Diagnosis of Early Endometrial Cancer and Precancerous States

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ABSTRACT

After a brief epidemiologic survey of endometrial cancer, the subject of detection and diagnosis of early lesions is addressed. Emphasis is placed on major gaps that exist in the knowledge of natural history of the disease. Cytologic and histologic detection and diagnostic techniques are reviewed and their advantages and disadvantages discussed.

The Disease and Its Epidemiology

Carcinoma of the endometrium is a disease affecting primarily women over 45 years of age with peak incidence between the ages of 55 and 79 (table I). Within the recent years, several observations have been made that suggest that the rate of this disease is increasing not only in the United States but also in other industrialized countries such as Japan. It has been estimated for 1976 and 1977 that the annual number of new cases of invasive endometrial carcinoma in the United States will surpass the number of invasive cancers of the uterine cervix and of the ovary (27,000 cancers of the endometrium to 20,000 cancers of the cervix and 17,000 cancers of the ovary).

One of the reasons for this increase may have been the indiscriminate administration of exogenous estrogens. The risk ratio for estrogen users has been most recently estimated at 8.1. It is of interest that as early as 1961 Gusberg and Hall considered exogenous estrogens as an important epidemiologic factor in this disease.

There are several other epidemiologic factors that have been associated with endometrial carcinoma. These have been carefully analyzed by Wynder et al. Obesity emerged as the most important single factor, although factors such as late menopause, hypertension, diabetes or abnormal glucose tolerance and excessive height were of statistical significance.

It is also known that abnormalities of ovulation, such as Stein-Leventhal syndrome and certain ovarian tumors with hormonal activity (thecoma, granulosa cell tumor), may lead to endometrial cancer.

There appears to be a racial and socioeconomic bias in the distribution of the disease. White women of satisfactory or high economic level appear to be more frequently affected than non-white patients of low economic standing.
estimated for 1976 that 25,000 cases of endometrial cancer will occur in white females but only 2,000 cases in non-white females, a ratio of 12.5, whereas for cancer of the uterine cervix the ratio is 3.\(^1\) While the behavioral factors leading to cancer of the uterine cervix have been carefully analyzed and are beyond the scope of this discussion, a similar prospective analysis of carcinoma of the endometrium has not been carried out on a large population of risk.

Detection of Endometrial Carcinoma

To date, there has been no determined effort at a major detection program for endometrial cancer in asymptomatic women. There are several reasons for this. First of all, to make a cancer detection program cost effective, several postulates have to be fulfilled:

1. The disease must be observed with sufficient frequency in any given population to make a major expenditure of time and money worthwhile.

2. The disease must have an identifiable asymptomatic or non-specifically symptomatic precursor stage occurring several years before clinical disease.

3. The precursor stage must be amenable to treatment at a relatively slight cost to the patient and to the society.

### TABLE I

<table>
<thead>
<tr>
<th>Case Records of Endometrial Carcinoma</th>
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<tbody>
<tr>
<td>Cancer</td>
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<tr>
<td>Registry (CT)</td>
</tr>
<tr>
<td>Age Group</td>
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<td>----------</td>
</tr>
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<td>25-29</td>
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<td>30-34</td>
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<td>35-39</td>
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<td>40-44</td>
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<td>45-49</td>
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<td>50-54</td>
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<td>55-59</td>
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</tbody>
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*Preliminary

CT = State of Connecticut
NY = State of New York

4. It must be shown that the treatment of the precursor stage lowers the mortality from the malignant disease.

5. Means of detection of high specificity and sensitivity must be available and be sufficiently simple to be applicable on a large scale.

In contemplating carcinoma of the endometrium and our remarkably limited knowledge about its natural history, only tentative answers to these 5 points are permissible.

1. Based on statistics from the New York State and Connecticut Cancer Registries, shown in table I, the presumed minimal prevalence rate of endometrial cancer in white women between the ages of 45 and 64 is 8 per 1,000, and for older women 10 per 1,000. The rate would be presumably still higher in women at high risk (i.e., women receiving estrogens; obese, hypertensive and diabetics). It may be inferred that such a population could be profitably screened for this disease. There is virtually no information on the incidence of endometrial carcinoma. Data from Koss and Durfee,\(^19\) obtained several years ago on a modest group of patients suggested a five-year age difference between women with early endometrial cancer and advanced form of this disease. Thus, the true incidence of the disease is presumably five times lower than the prevalence (between 1.6 and 2 per 1,000 women age 45 or older).

2. There is, unfortunately, considerable controversy as to the identification and the role of precursor lesions of endometrial cancer.\(^5\) These abnormalities, generally known as endometrial hyperplasia of various types, are ill defined and thus the subject of diagnostic confusion. With the exception of special situations, such as ovarian tumors with estrogenic activity or disturbances of ovulation, nothing is known today about the prevalence or incidence of these abnormalities in an asymptomatic population. The patients with endometrial hyperplasia are usually
seen when symptomatic. Yet if one considers the racial and economic make-up of the majority of patients with endometrial carcinoma, some, if not all, of them must have received adequate medical care before the disease was diagnosed. If one assumes, as one should, that every endometrial carcinoma is preceded by a precursor lesion, then the obvious conclusion must be that a large proportion of the precursors does not cause symptoms and thus is undetectable by the ordinary clinical means. This is difficult to reconcile with the existing clinical concepts of endometrial hyperplasia and the point remains to be proven.

Prospective studies of patients with symptomatic endometrial hyperplasia are few and far apart. One must cite the study of Gusberg and Kaplan on patients with adenomatous hyperplasia, in which between 20 and 30 percent of patients developed endometrial carcinoma. If one considers that less conservative pathologists probably would have considered many of Gusberg’s lesions as early forms of endometrial cancer (or carcinoma in situ), the results are not surprising. Further prospective studies are unlikely to be successful because few symptomatic patients with endometrial hyperplasia are likely to be followed without some form of treatment. Thus, the information will presumably remain anecdotal and hard data will be difficult if not impossible to obtain. Nevertheless, detection of endometrial hyperplasia in asymptomatic women would be a worthwhile endeavor.

3. The answer to the 3rd point must be positive. Endometrial hyperplasia and early endometrial carcinoma are amenable to surgical treatment or to hormonal manipulation at a relatively small cost to the patient and to the society.

4. Does treatment of endometrial hyperplasia lower the rate of endometrial cancer? There is no clear-cut answer to this problem. Considering current trends in gynecology to treat all diagnosed cases of symptomatic endometrial hyperplasia, there has been no drop in morbidity from endometrial carcinoma. On the contrary, a recent increase has been noted. Thus, one is once again forced to assume that in many, perhaps most, patients, the precursor stages of endometrial cancer cause no alarming symptoms and remain undetected. If one considers that the overall five year survival of treated patients with endometrial carcinoma is estimated at 75 percent and that survival of patients with disease confined to the endometrium is 100 percent, then it is obvious that the major benefits from detection programs would be in prevention of spread of endometrial cancer to the uterine cervix or beyond the confines of the uterus. These latter events radically lower the survival from endometrial carcinoma.

5. Are simple and efficient means available for the detection of precursor stages of endometrial cancer or, for that matter, of endometrial carcinoma in its early stages?

Obviously this is the key question which must be examined at some length.

Endometrial Cancer Detection Systems

The lack of a simple, satisfactory detection system is perhaps best documented by the very large number of devices, each one claimed as the answer to the problem of cancer detection. These devices range from a negative pressure lavage of the uterine cavity, applicators for endometrial sampling, negative pressure biopsy instruments, cannula-syringe combinations, and an endometrial pistol developed in Switzerland. A number of other devices, such as an endometrial sponge, brush or their equivalents, have been also developed. All of these devices share a variety of characteristics: they are generally costly to use and they usually receive an enthusiastic endorsement from initial users but not necessarily from subsequent investigators. Also, all of them cause some measure of
discomfort to the asymptomatic postmenopausal patient, who should be the primary target for the search for endometrial cancer and its precursor states.

The controversy does not end there. The manner in which the material obtained from the endometrial cavity should be examined has also been a subject for some debate. Some of the users claim that a cytologic preparation, or a smear, should be made from the material aspirated. Others claim that the material does not lend itself to cytologic interpretation and that a histologic type of preparation, based on embedding in paraffin of the centrifuged sediment is more reliably used.

Forgotten in this controversy is the fact that when Papanicolaou and Traut published their book on uterine cancer detection in 1943, they used a vaginal smear obtained by means of a pipet for the detection of cervical and endometrial carcinoma. Direct sampling methods of the uterine cervix have been since devised which have been shown to be much more efficient in the detection of cervix cancer and precancerous states. Thus, the vaginal smear has been largely abandoned mainly because the vaginal material is much more difficult to screen and to interpret than a smear obtained directly from the cervix. Yet, it has been shown some years back that the vaginal smear is extremely efficient in the discovery of endometrial cancer in the asymptomatic patient. Similar results were published by Reagan and Ng with the use of an endocervical aspiration smear.

Thus, we have at our disposal two means which are inexpensive to use, which do not cause any major discomfort, and which have been shown repeatedly to be capable of the discovery of asymptomatic endometrial cancer. To be sure, the cytologic evidence of these abnormalities is difficult to assess and calls for a very considerable skill on the part of the examiner. It is likely that this skill is not generally available today but could be developed without excessive cost to the public. The cytologic features observed in early endometrial cancer can be summarized as follows:

1. In menopausal patients there is often an excessive maturation of squamous epithelium pointing towards a possible high level of estrogen activity.

2. The presence in the vaginal smears of histiocytes or histiocyte-like cells also suggests that an endometrial lesion may be present. This association of endometrial cancer with histiocytic activity, presumably originating in the endometrial stroma, is not well explained but is nevertheless an important sign on which a further search should be placed.

3. The presence of endometrial cells in the postmenopausal patient, whether or not morphologically abnormal, calls for an immediate investigation of the endometrium.

In evaluating this sort of evidence, one will be inevitably subject to a number of false alarms and a number of unnecessary endometrial biopsies or perhaps even curettages will be performed. However, one is rewarded under these circumstances with the discovery of a fair number of very early endometrial cancers which, if untreated, would have very likely caused serious disability or even death within some years.

The interpretative difficulties extend to the material aspirated directly from the endometrium. The statements that such cytologic preparations are easy to interpret and accurate must be critically reexamined. It is probably simpler to examine such material in histologic form. This has been documented many years ago by Dr. Virginia Pierce and this author with the use of a small curet and a syringe with a cannula to secure "microbiopsies" of endometrial material.

Thus, the choice for the endometrial cancer detection is two-fold: (1) the vaginal pool smears and the endocervical aspi-
ration smears, with both procedures being within the reach of most practitioners; (2) the microbiopsy of the endometrium, obtained by means of one of the many available instruments, a procedure which carries with it the necessity of penetrating the internal os and thus causing the patient considerable discomfort. The controversy cannot be considered settled. A study of endometrial abnormalities in several thousand asymptomatic premenopausal women has been initiated at Montefiore Hospital in January of 1979. It is hoped that this study will provide objective evidence as to whether or not endometrial cancer detection is applicable on a large scale and if any of the existing methods do contribute to the salvage of patients.

References


