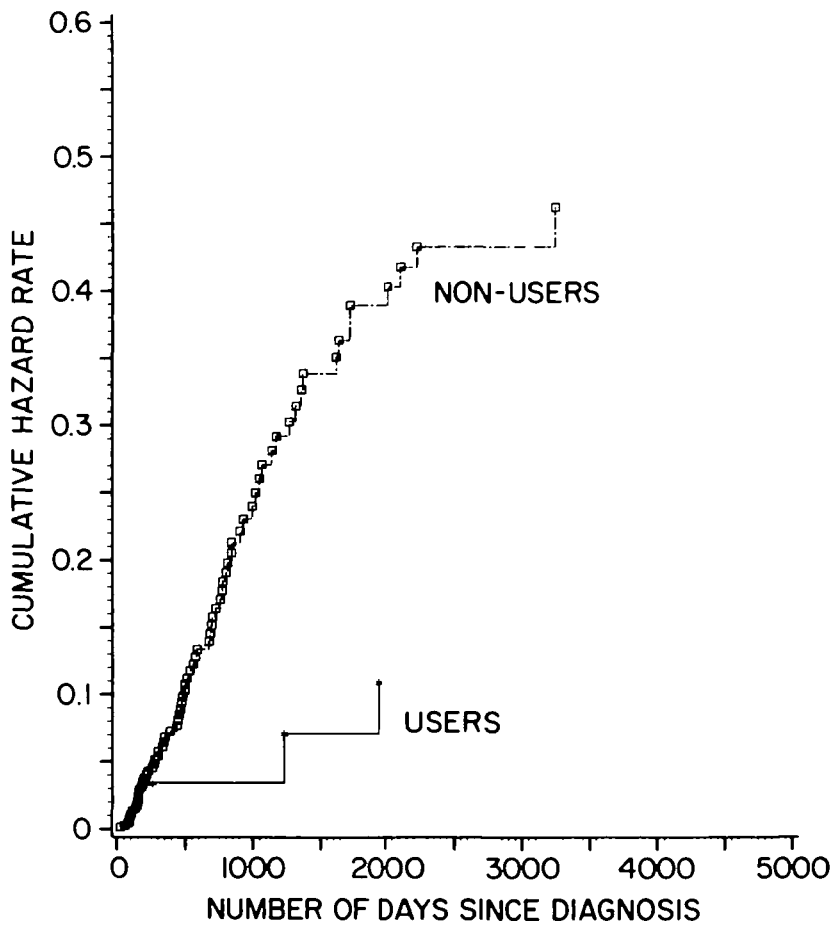

FIGURE 2. Adjusted cumulative hazard rate for deaths due to endometrial cancer in 1982, adjusted for age, grade, stage, obesity, treatment, and year. Study population consists of women who were diagnosed with endometrial cancer at North Carolina Memorial Hospital, Chapel Hill, NC, 1970–1976.

TABLE 4

Influence of exogenous estrogen use and confounding variables on the hazard rate from endometrial cancer in 1982 among women diagnosed with endometrial cancer at North Carolina Memorial Hospital, Chapel Hill, NC, 1970–1976, using Cox's regression model

Variable	Regression coefficient	Standard error	Hazard ratio*	95% confidence interval
Estrogen use	−1.3889	0.6082	4.01	1.22–13.21
Age	0.0290	0.0126	1.46	1.06–2.01
Grade				
II	0.7827	0.3146	2.19	1.18–4.05
III	0.6890	0.3655	1.99	0.97–4.08
Stage				
IB	−0.7897	0.4093	2.20	0.99–4.91
II	0.2677	0.3113	1.31	0.71–2.41
III, IV	1.2231	0.3385	3.40	1.75–6.60
Obesity	−0.6881	0.2537	2.00	1.21–3.27
Race	−0.8048	0.2874	2.24	1.27–3.92
Treatment				
Surgery only	−1.2910	0.5544	3.64	1.23–10.78
Radiation only	−0.4516	0.3243	1.57	0.83–2.97
Radiation and surgery	−1.6610	0.3687	5.26	2.56–10.84
Years of diagnosis	−0.6043	0.2744	1.83	1.07–3.13

* Ratio of hazard rates for categories of each variable. The ratio contains the hazard rate for the "unfavorable to survival" category in the numerator and the "favorable to survival" category in the denominator. Unfavorable categories are no estrogen use; grades II and III; stages II, III, and IV, and stages I and IA, only when compared with stage IB; nonobese; black; treatment other than surgery only, radiation only, and radiation and surgery; and years of diagnosis 1970–1973. Favorable categories are estrogen use; grade I; stages I and IA, except when compared with stage IB (then stage IB is the favorable category); obese; white; surgery only, radiation only, and radiation and surgery; and years of diagnosis 1974–1976. For the continuous variable, age at diagnosis, age 68 (the third quartile) is the value unfavorable to survival, and age 55 (the first quartile) is the value favorable to survival.

in the hazard ratio for estrogen use. The hazard ratio for estrogen use for all causes of death combined in this subset of the data was 1.97 (95 per cent CI 0.91–4.22), and the hazard ratio for estrogen use for deaths from endometrial cancer was 3.69 (95 per cent CI 1.11–12.11).

Figure 3 shows no difference between the cumulative hazard rates for estrogen users and nonusers when the causes of death other than endometrial cancer are considered separately. In table 5, the hazard ratio of 1.10 reflects the similarity of the cumulative hazard rates for estrogen use and nonuse shown in figure 3.

DISCUSSION

Women with endometrial cancer who have used exogenous estrogen prior to diagnosis have a survival advantage from all causes of death. The source of this advantage is the lower death rates from endometrial cancer among former estrogen users. That the survival advantage of exogenous estrogen users is not solely due to selection bias (i.e., that women who were selected to use estrogen are healthier and would have lived longer had they not consumed estrogen) is suggested by the observation that the hazard ratio for estrogen use is 1.10 for causes of death other than endometrial cancer. If women who received estrogen were inherently healthier than women who did not, we would expect estrogen users to have lower hazard rates from causes of death other than endometrial cancer.

Several authors have reported better survival from all causes of death combined for estrogen users (6, 8, 10). Collins et al. (8) estimated that the risk of death from all causes among women who did not use estrogen was 2.7 times greater than that among those who did. The hazard ratio we observed was similar (2.05, table 3). In contrast, Robboy and Bradley (7) and Smith et al. (9) found that when histologic grade was added to the model, the survival advantage of estrogen users disappeared. In neither one of these study populations was the number of deaths as great as the number that we observed in our sample. It is possible, therefore, that the authors did not have the statistical power to detect a sur-

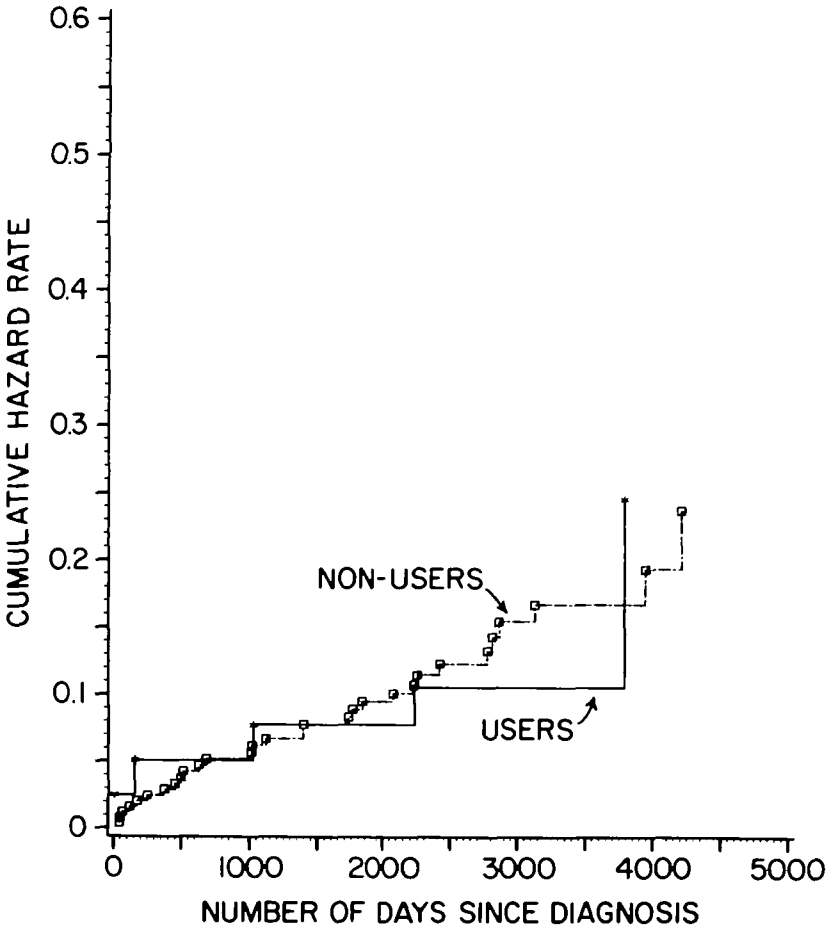

FIGURE 3. Adjusted cumulative hazard rate for causes other than endometrial cancer in 1982, adjusted for age and diabetes. Study population consists of women who were diagnosed with endometrial cancer at North Carolina Memorial Hospital, Chapel Hill, NC, 1970–1976.

vival advantage among estrogen users after histologic grade was controlled.

For example, Smith et al. (9) estimated a statistically significant hazard ratio of 3.3 for estrogen nonuse for a sample of 182 women diagnosed with endometrial cancer, 29 of whom died. When histologic grade was included in the proportional hazards regression model (which already included age and clinical stage), the hazard ratio dropped to 2.20 and was no longer statistically significant.

Although Chu et al. (10) found a survival advantage for estrogen users, they did not adjust for stage or histologic grade. A rationale for not adjusting is that estrogen itself is responsible for the development of endometrial cancer of lower stage and grade. To the extent that the early stage and lower grade observed in estrogen users represent the results of a biologic process that produces less aggressive disease, stage and grade are intervening variables and should not be controlled. To the extent that estrogen use causes a woman to be examined earlier and to be diagnosed at an earlier stage or with a tumor of lower histologic grade, stage and grade are confounding variables and should be controlled in the model. Although stage and grade may be, simultaneously, confounding and intervening variables, we have controlled for them to exclude their confounding effects. In so doing, we have lowered the hazard ratio for

TABLE 5

Influence of exogenous estrogen use and confounding variables on the hazard rate from causes other than endometrial cancer in 1982 among women diagnosed with endometrial cancer at North Carolina Memorial Hospital, Chapel Hill, NC, 1970–1976, using Cox's regression model

Variable	Regression coefficient	Standard error	Hazard ratio*	95% confidence interval
Estrogen use	−0.0977	0.5257	1.10	0.39–3.09
Age	0.0871	0.0184	3.10	1.94–4.96
Diabetes mellitus	0.9438	0.3471	2.57	1.30–5.07

* Ratio of hazard rates for categories of each variable. The ratio contains the hazard rate for the "unfavorable to survival" category in the numerator and the "favorable to survival" category in the denominator. Unfavorable categories are no estrogen use and diabetes; favorable categories are estrogen use and no diabetes. For the continuous variable, age at diagnosis, age 68 (the third quartile) is the value unfavorable to survival, and age 55 (the first quartile) is the value favorable to survival.

estrogen use (by adjusting for an intervening variable) and have provided a conservative estimate of the survival advantage for estrogen users.

Of the five previous survival studies of estrogen use (6–10), none provided a separate estimate of the risk of death from endometrial cancer only, for estrogen nonusers relative to that for estrogen users. Collins et al. (8) found that the relative odds for death from cancer at all sites for estrogen nonusers compared with estrogen users was 5.4, which can be compared to a hazard ratio of 4.01 observed in our study for deaths from endometrial cancer only.

In support of a biologic role for estrogen in producing less aggressive tumors is the observation in our data that obesity protects against death from endometrial cancer. In table 4, nonobese women are shown to have a risk of death from endometrial cancer twice that of obese women. In postmenopausal women, endogenous estrogens are produced in adipose tissue from androgenic precursors, and those who are obese have higher serum estrogen levels than those who are nonobese (16). Endogenous estrogen production may be the mechanism whereby obese women with endometrial cancer have a survival advantage over nonobese endometrial cancer patients.

Also consistent with a biologic role for estrogen is the observation that nonusers had hazard rates from endometrial cancer 11.82 times greater (95 per cent CI 1.62–86.48) than women who used exogenous estrogen for 3.5 years or more. The hazard rate for estrogen nonusers was only 2.30 times greater (95 per cent CI 0.82–6.44) than that of women who had used exogenous estrogen for less than 3.5 years. These observations are consistent with a dose-response relation. For women with endometrial cancer, long-term estrogen use prior to diagnosis has a greater effect on survival than short-term use. These results do not detract from the literature, which shows an increased risk of endometrial cancer resulting from exogenous estrogen use.

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