Commentary

The Epidemic of Endometrial Cancer: A Commentary

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Abstract: Vital statistics show that a rise in incidence of endometrial cancer began in the mid-1960s on the West Coast of the United States. This rise was continuous and reached a peak in 1975. Elsewhere, incidence rates for endometrial cancer rose during the 1970s. It now seems evident that much of the rise in all areas of the country was due to replacement estrogen treatment. We estimated from data obtained from the Commission on Professional and Hospital Activities-Professional Activity Study of Ann Arbor, Michigan, that over 15,000 cases of endometrial cancer were caused by replacement estrogens during the five-year period 1971–1975 alone. This represents one of the largest epidemics of serious iatrogenic disease that has ever occurred in this country. With the substantial fall in estrogen sales starting in January 1976, there has been an associated decline in the incidence rates of endometrial cancer nationwide. (*Am J Public Health* 70:264–267, 1980.)

Vital statistics obtained from numerous local cancer registries throughout the United States have consistently shown a large rise in the incidence of endometrial cancer from 1970 through 1975.[1] While the Third National Cancer Survey showed little change in the incidence of this disease between 1947 and 1970,[2] and no increase was noted in England, Wales, or Canada during that same time,[3] a marked increase in incidence began in California's Alameda County in the mid-1960s.[4] Indeed, the incidence there approximately doubled from 1965 to 1970 and subsequently continued to rise steeply.[4]

Information obtained from the Commission on Professional and Hospital Activities-Professional Activity Study (CPHA-PAS) of Ann Arbor, Michigan confirms the national rise in endometrial cancer incidence from 1970 to 1975.[5] CPHA-PAS obtains discharge diagnosis information on over 35 per cent of hospitalizations in the United States. From these data they construct a 1 per cent sample of hospital discharges in the United States which is designed to be representative of discharges in the country as a whole with regard to census region, hospital size, and ownership (governmental and nongovernmental). According to these data, the estimated number of new cases of endometrial cancer treated by hysterectomy in the United States rose from 10,500 in 1970 to 18,000 in 1975 among women aged 50–69 years.[5] The rates were consistently highest in the western United States and the rise in incidence over time was largest there. The combined experience from various sources leaves little doubt that a dramatic rise in the reported incidence of endometrial cancer occurred in the early 1970s.

Greenwald, et al, reported that there was a plateauing, or even a light downturn, of the progressive rise in incidence rates in 1976.[6] According to information obtained from CPHA-PAS, the incidence rates of endometrial cancer had fallen nationwide after 1975 by 27 per cent by the end of 1977.[7] Our most recent information from CPHA-PAS encompassing discharges to the end of 1978 shows that by the end of that year the estimated incidence rates had fallen to about the level prevailing in 1970.* This fall occurred after the publication in late 1975 of two papers[8,9] describing a strong positive association between replacement estrogen use and endometrial carcinoma which led to a dramatic decrease nationwide in the prescribing of these drugs.[10]

Four years have elapsed since the publication of the first major studies concerning the relation of replacement estrogens to endometrial cancer. Sufficient information has now accrued to describe the nature and scope of this problem in some detail and to consider why the discovery was delayed.

Confounding Circumstances

A major factor contributing to the substantial delay in discovery of the connection between estrogens and endome-

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TABLE 1—Estrogen Use among Postmenopausal Women in Boston, 1972*

	Non-Users	≤ 5 years	> 5 years
Natural Menopause‡	664 (96%)	22 (3%)	8 (1%)
Surgical Menopause‡	318 (87%)	26 (7%)	21 (6%)

*Women age 50 and older admitted to 24 Boston-area hospitals during the first ten months of 1972. Patients with conditions possibly related to estrogen use were excluded (major exclusion categories: gynecologic disease, cancer, cardiovascular disease, gallbladder disease).

‡The "Natural Menopause" group includes an unknown number of women with hysterectomy after menopause. The age distributions in the "Natural Menopause" and "Surgical Menopause" categories are similar.

TABLE 2—Estrogen Use* among Non-Hysterectomized Women without Endometrial Cancer

Area (years)	Estrogen Use among Controls with Uteri*	Proportion Using Estrogen
Los Angeles (1970-1974) (9)	29/188	0.15
Los Angeles (1971-1975) (16)	126/252	0.50
New Haven (1974-1976) (20)	4/119	0.03
Baltimore (1973-1977) (19)	16/406	0.04

*"Estrogen Use" is defined here as current or past use of replacement estrogens.

trial cancer is the high prevalence of previous hysterectomy among women in the age range in which replacement estrogens are most likely to be prescribed. More than 30 per cent of American women over 50 years of age have had a hysterectomy,[11] and this proportion has been progressing steadily upward for over a decade.[12] As a consequence, national statistics on the incidence and mortality from endometrial cancer (and probably cancer of the cervix) have been distorted, because they have not been based on the actual population at risk, which comprises women who still have their uteri.[12] This problem was compounded by a much greater tendency to prescribe estrogens to hysterectomized women. In a survey of 24 Boston-area hospitals during the first ten months of 1972,[13] the proportion of women with surgical menopause who received estrogens was substantially greater than the proportion of women with natural menopause who took these drugs (Table 1). In our recent study in Seattle, 22 of 36 control women (61 per cent) taking estrogens had had a prior hysterectomy.[7] The failure of individual physicians to notice a rapid increase in incidence of endometrial cancer among their estrogen-using patients may have resulted at least in part because many of these women had already had a hysterectomy and were not at risk to develop endometrial cancer.

It is no surprise that the connection between estrogens and endometrial cancer was first suspected, studied, and documented on the West Coast, where estrogen use has been substantially more popular than it has been elsewhere. Table 2 gives the proportion of estrogen users (current and past use combined) among control groups from the studies that have limited their attention to estrogen use since 1960. The data in Table 2 indicate that estrogen use among non-hysterectomized women was substantial on the West Coast and modest in the East. The data from Boston in Table 1 showed only 1 per cent of women with natural menopause had taken replacement estrogens for more than five years in 1972. It is likely that no important drug effect could have been demonstrated in the East through the early 1970s because long-term exposure to estrogens had not yet taken place. By contrast, the strong positive association between estrogens and endometrial cancer found by Smith, et al, in Seattle was based on cases occurring before the end of 1972, and the effect was apparent in cases diagnosed prior to 1968.[9] Vital statistics elsewhere on the West Coast for this period showed remarkable changes: in Alameda County, California, the incidence of invasive cancer of the endometrium in 1968 was already 50 per cent higher than it had been five years before.[4] No such changes were seen in Connecticut, where rates were nearly constant throughout the 1960s.[14]

Nature and Extent of the Causal Connection

For non-hysterectomized women, there is a strong association between replacement estrogens and endometrial cancer.[7, 8, 9, 15–18] It now appears that the estrogen-related risk is: a) concentrated in women who have taken replacement estrogens for at least five years, and b) very strong in such women—ten to thirty-fold relative to non-users.[5, 15–18] The absolute risk is estimated to be 1 to 3 per cent each year.[5]

The credibility of risk estimates from these studies is strengthened by a consistency with national incidence rates estimated from CPHA-PAS data.[5, 7] It can be roughly estimated that: a) the proportion of the 21,000,000 United States women aged 50–69 years with an intact uterus was about 65 per cent in 1975, b) the proportion of these women with uteri who took estrogens during that year was about 10 per cent,[7, 8, 15, 18, 19] c) the proportion of estrogen users who had taken the drug for five or more years that year is approximately 30 per cent,[7, 8, 15, 18] and d) the annual risk of endometrial cancer among women who take estrogens for five or more years is about 1.5 per cent.[7] Under these assumptions, in 1975 there would have been (21,000,000) (0.65) (0.1) (0.3) (.015) = 6,000 cases among long-term users. The actual excess of cases in 1975 estimated from CPHA-PAS data in the age group 50-69 years was about 7,500 cases compared with 1970.

The above calculation suggests that most, if not all, of the rise in the incidence of endometrial cancer in the United States from 1970 to 1975 may be ascribable to replacement estrogen therapy. If these assumptions are correct, over 15,000 cases of endometrial cancer were caused by replacement estrogens during the five-year period 1971-1975—surely one of the largest epidemics of serious iatrogenic disease that has ever occurred in this country.

Mitigating Factors

There are, fortunately, important mitigating circumstances. Endometrial cancer tends to have a favorable prog-

nosis. The five-year survival rate is between 70 per cent and 80 per cent overall, and better than 80 per cent if the cancer is diagnosed in the earlier stages.[20-22] Among estrogen users the tumor tends to have, on average, a more favorable histologic type and is less invasive than that in non-users.[15, 18] It may be that relatively few deaths have resulted from the estrogen-induced epidemic. The costs in terms of suffering and money, however, have been undeniably large.

A second mitigating factor is that discontinuation of estrogens, even in long-term users, appears to be associated with a rapid decrease in risk. Strong evidence for this is present from the experience at Group Health Cooperative of Puget Sound.[7] Similar findings have been reported by Weiss, et al.[23] Additional evidence comes from nationwide data. National estrogen sales declined substantially starting in January 1976.[10] Most of this decline is very likely to have occurred among estrogen users who had intact uteri. By 1978 the incidence of endometrial cancer in women in their 50s had fallen from its peak value in 1975 by an estimated 46 per cent nationwide.* Over 5,000 cases of endometrial cancer may have been prevented as a result of the decline in estrogen use after 1975, compared with a continuation of use at 1975 levels.

Finally, it is apparent that women who use estrogens only for a short time run a far smaller risk of endometrial cancer than do long-term users.[7, 8, 15-18] Many may feel that the potential benefits of hormone treatment for no longer than two or three years for women with menopausal symptoms will outweigh the reported two-fold increase[18] in endometrial cancer risk.

Alternative Views

If estrogens do not cause endometrial cancer, the large rise and fall in the reported incidence of this disease must be considered an artifact. Shanklin[24] and others have suggested that benign conditions may often be misdiagnosed as cancer. Kistner[25] has contended that cellular patterns pathologically identical to cancers in appearance, when induced by estrogens, may in fact be non-malignant. Estrogens, however, have been shown to raise the risk for invasive and metastatic disease, albeit to a lesser degree than for carcinoma in situ.[15, 17, 18] Furthermore, the incidence of these more malignant manifestations of endometrial cancer rose in the early 1970s along with the incidence of in situ disease.[4, 14]

It has also been argued that estrogens merely cause an existing cancer to be diagnosed.[19] Under this hypothesis, most women taking estrogens and diagnosed as having endometrial cancer would not have been diagnosed if they were not taking estrogens. If this view is correct, to explain the strong associations observed, endometrial cancer would have to be a common, extremely benign disease which remains undiagnosed in 90 to 95 per cent of estrogen non-users. Assuming that the entire observed estrogen effect is due to a diagnostic bias, the 1 to 3 per cent annual incidence found among long-term users[7] must be characteristic of all women of similar age, users and non-users alike. Such an annual incidence would imply a prevalence of undiagnosed uterine cancer of about 25 per cent by age 65. A prevalence this high is not found in autopsy series.[17]

Other possibilities that have been proposed are that the "post-menopausal syndrome" which is treated with estrogens may itself indicate a high risk for endometrial cancer, or the earliest stages of cancer may be commonly treated symptomatically with estrogens.[26] Under such circumstances, the prescription of estrogens would be a marker, but not a cause, of disease later to be diagnosed. Temporal trends[4, 14] and regional variation[5] in incidence rates remain unexplained by these hypotheses. The similarity in risk associated with estrogens in populations with ten-fold differences in estrogen prescription rates[15, 18] make such non-causal hypotheses implausible.

The epidemic of endometrial cancer went essentially undiscovered until 1975, some ten years after a decided upward trend in the incidence of the disease began in Alameda County.[4] Such a long delay in the discovery of important drug-induced illness might be avoided in the future by: a) close scrutiny of registry and vital statistics data—such scrutiny uncovered the epidemic of deaths due to asthma medication in children in Britain,[27] b) sensitivity to the potential of long-term drug use to induce serious illness, and c) the identification and follow-up of drug users to provide earlier alerts, particularly for new drugs. The possibility of implementing formal systems of postmarketing follow-up has recently been considered and found to be feasible, in principle, at an acceptable cost by the use of automated recording of drug exposures and outcome illnesses.[28]

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REFERENCES

1. Weiss NS, Szekely DR, Austin DF: Increasing incidence of endometrial cancer in the United States. N Engl J Med 294:1259-1262, 1976.
2. Cutler SJ, Young JL, (eds): Third National Cancer Survey: Incidence Data. National Cancer Institute, Monograph 41, Bethesda, MD, 1975.
3. Kinlen LJ, Doll R: Trends in mortality from cancer of the uterus in Canada and in England and Wales. Br J Prev Soc Med 27:146-149, 1973.
4. Austin DF, Roe KM: Increase in cancer of the corpus uteri in the San Francisco-Oakland standard metropolitan statistical area, 1960-75. J Natl Cancer Inst 62:13-16, 1979.
5. Walker AM, Jick H: Cancer of the corpus uteri: Increasing incidence in the United States, 1970-1975. Am J Epidemiol 110:47-51, 1979.
6. Greenwald P, Caputo TA, Wolfgang PE: Endometrial cancer after menopausal use of estrogens. Obstet Gynecol 50:239-243, 1977.
7. Jick H, Watkins RN, Hunter JR, et al: Replacement estrogens and endometrial cancer. N Engl J Med 300:218-222, 1979.
8. Ziel HK, Finkle WD: Increased risk of endometrial carcinoma among users of conjugated estrogens. N Engl J Med 293:1167-1170, 1975.
9. Smith DC, Prentice R, Thompson DJ, et al: Association of Exogenous estrogen and endometrial carcinoma. N Engl J Med 293:1164-1167, 1975.
10. Burke LB, Crosby DL, Lao CH: Estrogen prescribing in menopause. Paper presented at the 105th annual meeting of the

American Public Health Association, Washington, DC, November 2, 1977.
11. Walker AM, Jick H: Temporal and regional variation in hysterectomy rates in the United States, 1970-1975. Am J Epidemiol 110:41-46, 1979.
12. Lyon JL, Gardner JW: The rising frequency of hysterectomy: Its effect on uterine cancer rates. Am J Epidemiol 105:439-443, 1977.
13. Boston Collaborative Drug Surveillance Program: Oral contraceptives and venous thromboembolic disease, surgically confirmed gallbladder disease, and breast tumours. Lancet 1:1399-1404, 1973.
14. Marrett LD, Elwood JM, Meigs JW, et al: Recent trends in the incidence and mortality of cancer of the uterine corpus in Connecticut. Gynecol Oncol 6:183-195, 1978.
15. Mack TM, Pike MC, Henderson BE, et al: Estrogens and endometrial cancer in a retirement community. N Engl J Med 294:1262-1267, 1976.
16. Gray LA, Christopherson WM, Hoover RN: Estrogens and endometrial carcinoma. Obstet Gynecol 49:385-389, 1977.
17. McDonald TW, Annegers JF, O'Fallon WM, et al: Exogenous estrogen and endometrial carcinoma: case-control and incidence study. Am J Obstet Gynecol 127:572-580, 1977.
18. Antunes CMF, Stolley PD, Rosenshein NB, et al: Endometrial cancer and estrogen use. N Engl J Med 300:9-13, 1979.
19. Horwitz RI, Feinstein AR: Alternative analytic methods for case-control studies of estrogens and endometrial cancer. N Engl J Med 299:1089-1094, 1978.
20. Ng ABP, Reagan JW: Incidence and prognosis of endometrial carcinoma by histologic grade and extent. Obstet Gynecol 35:437-443, 1970.
21. Jones WE, Kanner HM, Kanner HH, et al: Adenocarcinoma of the endometrium. Am J Obstet Gynecol 113:549-557, 1972.
22. Homesley HD, Boronow RC, Lewis JL: Treatment of adenocarcinoma of the endometrium at Memorial-James Ewing Hospitals, 1949-1965. Obstet Gynecol 47:100-105, 1976.
23. Weiss NS, Szekely DR, English DR, et al: Endometrial cancer in relation to patterns of menopausal estrogen use. JAMA 242:261-264, 1979.
24. Shanklin DR: Estrogens and endometrial cancer (letter). N Engl J Med 294:897, 1976.
25. Kistner RW: Estrogens and endometrial cancer. Obstet Gynecol 48:479-482, 1976.
26. Feinstein AR, Horwitz RI: A critique of the statistical evidence associating estrogens with endometrial cancer. Cancer Res 38:4001-4005, 1978.
27. Inman WHW, Adelstein AM: Rise and fall of asthma mortality in England and Wales in relation to use of pressurised aerosols. Lancet 2:279-285, 1969.
28. Jick H, Walker AM, Spriet-Pourra C: Postmarketing follow-up. JAMA 242:2310-2314, 1979.

Conference on Disaster Planning Scheduled

The University of California, San Francisco, Continuing Education in Health Sciences will sponsor a symposium on "Disaster Planning: National, Regional & Hospital Plans," April 12-13, 1980. This symposium will focus on disaster preparedness in the context of natural events such as earthquake or nuclear power plant emergencies.

The program will begin with identification and description of the medical response at the state and federal levels and how resources can be used to interface with regions and, ultimately, hospitals. Within this context nuclear power plant safety and implications for disaster planning will be discussed. There will be a presentation of comparative data on what impact the Three Mile Island Disaster has had on hospital planning.

The objectives of the program are to: Identify disaster planning resources and coordinators at all levels of government; relate these resources to the hospital planning level; and consider modifications necessary for future disaster planning based on possible nuclear power plant emergencies. Education credit is available.

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