
Preliminary Communications

CANCER OF THE UTERINE CORPUS AFTER HORMONAL TREATMENT FOR BREAST CANCER

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Summary Among 45 853 women in whom breast cancer was diagnosed after age forty-nine, from the series of the End Results Program of the National Cancer Institute, cancer of the uterine corpus subsequently developed in 203. The risk was greater among those women receiving hormones than in other treatment groups, and tended to rise with increasing interval from first treatment. One method of estimating an expected value indicated that the excess risk of corpus cancer in breast-cancer patients was restricted to those treated with hormones. Given the time period under study, it may be assumed that the hormones were primarily non-steroidal oestrogens.

INTRODUCTION

EVIDENCE suggests that women receiving conjugated oestrogens for menopausal symptoms are prone to endometrial cancer.^{1 2} Non-steroidal forms of oestrogen have been proposed as an alternative therapy in postmenopausal women,³ although these agents have previously been linked with carcinomas of the genital tract in daughters of women treated during pregnancy,^{4 5} and in young patients treated for ovarian agenesis.⁶⁻⁸ Non-steroidal oestrogens are given also to postmenopausal women with breast cancer, a group reportedly predisposed to endometrial cancer. We have tried to determine whether oestrogenic therapy influences the risk of endometrial cancer associated with breast cancer.

METHODS

Data submitted by participants in the End Results Program of the National Cancer Institute were used for this investigation.⁹ From this series of cases diagnosed during the years 1935-1971, all women over forty-nine years of age with primary carcinoma of the breast were selected. To evaluate the risk of endometrial cancer in this group, the study was limited

to patients whose initial course of treatment (within four months of diagnosis) did not include ablation or irradiation of pelvic organs as covered by codes for "endocrine surgery" or "endocrine irradiation". The standard therapy information collected on all patients was such that oestrogen-treated women were listed only as receiving "hormones". However, during the period under study, hormonal treatment of breast-cancer patients diagnosed after menopause nearly always involved non-steroidal oestrogens.

The study group was then subdivided according to hormone treatment: (1) none received; (2) received during initial course of treatment; and (3) received only in a subsequent course of treatment. The computer records were searched to identify women with a subsequent diagnosis of primary cancer of the uterine body or corpus.

Expected numbers of cancers of uterine body were calculated by applying the age and time specific incidence-rates from the general population to the corresponding person-years of follow-up in the breast-cancer patients. The rates used were from the Connecticut Tumor Registry.¹⁰⁻¹² Since 37% of the breast-cancer cases came from hospitals participating in the Connecticut Registry, this seemed an appropriate comparison group. Two expected values were calculated: one based only on the rates for cancer of the uterine-body specified as primary, and the other which included also the rates for "uterus not otherwise specified." The unspecified category was substantial in earlier years, representing mostly uterine-corporis cancers,¹³ so that the rates used for most analyses include the unspecified category.

Person-years were counted from the diagnosis of breast cancer to the diagnosis of uterine cancer, date of death, or closing date of the study (December, 1972), whichever came first. Losses to follow-up (7%) were removed in the year the patient was last known to be alive. Counting risk from the time of diagnosis overestimates the expected number of uterine cancers among patients receiving hormones during a subsequent course of treatment. Calculations could not be refined to take into account time from hormone administration, since the actual date of subsequent therapy was not recorded.

The strength of association was measured by the ratio of observed to expected numbers—i.e., the relative risk. The test of significance for the difference between relative risk and 1.0 is the usual one of comparing a random variable with its expected value under the Poisson assumption.¹⁴

RESULTS

The study group was composed of 45 853 women over age forty-nine with primary breast cancer, of whom 41 641 never received hormones during their follow-up. 1660 received hormones during the initial treatment and 2552 only during a subsequent course. As anticipated, the variation in survival between the 3 groups resulted in different average follow-ups (six years for the never treated, two for the initially treated, and three for the subsequently treated).

TABLE I—OBSERVED AND EXPECTED NUMBERS OF CANCERS OF UTERINE BODY AND RELATIVE RISK FOR WOMEN WITH PRIMARY BREAST CANCER DIAGNOSED AFTER AGE 49, BY TREATMENT CATEGORY

| | Treatment with hormones | | |
|----------------|-------------------------|-----------------------|--------------------------|
| | None | During initial course | During subsequent course |
| Observed no. | 184 | 5 | 14 |
| Expected no.* | 127.2 | 1.6 | 6.7 |
| Relative risk† | 1.4‡ | 3.1§ | 2.1§ |
| Expected no.† | 185.4 | 2.4 | 9.4 |
| Relative risk† | 1.0 | 2.1 | 1.5 |

*Based on rates for primary cancers of uterine body.

†Based on rates for primary cancers of the uterine body, plus unspecified uterine cancers.

‡p < 0.01

§p < 0.05

TABLE II—OBSERVED AND EXPECTED NUMBERS OF CANCERS OF UTERINE BODY AND RELATIVE RISK FOR WOMEN WITH PRIMARY BREAST CANCER DIAGNOSED AFTER AGE 49, BY TREATMENT CATEGORY AND INTERVAL SINCE THE DIAGNOSIS OF BREAST CANCER

| Treatment with hormones | Interval (yr) | | | | | Total |
|----------------------------------|---------------|------|------|-------|------|-------|
| | <2 | 2-4 | 5-9 | 10-14 | 15+ | |
| <i>None:</i> | | | | | | |
| Observed no. | 53 | 52 | 55 | 16 | 10 | 184 |
| Expected no. | 53.6 | 52.7 | 48.3 | 20.5 | 10.2 | 185.3 |
| Relative risk | 1.0 | 1.0 | 1.1 | 0.8 | 1.0 | 1.0 |
| <i>During initial course:</i> | | | | | | |
| Observed no. | 3 | 2 | 0 | 0 | 0 | 5 |
| Expected no. | 1.5 | 0.6 | 0.2 | 0.1 | 0 | 2.4 |
| Relative risk | 2.0 | 3.3 | 0 | 0 | 0 | 2.1 |
| <i>During subsequent course:</i> | | | | | | |
| Observed no. | 4 | 5 | 3 | 2 | 0 | 14 |
| Expected no. | 3.5 | 3.1 | 2.0 | 0.6 | 0.3 | 9.5 |
| Relative risk | 1.1 | 1.6 | 1.5 | 3.3 | 0 | 1.5 |

Table I gives the observed numbers of patients with cancer of the uterine body, and two estimates of the expected value for each subgroup of patients. Using either method of ascertaining an expected value, the risk was greatest for women receiving hormones initially, and lowest for those receiving no hormones at all. Using only rates for cancer of the uterine body for calculating expectation, the excess rose from 40% among women receiving no hormones, to 100% for those treated in a subsequent course only, to 200% for those receiving hormones initially. When the rates for unspecified uterine cancer were added to the calculation, the observed value equalled the expected value for women never receiving hormones, but a 50% excess was found among those receiving hormones in a subsequent course, and a 100% excess among those treated initially.

Table II presents the risks of uterine-body cancer according to intervals after the diagnosis of breast cancer. The expected values for this analysis were based on rates which include unspecified uterine cancer. For patients receiving no hormones, the observed number approximated to the expected in every interval. When hormones were used in a subsequent course, there was no excess risk in the first two years after breast cancer was diagnosed; but thereafter the risk of cancer of the uterine corpus was excessive and, although the numbers are small, seemed to increase with lengthening follow-up. For patients treated initially with hormones, the excess risk developed within two years and, although the numbers are small, appeared to increase over time.

DISCUSSION

The preliminary nature of this report should be emphasised since the data were derived from a series designed to indicate overall trends in survival for a large sample of cancer patients across the U.S.A., and important treatment variables, such as the type, dose, and dates of oestrogen therapy, were not specified. Efforts are underway to abstract the original hospital records to verify the diagnosis of uterine cancer, and to search for case-control differences in the type of therapy and other variables. It seemed important, however, to communicate the information at hand, so other investigators may conduct similar evaluations. Also, the findings suggest that physicians considering use of non-steroidal oestrogens for women with the menopausal syndrome should be cautious.

Previous attempts to assess the hazards of oestrogen

treatment of inoperable breast cancer revealed no cases of uterine cancer,^{15 16} perhaps because of the limited number of patients and period of follow-up. On the other hand, studies of multiple primary cancers often have pointed to an excess risk (relative risk 1.3–2.0) of endometrial cancer among patients with a primary breast cancer,^{17–19} but some investigators have not confirmed this finding.²⁰ The discrepancies may be due to the manner in which expected values were calculated in various studies. As noted in this study (table 1), the decision on how to handle rates for “uterus not otherwise specified” can greatly influence the numbers generated and estimates of risk. Also, the discrepancies between studies may result from variations in therapy. While the numbers in our study are small, the risk of cancer of the uterine corpus associated with breast cancer seemed to be limited to oestrogen-treated women, and increased with the interval after treatment. Thus, exogenous oestrogens may account for at least part of the excess risk of endometrial cancer in patients with breast cancer, and the extent of its usage may be responsible for the fluctuating risk of endometrial cancer in different series of breast-cancer patients. The findings add to the evidence that exogenous oestrogens are carcinogenic to the female genital tract, and suggest a clue to the pathogenic mechanisms responsible. Non-steroidal oestrogens have been linked to adenosquamous carcinoma of the endometrium in patients with gonadal dysgenesis,⁶ and to vaginal and cervical adenocarcinoma in young women exposed during fetal life.⁴ From these observations, however, it was difficult to determine whether the carcinogenic effects of oestrogens were limited to non-steroidal compounds, or were influenced by the unusual host susceptibility of the exposed groups. In the present study of breast-cancer patients, the predisposition to cancers of the uterine corpus was found mainly among women receiving hormones which, given the period under study, were predominantly non-steroidal oestrogens. Furthermore, the risk of endometrial cancer is increased in women treated with conjugated oestrogens for menopausal symptoms,^{1 2} and possibly in women taking sequential oral contraceptives.²¹ Since many forms of exogenous oestrogens have been linked to cancers of the female genital tract, it seems likely that the pathogenic mechanism is related to oestrogenic stimulation rather than some other feature of the chemical structure of oestrogens.

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