Enzyme-Linked Immunochemical Measurement of Estrogen Receptor in Gynecologic Tumors, and an Overview of Steroid Receptors in Ovarian Carcinoma

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We tested whether a newly available enzyme-linked immunoassay (EIA) validly measures estrogen receptor (ER) in gynecologic tumors. We first documented that ER so measured agreed with results by established radioligand-based assays [dextran-coated charcoal (DCC) and hydroxylapatite (HAP)] for in-house breast carcinomas and for proficiency testing specimens. Then, for gynecologic tumors, we found strong correlations between results for ER as measured by the two methods; e.g., for 27 ovarian carcinomas, r = 0.86. The same was true for ER measured in nine specimens of ovarian carcinoma from women who had undergone chemotherapy: r = 0.94. Radioinert estradiol or serum had no discernible effect on EIA measurements of ER, whereas our DCC assay was rendered uninterpretable. Evidently the EIA validly measures ER in steroidogenic tissues, including ovarian, and also in breast and uterine carcinomas. Clinical management of the latter is now based in part on results of steroid receptor assays. For ovarian carcinomas, ER assay can be helpful for determining the probable primary site of adenocarcinomas of unknown origin, and it is providing a rational basis for development of new diagnostic and therapeutic strategies.

Additional Keyphrases: breast cancer · uterine cancer · steroids · radioligand-based assay compared

Our objective in these studies was to test whether the concentration of estrogen receptor (ER) protein in gynecologic tumors can be measured accurately with an enzyme-linked immunologic assay (EIA) that was developed recently for measurement of ER in breast carcinoma (1, 2). A potential advantage of the ER-EIA is that endogenous ER ligands, e.g., circulating steroids, would not be expected to interfere with such an assay (1, 2). This may be particularly useful when ER is measured in ovarian carcinomas, because the ovaries may contain endogenous steroids that may invalidate receptor assays in which radiolabeled ER ligands are used. For similar reasons, an immunologic assay of ER would presumably be useful for advantage for tumors from patients being treated with steroids or antiestrogens, e.g., postmenopausal women being treated with replacement estrogens and women whose breast or uterine carcinomas were being treated with high-dose estrogen or with anti-estrogen at the time of biopsy (3–8). For ovarian carcinoma, there are numerous current reports of clinical and investigative approaches to adjunctive endocrine management, including the use of anti-estrogen (9–18); these approaches are based in part on the presence of relatively high concentrations of ER and (or) progesterin receptors in more than 50% of these tumors seen in clinical practice and have led to an increased demand for receptor assays of ovarian tumors and requests to clinical laboratories for guidance in interpreting the results.

To determine the efficacy of an ER-EIA, we compared ER values obtained by EIA with results obtained by methods that are based upon occupancy of the estrogen-binding site on ER by radiolabeled ER ligands. In these latter methods, dextran-coated charcoal (DCC) or hydroxylapatite (HAP) is used to separate receptor-bound from unbound radiolabeled ligand. In addition to measuring ER in gynecologic tumors, we included an initial series of control and breast specimens to validate our use of the EIA and to investigate possible effects of serum, and of the addition of estrogen, on results obtained with the EIA. Control samples included specimens provided by the proficiency survey programs of the College of American Pathologists (CAP) and the National Surgical Adjuvant Project for Breast and Bowel Cancers (NSABP). We measured ER in breast carcinomas of patients to facilitate comparisons of results obtained by the ER-EIA for various types of tumors, including ovarian carcinomas, with those obtained by other assay methods, and to facilitate intercomparisons among laboratories.

Materials and Methods

Portions of routinely obtained surgical specimens of human tissue were released for study by pathologists experienced in processing and diagnosing gynecologic and breast malignancies. This procedure did not interfere with patient care. The pathologists classified each tumor according to histopathological criteria published by the World Health Organization or the Armed Forces Institute of Pathology (19, 20).

Portions of 16 specimens of primary breast carcinoma and one metastasis, from 17 women who had no history of chemotherapy, were assayed for ER.

We examined seven specimens of the primary tumor and 27 specimens of metastases, from a total of 17 donors with ovarian carcinoma. From five of these patients, specimens of the primary and of one or more of its metastases were obtained concomitantly. Twelve of the patients had not undergone chemotherapy; we also analyzed cancerous tissue collected from one of these 12, after subsequent administra-
tion of chemotherapy. We examined four specimens of malignant mixed mullerian tumors obtained from two donors; these specimens were unexposed to chemotherapeutic agents. We also included papillary cystadenomas of the ovary from two patients and one specimen of endometrial adenocarcinoma.

Equal amounts of serum collected from five normal post-menopausal women were pooled for addition to selected preparations of cytosol prior to assay for ER. In a similar fashion and for a similar purpose, we pooled serum from five men and also, separately, serum from five women who were in the first trimester of pregnancy. For competitive inhibition of the labeled ligand (100-fold molar excess in routine assays), crystalline estradiol or diethylstilbestrol (Sigma Chemical Co., St. Louis, MO) was dissolved in ethanol and was added in volumes of 5 μL or less to the assay tubes.

Proficiency-testing specimens AB-106, AB-108, and AB-109, which were provided for quality assurance for the NSABP, were received directly from Dr. James L. Wittliff, Hormone Receptor Laboratory, School of Medicine, University of Louisville, Louisville, KY. From this same source we received specimens HR-A1, HR-A2, and HR-A3, which were part of the College of American Pathologists' Official 1985 Hormone Receptor Assay Survey. All specimens were received frozen on solid CO₂ and were stored under liquid nitrogen for assay within the stipulated time limit, i.e., for the latter specimens, within 12 working days after receipt.

To store and process the various specimens, and to prepare cytosol from them, we used procedures that we have described previously (21-23). To measure ER by routine chemical methods, we used the HAP assay of Garola and McGuire (24, 25), performed as we have reported earlier (22), or the DCC assay. We carried out the DCC assay in duplicate, with a single saturating dose of receptor ligand in the presence and absence of a 100-fold molar excess of radioinert diethylstilbestrol (22, 23, 25). In most assay runs, the same preparations of cytosols were used in the DCC and HAP assays and in the ER-EIA. Protein concentrations of the cytosol preparations were adjusted to 1 mg/mL and calibrated against bovine serum albumin as the protein standard in a Lowry-type procedure (26, 27).

Briefly, in the DCC assay, 200 μL of a low-salt 100 000 or 250 000 × g tumor extract supernate, adjusted to contain approximately 1 mg of soluble cytosol protein per millilitre of sodium phosphate buffer (5 mmol/L, pH 7.4, and containing chelating and stabilizing agents), is incubated at 2 °C for 18 h with 6.4 nmol of [³H]estradiol per liter in the presence and absence of a 250-fold molar excess of diethylstilbestrol. Unbound [³H]estradiol is removed with dextran-coated Norit A charcoal and by centrifugation. The supernatant fluid, containing receptor-bound [³H]estradiol, is decanted into counting vials for measurement.

In the HAP assay, the receptor in a low-salt 100 000 × g supernate is adsorbed onto hydroxyapatite. Available receptor sites are loaded by incubation with 8 nmol/L [³H]estradiol overnight at 4 °C, in the presence and absence of a 100-fold molar excess of DES. After unbound [³H]estradiol is washed away, bound [³H]estradiol is eluted with ethanol into counting vials for measurement.

The lower threshold of sensitivity of both the DCC and HAP assays is usually 3 fmol of ER per milligram of soluble protein or 150 fmol of ER per gram wet weight; these values are derived from the variance in background counts in assays performed on specimens that do not contain ER.

The Abbott ER-EIA monoclonal procedure (Abbott Labo-

ratories, Inc., North Chicago, IL) is a solid-phase enzyme immunoassay (2) with a "sandwich" immunoabsorbent type of configuration. We performed this assay according to the methods described by the manufacturer. In brief, beads coated with monoclonal anti-ER (antibody D547, solid-phase anti-ER) are incubated with specimen cytosol (approximately 1 mg of soluble cytosol protein per milliliter) or with the appropriate standards or controls. ER present in the specimen, standards, and controls is bound to the solid-phase anti-ER immunologically. The remaining cellular materials are removed by aspirating the fluid and washing the beads. A second monoclonal anti-ER, H222, conjugated with horseradish peroxidase (EC 1.11.1.7), is incubated with the beads, and, if the specimen contains ER, the anti-ER-enzyme conjugate is bound to the ER on the beads. Unbound conjugate is removed by aspiration, and the beads are washed. The "sandwich" consists of the complex, [solid-phase anti-ER] + [ER] + [anti-ER conjugated to enzyme]. Next, the beads (and the sandwiched ER and antibody conjugated to enzyme) are incubated with hydrogen peroxide and o-phenylenediamine -2 HCl as substrate for the development of color, which is a measure of the amount of ER-bound conjugate. The enzyme reaction is stopped by adding dilute (1 mol/L) sulfuric acid, and the color intensity is read in a spectrophotometer, at 492 nm. Color intensity is proportional to the concentration of ER in the specimen within the range of the standard curve for the assay, 0 to 500 fmol.

Statistical analyses were based on principles and procedures described by Snedecor and Cochran (28) and by Steel and Torrie (29).

**Results**

**Data Set 1: In-house validation of ER-EIA on specimens of breast carcinoma.** Our objective in the first set of experiments was to validate the use of the ER-EIA procedure in our laboratory by measuring ER both by the DCC assay and by EIA in proficiency-testing specimens. We also performed repeated assays for ER on in-house quality-control specimens of a breast carcinoma. The results are summarized in Table 1. In our hands, the resolution for measurement of ER by the EIA, based on twice the standard error of the mean for repeated assays of a breast-cancer specimen (no. 17) that contained a mean of 1742 fmol of ER per gram wet weight (or 50 fmol/mg of soluble cytosol protein), was 96 fmol/g wet weight (or 2 fmol/mg of soluble cytosol protein) (see Table 1, *Intra-assay, d*). The intra-assay CV for the ER-EIA was approximately 6% whether calculated per gram wet weight or per milligram of soluble cytosol protein (Table 1). These values compared favorably with the resolution and 7% CV obtained with the DCC assay for ER, which we performed on the same specimen and analyzed concomitantly with the EIA assay (Table 1, *Intra-assay, a*).

In assaying samples provided by CAP and NSABP, we found close agreement between the results of the EIA and DCC procedures (Table 1, *Inter-assay, a through f*). Our values with either method are consistent with those obtained by the 50 laboratories surveyed by CAP, which used a variety of procedures (CAP Set HR-A Hormone Receptor Assay Survey 1985 Survey Report, available from CAP, Skokie, IL), and they were within acceptable limits set by the NSABP. Thrice-repeated ER-EIA on CAP and NSABP samples gave CVs ranging from 1 to 18% (Table 1, *Inter-assay, a, b, c*). These results made us confident in our
Table 1. Intra- and Interassay Variations in Measurements of ER by DCC and EIA Procedures Performed on In-
House Breast Carcinoma Specimens and Extramural Proficiency Testing Samples from CAP and NSABP

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I.D.: identification. n = number of specimens analyzed. x = mean; SE = standard error. Breast CA 17 = in-house specimen of breast carcinoma. a through f: assays performed on separate days.

ability to perform the ER-EIA, and in the stability of the reagents used in the assay.

Data Set 2: Comparison of EIA with DCC and HAP results for ER in multiple breast carcinomas. We next sought to compare, for multiple specimens of breast carcinoma, ER values obtained from DCC assays with results from ER-EIA. This approach provides an indirect indication of the sensitivity and specificity of the ER-EIA with respect to clinical response to therapy; i.e., for some types of cancers that include a subgroup whose growth is estrogen-sensitive (breast or endometrial), the DCC assay is known to predict the probable clinical response of a tumor to endocrine-manipulative management for individual patients.

Figure 1 depicts a comparison of results for ER with the DCC assay and the ER-EIA for 17 specimens of breast carcinomas. The correlation coefficients are 0.997 and 0.991 when results are compared as fmol/g wet wt. and fmol/mg of soluble cytosol protein, respectively. One of the specimens was a metastasis to the liver that was strongly ER-positive in both assays with both modes of expressing the results (26166 and 31953 fmol/g wet wt. for DCC and EIA, respectively, and 534 and 649 fmol/mg soluble cytosol protein for DCC and EIA, respectively). In another liver specimen, we detected only trace amounts of ER by either assay in non-diseased tissue, i.e., liver biopsy material that showed no disease on histological examination (data not shown). These observations on liver tissue added to our confidence that it is possible to measure ER with the

EIA procedure, because the liver is rich in substances, including enzymes and steroid-binding proteins, that could conceivably interfere with an ER assay.

Data Set 3: Comparison of EIA with DCC and HAP results for ER in gynecologic carcinomas. When we assayed 27 specimens of ovarian carcinomas, originating from 17 patients, we found a strong correlation between values obtained with the DCC or HAP procedure and those obtained with the EIA (Figure 2, for panels A and B, r ≥ 0.86), whether the data were expressed per gram wet weight of tumor (Figure 2, panel A, r = 0.89) or per milligram of...
soluble cytosol protein (Figure 2, panel B, \( r = 0.86 \)). In addition, two ovarian serous papillary cystadenomas of borderline malignancy had ER contents per gram wet weight of 1355 and 1847 fmol by DCC, and 1480 and 2170 fmol by EIA, respectively. The ER content of four specimens of malignant mixed mullerian mesodermal carcinoma was measured by EIA and DCC; in both assays, each specimen had less than 370 fmol of ER per gram wet weight. For an endometrial carcinoma, the ER content was 564 and 654 fmol per gram wet weight by EIA and DCC assay, respectively.

In combination with the validation results in Data Sets 1 and 2, the results in Data Set 3 document that the EIA procedure provides an accurate assessment of ER in gynecologic malignancies, consistent with values accepted by CAP and NSABP for reporting ER in breast carcinoma.

Data Set 4: Effects of clinical variables on results of ERIA and DCC ER assay. We wanted to determine whether certain clinical and specimen variables affected the outcome of the ER-EIA. In particular, for ovarian carcinomas, we wanted to know whether results are affected by (a) prior chemotherapy, (b) the presence of serum, or (c) endogenous steroids.

We assayed nine specimens of ovarian carcinoma, from patients known to have received chemotherapy, by the DCC and EIA procedures. As shown in Figure 3, for these specimens there was generally a good correlation between ER measured by DCC assay and EIA (panel A, fmol/g wet wt., \( r = 0.94 \); panel B, fmol/mg protein, \( r = 0.94 \)). This result indicates that expression of immunoreactive ER persists in specimens exposed to chemotherapeutic drugs prior to their collection, and that such exposure is unlikely to cause systematic changes in the results of the ER-EIA.

When we assayed ER by EIA in a specimen of primary ovarian carcinoma, and in one of its metastases to the omentum, from a woman who had not yet received chemotherapy, the results were 2902 and 1389 fmol/g wet wt. and 33 and 26 fmol/mg of soluble cytosol protein, for the primary and metastatic tumor specimens, respectively. Two additional tumor specimens, one from the abdominal wall and one from the transverse colon, were obtained after this patient had received maximal cumulative doses of triple-agent chemotherapy. By EIA, the ER content was 711 fmol/g wet wt. and 18 fmol/mg of soluble cytosol protein for the metastasis in the abdominal wall, and 1006 fmol/g wet wt. and 26 fmol/mg of soluble cytosol protein for the metastasis in the colon. For the metastasis in the abdominal wall, ER as measured by our DCC procedure was 591 fmol/g wet wt. and 15 fmol/mg of soluble cytosol protein. For the metastasis in the colon, the DCC failed to detect ER (quality-control parameters were within normal limits and there were no remarkable or unusual conditions or circumstances). These last DCC assay results notwithstanding, the cumulative results suggest that there is little apparent systematic effect of chemotherapy upon the EIA measurements of ER in ovarian carcinomas and their metastases.

Adding 10 \( \mu L \) of any of three pools of human sera (from men, pregnant women, or postmenopausal women) to the cytosol to be assayed made the results of the DCC assay uninterpretable (Table 2) because of high nonspecific binding of \([3H]\)estradiol to the cytosol preparation. The values for ER we obtained with the EIA procedure, on the other hand, were unaffected by the added sera. With the EIA, no ER was detected in the serum pools alone (data not shown).

Addition of estradiol to cytosol preparations of ovarian and breast tumors, in amounts likely to occur in vivo, yielded lower values for ER by the DCC method, whereas the results obtained with the EIA procedure were unaffected (Table 3).

Discussion

Data Sets 1 and 2 established that the EIA procedure, in our experience, is a reliable method for measuring ER in specimens of breast carcinoma. In combination with information from the first two data sets, the comparisons in Data Set 3 of ER results obtained by the different approaches made us confident that, with the EIA procedure, we measured ER rather than extraneous estrogen binding in gynecologic cancers. The results in Data Set 4 indicated that the findings in routine ER-EIA are practically unaffected by previous exposure of the tumor specimen to chemotherapeutic agents, or by contamination of specimens with serum or endogenous estradiol. Data Set 4 assured us that the ER-EIA gives reliable results even in the presence of as much as 10 \( \mu L \) of serum or of 0.4 nmol/L concentrations of endogenous steroids (Tables 2 and 3). In contrast, the DCC assay was unreliable under similar conditions of serum contamination, and the presence of estradiol significantly decreased the values measured for ER. This result is important with respect to the selection of an effective mode of clinical management for breast and endometrial carcinoma. Our findings indicate that, in a clinical specimen assayed for ER by the EIA, the presence of serum would be unlikely to produce a false-positive result; thus, a woman would not be treated with endocrine-manipulative therapy if, in fact, the probability were low that she would respond favorably to such therapy.
The presence of steroid-binding components of serum in tumor specimens can create errors when ER is assayed with radiolabeled receptor ligands (30, 31). An approach for correcting these errors is to measure the specimen's albumin content and then use such measurements as a basis for calculating the effects of serum binding by the radiolabeled ligand in use (30, 31)—a practice not uncommonly followed by most clinical laboratories that assay for ER, although most workers in this field are (or should be) aware of the problem.

Our study involving breast and uterine carcinomas was not a prospective one with respect to clinical response to endocrine management. However, we believe it would be possible, with reasonable assumptions, to estimate specificity and sensitivity of the ER-EIA in regard to probable clinical outcome of endocrine management for advanced carcinomas of the breast and endometrium. The principal assumption in these estimates would be that results of well-controlled DCC assays indicate the probable response to endocrine regimens. The results of our DCC assay have consistently been well within the limits set by CAP and NSABP proficiency-testing programs.

For individual tumor specimens, discrepancies between our results with the EIA and the DCC assay are consistent with the possibility, in the latter, of (a) interference from serum, (b) firm binding of endogenous ligands to the estrogen-binding site on the receptor proteins, or (c) the presence of endogenous substances that dilute the specific activity of the radiolabeled ligand (in this series of experiments, \(^{3}H\)estradiol), or some combination of these. Also, for assays based on displacement of radiolabeled ligand by excess radiinert ligand, the radiolabeled estradiol possibly is displaced by the excess radiinert ligand from binding sites on a modified receptor protein that is not recognized by the antibody components of the EIA—e.g., a receptor protein that has been clipped by proteolytic action. The clipped receptor protein still exhibits displacable binding of radiolabeled ligands, but may have altered immunoreactivity as a consequence of lost antigenic determinants or changes in tertiary structure. Indeed, proteolytic studies with a library of monoclonal antibodies specific for separate regions of ER from breast cancers have shown that the receptor protein can be clipped extensively without losing its ligand-binding capacity, whereas the region or regions that are presumed to bind to DNA are readily cleaved from the steroid-binding region (1).

The monoclonal antibodies D547 and H222 that are used in Abbott Laboratories’ ER-EIA have been shown previously to be highly specific for the ER protein (1, 32, 33). Both antibodies, and also antibody H226, have been used for demonstration by immunocytochemical means, at both the light- and electron-microscopic levels, that the ER protein is present in cells of breast tissue as well as gynecologic carcinomas (33–38). There is strong agreement between results by immunocytochemical and biochemical methods (DCC, HAP, and sucrose gradients) as to the amounts of ER estimated to be in tumors, including gynecologic tumors (35–38). Further evidence that antibodies D547 and H222 recognize ER in ovarian carcinomas is provided by their capacity to alter the sedimentation velocity of the estrogen-binding component in extracts of such carcinomas (39, 40). In addition, competitive-inhibition studies on sucrose gradients, with a variety of steroids, demonstrated that the estrogen-binding moiety in ovarian carcinoma that is recog-
ized by D547 and H222, and by other monoclonal antibodies against ER, is highly specific for estrogens and anti-estrogens (39, 40).

Very probably the ER recognized by the antibodies used in the ER-EIA is biologically active with regard to concentrating estrogen in the cell’s nucleus. This conclusion is derived from results of intravascular infusion of radioactive estrogens into animals in vivo. Autoradiography after the infusion shows the radioactivity to be concentrated only in those cells that have been identified immunocytochemically (by use of anti-ER monoclonal antibodies D547 and H222) as ER-positive (38, 41, 42). Furthermore, when the nuclear fraction of portions of the target tissue is extracted and analyzed on sucrose gradients, monoclonal antibody D547 recognizes the moeity to which the radioactive estrogen is bound (42). These observations indicate that the cellular moeity recognized by the antibodies against the putative estrogen receptor is associated with concentrating estrogen in target cells and therewith performs an important biological function.

Overview of Steroid Receptors in Ovarian Tumors

In broad context, the expression of steroid receptors in ovarian carcinoma is of interest because this remains the most lethal of the gynecologic carcinomas, with a well-defined increase in incidence after menopause (43). Thus, an increased health care problem may be created by ovarian carcinoma as the proportion and number of women in North America who reach menopause continue to grow. Relatively little information is available about the biology of ovarian carcinoma as compared with that of breast carcinoma. It has become known only within the past few years that many primary ovarian carcinomas and their metastases are rich in receptors for steroid hormones (14–18, 22, 31, 44–62).

As confirmed in this study, estrogen receptor continues to be expressed in patients with advanced disease, even after chemotherapy (15, 23, 31), whereas receptor for progestins reportedly is lower if the patient has received chemotherapy (15, 31). Thus, it is possible to measure estrogen receptor in tumors from patients with advanced disease that have been treated medically, and this provides the rationale for possible new management modalities such as the use of radioiodinated ER ligands for imaging and treatment of ER-rich malignant tumors (22, 39, 40).

Types of steroid receptor proteins in ovarian tumors.
The four receptor proteins most frequently observed in ovarian tumors are those for estrogens and progestins (14–16, 31, 44–62), glucocorticoids (52), and androgens (51, 52, 54, 60). Physicochemical data indicate the receptor proteins for steroid hormones in ovarian carcinomas to be, in most instances, indistinguishable from such proteins found in the classic steroid-sensitive target tissues and in cancers of the breast and reproductive tract. Therefore, analytical procedures developed for measurement of steroid receptor proteins in other types of tissue have hitherto been applied with little or no modification to ovarian tumors, and vice versa (14, 22, 35, 38–42, 57, 58, 63). We have previously reported close correlations between results of measurements of ER in ovarian carcinoma by DCC, HAP, controlled-pore glass-bead, and sucrose density-gradient procedures (22). It is now possible to localize ER immunocytochemically in ovarian cancers (35), in addition to breast carcinomas (33, 37) and endometrium (36, 64).

Amounts of estrogen and progestin receptor in ovarian tumors. The amounts of ER that are measured in low-salt extracts of tumors originating in the epithelium of the ovary are of the same order of magnitude (150 to 10 000 fmol/g wet weight, 3 to 400 fmol/mg of protein, or 15 to 1600 fmol/mg of DNA) as those measured in breast cancer and in cancerous or normal endometrial tissue (14–16, 31, 44–46, 53–62, 65); extracts of more than 50% of ovarian carcinomas seen clinically contain at least 20 fmol of ER per milligram of protein, or at least 500 fmol/g wet weight (14–16, 31, 44–47, 49–61, 65).

In a patient with ovarian carcinoma, the concentrations of estrogen and progestin receptors may vary among sites of metastatic disease (23, 31, 35, 44, 47, 49, 58–60, 65); however, ER concentrations in omental metastases are not consistently higher or lower than those at the ovarian site (15, 31, 44, 50). If steroid receptor proteins are absent from a specimen of the primary ovarian cancer, they are rarely present in its metastases (14, 15, 31, 44, 47, 49, 58, 69). The presence of receptor for progestin in ovarian carcinoma is usually accompanied by the presence of receptor for estrogen (31, 44–53, 55, 56, 59–63). The amounts of receptors for sex-steroid hormones in ovarian adenocarcinomas are believed to be independent of the stage of disease (23, 31, 35, 44–49, 58, 65, 66). In some series, however, patients with recurrent disease have occasionally been noted to have low receptor values (45, 46). The mean concentrations of sex-steroid hormone receptors in ovarian carcinomas appear to be lower in premenopausal than in postmenopausal patients (14, 47, 53). We do not know the effects of radiation therapy on the receptor content of ovarian carcinomas when the radiation is incident directly on the tumor or on a site at which tumor subsequently grows (49).

As might be expected, metastases to the ovaries from primary carcinomas of non-steroid-sensitive tissues, such as the bowel, do not contain receptors; however, receptor-rich breast and endometrial cancers may express steroid receptor activity in their metastases to the ovary (14, 15, 31, 47, 49, 61).

All of the principal types of epithelial and sex-cord-stromal cancers of the human ovary reportedly contain steroid receptors (31, 44–63, 65–67). In most laboratories, sex-steroid receptors are detected frequently in endometrioid tumors. In contrast, germ-cell tumors rarely, if ever, contain sex-steroid receptor proteins (68). The serous-type tumors express steroid receptors more frequently than do mucinous tumors. This is relevant to the development of radiolabeled imaging agents and of therapeutic ER ligands, because serous epithelial cancers are the most common and lethal of the ovarian carcinomas.

Grade and receptor content of ovarian tumors. Up to this time, no clear relationships have been described between the amounts of sex-steroid hormone receptors and the degree of differentiation of an ovarian carcinoma (14–16, 31, 35, 44–50). However, a recent preliminary study, in which no significant association between ER status and ploidy was found, did demonstrate an association between aneuploidy and lack of progestin receptor in ovarian epithelial carcinomas (69). Most benign ovarian tumors have low or non-detectable levels of sex steroid receptors (14–16, 31, 35, 44–62, 66).

Summarizing comments on steroid-receptor measurements in ovarian tumors. The newly developed ER-EIA assay and its companion reagents for immunocytochemical localization of ER in tissue sections (33–38, 64) add to the clinical laboratory’s capability for measuring and localizing ER in cancers. To date, the correlation of the immunocytochemical
with the biochemical results of ER measurements has been strong (35, 37). Because experience with patients is as yet still limited, it has not been possible to establish the prognostic significance of the ER content in ovarian carcinomas, with or without information on progesterone receptor (14–18, 23, 31, 44–46). Probably the receptor status will not have as broad a prognostic value for ovarian carcinomas responding to endocrine-manipulative management as it has for carcinomas of the breast (14–18, 23, 31, 44–46) and endometrium (5, 8, 46). At this time, a conservative position with regard to the potential usefulness of receptor assays on ovarian carcinomas is that such measurements provide adjunctive biochemical information that can enhance the histopathological and immunocytochemical classification of these adenocarcinomas by making it possible to distinguish, in some cases, a more probable site of origin—e.g., the gastrointestinal or reproductive tract. In addition, information on the receptor content of ovarian carcinomas may become useful for the selection of optimal clinical management, and in providing a basis for the rational development of new approaches in the management of ovarian carcinoma.

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References


