Is Hormone Replacement Therapy an Option for Women with a History of Breast Cancer?

by Kerry L. Wright and Dawn Chalaire

For years, postmenopausal women have taken hormone replacement therapy (HRT) to prevent osteoporosis, decrease their risk of cardiovascular disease, and alleviate the common vasomotor, genitourinary, and psychological symptoms of menopause in one fell swoop. And for years, the risks and benefits of taking hormones (estrogen alone or estrogen plus progestin) have been the subject of research and debate.

Now, in light of new evidence that HRT may increase rather than decrease the risk of heart disease and stroke, physicians must weigh the therapy's benefits against possible risks. (Continued on next page)
advantages and disadvantages for each woman more carefully than ever. And if the woman is potentially cured of breast cancer, deciding whether to prescribe HRT becomes even more complicated.

Estrogen has long been implicated in increasing the risk of breast cancer, and conjugated estrogens have been listed on the U.S. Department of Health and Human Services National Toxicology Program’s Annual Report on Carcinogens since 1985. In July, a Women’s Health Initiative (WHI) study of estrogen plus progesterin in postmenopausal women (published in the July 17 issue of the Journal of the American Medical Association (JAMA)) was halted because of the finding that the risks of HRT exceeded its benefits. Specifically, the risk of invasive breast cancer went beyond the study’s predetermined stopping boundary. But the most important finding was that instead of helping to prevent heart disease, HRT slightly increased the risk of coronary heart disease and stroke in the women studied.

Two meta-analyses published in August support this finding. In one study, published in the August 20 issue of the Annals of Internal Medicine, the relative risk for cardiovascular disease was 1.28 among women who used or had used HRT. The second study, which appeared in the August 21 issue of JAMA, found no coronary heart disease benefit or harm associated with HRT use. Both analyses concluded that socioeconomic status had been a confounder in at least some of the earlier studies that showed a cardiovascular benefit to HRT.

However, another WHI study investigating the use of estrogen alone in women who have had a hysterectomy continues because no increase in the risk of breast cancer or cardiovascular disease has been noted. HRT remains the most effective treatment for many symptoms of menopause, and the two JAMA studies reported a lower risk of osteoporotic fractures and colorectal cancer among women who took HRT.

When it comes to treating menopausal symptoms in women with a history of breast cancer, “You can’t make rigid rules,” suggested Rena Sellin, M.D., a professor in the Department of Endocrine Neoplasia and Hormonal Disorders at The University of Texas M. D. Anderson Cancer Center. Most health care providers and physicians are reluctant to prescribe HRT for women who have had breast cancer, said Dr. Sellin, but the prevailing opinions against the practice are less unified than they once were.

“A postmenopausal woman with a history of breast cancer who has no symptoms would not be likely to choose hormone replacement therapy because of its contraindications,” said Dr. Sellin. But for women who have unpleasant symptoms—hot flashes, night sweats, mood swings, declining libido, loss of bone density, and weight gain, among others—hormone replacement may be an option.

Only a few small, retrospective studies have been conducted to assess the risk of HRT in postmenopausal women who have battled primary breast cancer. Dr. Sellin is the principal investigator of a prospective study, begun at M. D. Anderson in 1990, in which about 100 postmenopausal women with a history of estrogen-receptor-negative breast cancer were randomly assigned to receive estrogen replacement therapy or undergo observation only. The study, which has been accepted for publication in Cancer, found that conjugated estrogen did not affect disease-free survival in this group of women after a follow-up of at least five years.

Although several nonhormonal drugs have been approved by the U.S. Food and Drug Administration for the prevention of osteoporosis or heart disease, they do not alleviate the other common symptoms of menopause, such as bladder problems, hot flashes, mood swings, and night sweats. Vaginal estrogen rings are sometimes prescribed to treat symptoms such as vaginal dryness and vulvar atrophy, without the adverse effects and risks of systemic estrogen therapy.

Despite having a history of breast cancer, many women will consider HRT if they have severe symptoms that are not being treated effectively with other medications, said Martha Beck, M.S.N., an advanced practice nurse in the Life After Cancer Care Clinic at M. D. Anderson. Most of the women seen at the clinic who are considered for HRT have severe vasomotor instability, said Beck, and many are ready to try hormone replacement. If the benefits seem to outweigh the risks, HRT is often prescribed for two or three months. Then, if the woman’s symptoms are relieved, the therapy is considered for a longer term, Beck said.

Taking into account a woman’s attitude about HRT is important, said Mary Jean Klein, M.Ed., B.S.N., coordinator of the clinical research program in the Department of Endocrine Neoplasia and Hormonal Disorders and head research nurse of the estrogen replacement trial led by Dr. Sellin. Klein also emphasized the need to evaluate each woman on an individual basis. “Just because a woman has a history of breast cancer doesn’t eliminate the possibility of estrogen therapy, and not having a history of cancer doesn’t create a need for it,” Klein said.

For more information, contact Dr. Sellin at (713) 792-2841, Mary Jean Klein at (713) 792-2840, or Martha Beck at (713) 792-2840.
"I Have Something to Tell You."
Counselors Support Family Communication about Genetic Susceptibility to Cancer

by Kerry L. Wright

A woman has just received the results of a genetic susceptibility test showing that she carries a mutation in the BRCA1 gene. This puts her at a 50% to 85% lifetime risk of breast cancer and a 15% to 45% lifetime risk of ovarian cancer. Trying to come to terms with this new information, she begins discussing it with her genetic counselor. Because genetic mutations are often inherited, the discussion quickly shifts to the woman's family. Whom should she tell? How should she tell them? And when?

"Genetic testing not only provides information for the individual, it also provides information for the family," said Sara Michelson, M.S., a genetic counselor in the Section of Clinical Cancer Genetics at The University of Texas M. D. Anderson Cancer Center. In the Clinical Cancer Genetics Program at M. D. Anderson, risk assessments are performed and genetic counseling and testing are offered to individuals who may be at risk for hereditary cancers.

Many individuals interested in undergoing a cancer risk assessment are healthy but have a family history of cancer, or they have a personal history of cancer and are concerned for their children and other relatives. During an assessment, genetic counselors construct a family tree, or pedigree, that includes family members who have had cancer and those who have not. The type of cancer and age of the individual at the time of diagnosis are also recorded and used to assess risk.

"Even though the number and quality of genetic tests continue to improve, the family history is still the best tool we have for assessing the possibility of a hereditary cancer syndrome in a family," said Michelson. Once the family pedigree is complete, the counselors educate patients about the genetics of the particular cancer they are concerned with. If genetic testing is appropriate, they also discuss its benefits and limitations.

Approximately 5% to 10% of cancers are hereditary. More than 50 different genes that predispose individuals to cancer have already been identified, including genes for breast, ovarian, and colorectal cancers, melanoma, some thyroid and kidney cancers, and retinoblastoma.

"The most reliable tests are those for which there are distinct mutational 'hotspots' in the gene," said Louise Strong, M.D., a professor in the Section of Clinical Cancer Genetics and director of the Clinical Cancer Genetics Program. In some cancer-susceptibility genes, however, the DNA sequencing method commonly used to detect mutations may not identify every single rearrangement, large insertion, or deletion that is present, especially if it is a mutation that has not been observed previously.

According to the National Cancer Institute, genetic assessments are most beneficial if interventions that are recommended for people with a genetic susceptibility for a particular cancer differ from those recommended for individuals at average risk.

(Continued on page 4)
For example, the American Cancer Society recommends that individuals at average risk for colorectal cancer begin screening at age 50 (with a choice of three options: a fecal occult blood test every year plus flexible sigmoidoscopy every five years, double-contrast barium enema every five to 10 years, or colonoscopy every 10 years). Stricter screening guidelines are necessary for patients at risk for hereditary colorectal cancers to increase the number of cancers detected early, which may increase long-term survival rates. For patients with a family history of hereditary nonpolyposis colon cancer (HNPCC) or those who have tested positive for a mutation in one of the five susceptibility genes, guidelines recommend colonoscopy every one to two years starting at age 25 (or younger if family members were diagnosed with colorectal cancer before age 35).

Another consideration for patients contemplating genetic testing is whether they are emotionally ready for the implications of the results. "I think one of the biggest benefits to the patients who get tested is the removal of the unknown," said Dr. Strong. "But just like there is a subgroup of people for whom knowledge is an empowerment, I think there are some people who really just don't want to know."

One of the surprising findings early on in genetic testing, said Dr. Strong, was that some individuals live so long with an expectation that they are going to develop cancer because of a family history that if they find out through testing that they are not at higher risk of the disease, they actually feel a loss. Other patients develop survivor's guilt. "They think, 'I don't have the bad gene but my sister does. Why her? Why not me?'" said Dr. Strong.

Others, especially young, healthy individuals, are deterred from genetic testing because they fear that a determination of genetic susceptibility will cause them to lose their health insurance or their job, said Michelson. State and national laws protect patient privacy, however, and according to Dr. Strong, there has been little evidence to date of abuse of genetic information by the health care industry or employers.

While many considerations influence a patient's decision to have genetic testing, many more arise within the family after testing. As part of a large, longitudinal prospective study on the psychosocial aspects of genetic testing for HNPCC, Susan Peterson, Ph.D., M.P.H., an assistant professor in the Department of Behavioral Science, is leading a descriptive study of how patients convey genetic information about cancer to their families.

"We wanted to find out what some of the factors were that might underlie how families communicate about this and also how the dynamics of the family might influence the way that information is shared," said Dr. Peterson.

Because very little was known about how families communicate information about hereditary cancers, the study was designed to be qualitative, consisting of semistructured interviews (composed mostly of open-ended questions) with patients who had undergone or were currently undergoing genetic testing, as well as their spouses and biological relatives.

Dr. Peterson said that preliminary findings indicate that patients who discover they have a genetic predisposition to cancer are most likely to share that information with the relatives they are geographically or socially closest to. While some patients have no qualms about telling their immediate family, such as their children and siblings, they don't always feel a responsibility to communicate the information to other relatives. Along the same lines, spouses of patients do not always view themselves as being affected by the information and may not advocate notification of other members of the family. Dr. Peterson also observed that it is the proband (or patient who first gets tested) who often takes the most active role in ensuring that the genetic information gets spread throughout the family.

"All these research findings are important because when genetic counselors are disclosing genetic test results, it is important for them to also explore the family climate and different family relationships, particularly those relationships with family members who may benefit from knowing this information," said Dr. Peterson.

The genetic counselors in the Clinical Cancer Genetics Program do all they can to help patients inform family members of their genetic risks, said Michelson, even helping patients draft letters that can be sent to family members who may be at increased risk for cancer. This information gives others an opportunity to seek genetic counseling or testing on their own—a decision that could help them live longer, healthier lives.

For more information, contact Sara Michelson at (713) 745-8044, Dr. Strong at (713) 792-7555, or Dr. Peterson at (713) 792-8267.
Having cancer is always a life-altering event, but forwise, a veterinarian and mother of a young child, the changes go beyond physical scars and emotional upheaval. Since being diagnosed with BRCA2-positive breast cancer five years ago, has re-established contact with long-lost family members, given up her veterinary practice, and made it her life’s work to help other women who are at high risk for genetic cancers get the support and information they need.

Even though she was only 33 years old when her cancer was first detected, said that her physicians did not take seriously the possibility that her cancer might be genetic, despite the fact that her paternal grandmother had died young of “kidney cancer.”

Eight months after her diagnosis, read an article about the connection between hereditary breast cancer and ovarian cancer. She began to suspect that her grandmother might have died of ovarian cancer, which could easily have been mistaken for kidney cancer in the 1940s. Also, she decided to undergo genetic testing to determine if she was at high risk for further cancer.

Such testing was not available at her local hospital, so when came to M.D. Anderson for a second opinion in the treatment of her cancer, she asked about genetic testing and was told that she needed to speak to a genetic counselor first.

“I had a medical background, and I thought I knew everything I needed to know before the test, but I grossly underestimated the value of a relationship with a genetic counselor when questions come up.”

After genetic analysis revealed a BRCA2 mutation, which places her at extremely high risk for breast and ovarian cancers, began contacting family members, some of whom she had not spoken to in 20 years, to let them know about the genetic risk they might be facing.

“I became the red flag for the family because we didn’t have a strong family history of cancer,” said. “I gave them information on the genetic counseling process and where they could go to receive genetic counseling. For the most part, they appeared grateful. I was impressed with how gracious they were.”

All the while, Dr. said, she looked for support from women who were going through similar experiences. She searched the Internet for support sites but found none that specifically addressed the issue of hereditary risk.

“It was very clear to me that this was a group who needed a voice, a place to go,” said. “There was nothing out there, and we had psychosocial concerns that were not being met.

“I knew the Internet would be the perfect medium to get people together and give them a sense of community. I had to make decisions without any emotional support from people who knew what I was going through, and I didn’t want anyone else to have to go through what I did alone.”

a nonprofit organization for women who may be at high risk of cancer because of their family history or a genetic mutation, now has more than 600 registered users and receives more than 300,000 hits a month.

“It has grown beyond what I ever imagined,” said, who gave up her 11-year veterinary career a few months ago to work full-time.

said there are many women like herself who were not told about genetic testing. Others are referred for genetic testing but not for genetic counseling—or referred for counseling only after the genetic test has taken place.

“I get pretty upset when I hear about women who had the test and weren’t referred for genetic counseling,” said. “Once you have the test, you have the knowledge and you can’t take it back. I think the process is so important.”
Discovery Sheds Light on How Breast Cancer Cells Progress to More Aggressive Forms

by Karyn Hede

The ability of some breast cancer cells to suddenly stop responding to treatment and become more aggressive has frustrated clinicians for years. But a new finding may finally help to shed light on the mechanisms behind this devastating process.

In a study that appeared in the August 8 issue of the journal Nature, researchers at The University of Texas M. D. Anderson Cancer Center report finding a potential target that may lead to therapies that reverse the process of disease progression and restore hormone responsiveness to breast cancer cells.

A research team led by Rakesh Kumar, Ph.D., a professor in the Department of Molecular and Cellular Oncology, has discovered a new form of a protein that is associated with aggressive forms of cancer, including breast cancer. The new protein, called metastatic tumor antigen 1, short version (MTA1s), appears to intercept the key protein receptor that is responsible for communicating with estrogen inside cells.

About 60% of breast cancers are classified as estrogen-receptor positive by conventional evaluation methods. Patients with estrogen-receptor-positive breast cancer typically respond well to hormonal treatment with tamoxifen and other anti-estrogenic compounds, which block estrogen signals that tell the cancer cells to multiply. But after a period of time, some breast cancer cells suddenly become hormone independent, growing and multiplying more rapidly, even in the presence of anti-estrogen treatment.

"The underlying molecular mechanisms for aggressive tumor behavior and estrogen-receptor-negative tumors are poorly understood, and this is an area of intense research," Dr. Kumar said. "This research is an important step toward understanding how breast cancers become hormone independent. With greater understanding, we can design new therapies to prevent or perhaps reverse this transformation."

Dr. Kumar and his colleagues discovered the new protein while studying MTA1, which is known to contribute to the transformation of breast cancer tumors into more aggressive forms. MTA1s is a naturally occurring short form of MTA1, but while MTA1 interacts with the estrogen receptor in the nucleus, MTA1s appears to intercept the estrogen receptor in the cytoplasm and prevent it from entering the nucleus. Furthermore, estrogen receptors sequestered in the cytoplasm stimulate nongenomic effects, such as mitogen-activated protein kinase stimulation, which in turn might participate in the development of aggressive phenotypes.

In collaboration with Aysegul Sahin, M.D., an associate professor in the Department of Pathology, and Gabriel Hortobagyi, M.D., a professor in the Department of Breast Medical Oncology, Dr. Kumar and his research team studied tumors from 31 patients that were classified as estrogen-receptor positive or estrogen-receptor negative. They found that MTA1s was four times more abundant in tumors classified as estrogen-receptor negative by conventional methods. Moreover, they found that these cells actually contained estrogen receptors, but the receptors were being trapped in the cytoplasm by MTA1s.

"Currently, pathologists look for estrogen receptors in the nuclei of cancer cells," Dr. Kumar said. "If they don't find them there, they classify the tumor as estrogen-receptor negative. However, some of those tumors actually may have functional estrogen receptors that are being sequestered in the cytoplasm by MTA1s. The current method used to identify estrogen-receptor-positive cells can only locate estrogen receptors in the nucleus, not those sequestered in the cytoplasm."

Further study showed that by deleting the portion of MTA1s that attaches to the estrogen receptor, functional estrogen receptors could be restored to the nuclei of breast cancer cells in the laboratory.

"Since we have defined at least one of the mechanisms that is responsible for retaining the estrogen receptor in the cytoplasm, it may soon be possible to restore estrogen-receptor responsiveness to breast cancer cells in patients," Dr. Kumar said.

FOR MORE INFORMATION, contact Dr. Kumar at (713) 745-3558.
Just a Phase: Understanding Clinical Trials

Virtually all of the advances in health care over the past few decades—including many breakthroughs in the treatment of patients with cancer—were the result of extensive research. Occurring near the end of the long process of health care research are clinical trials, in which patients participate in the study of new treatments, prevention or screening strategies, or factors that affect quality of life.

Before a treatment can be tested in people, it must be shown to be safe and effective in laboratory and animal studies. Also, all clinical studies must be approved by the U.S. Food and Drug Administration before the study can begin. Cancer clinical trials take place in four phases. Each phase asks different questions and gathers data to support further research. The phase indicates how much research has been done and approximately how many people have participated in the study. According to the National Cancer Institute, it takes an average of almost nine years for an anticancer drug to be studied in phase I through phase III trials. (Phase IV trials, which are rare, occur after the new treatment has been approved for standard use and measure the long-term safety and effectiveness of the treatment.)

Phase I Trials
Phase I trials usually test a new treatment in humans for the first time but also can be used to evaluate an approved drug at higher doses or in a different disease. Fifteen to 30 people usually participate, and people with many types of cancer might be able to enter this trial. These patients have usually tried other treatments without success. In phase II trials, researchers focus on the safety of the treatment, studying the best way to administer the new treatment, the maximum dose based on safety considerations, and how often the treatment should be given.

One of the benefits of participating in a phase I treatment trial is being among the first to receive a new treatment that might prove to be effective against cancer. However, the effectiveness of the treatment in people has not been demonstrated. Another risk is that no one yet knows what side effects might occur or how severe they might be.

Phase II Trials
If the new treatment is shown to be safe in a phase I trial, the study progresses to phase II. In phase II trials, researchers continue to test the safety of a new treatment and begin to evaluate how well it works by comparing different dose regimens to see if the tumor has shrunk at those doses. These trials enroll fewer than 100 participants, and eligibility is usually based on prior treatment. Recruiting enough participants for a phase II trial may take up to two years.

Phase III Trials
Treatments that are shown to be effective in phase II trials are further refined and studied in phase III trials. Phase III trials, which compare a new treatment with the standard treatment for a particular disease, enroll from 100 to several thousand people. Participants are divided into two or more study groups, depending on the research questions being asked. Despite a popular misconception, placebos are rarely used in cancer treatment trials. Researchers instead try to find out if the new treatment works better than, the same as, or worse than the standard treatment in participants ranging from newly diagnosed patients to people with advanced disease. So while about half the patients in a phase III trial will not get the new treatment, those who don’t will receive the standard treatment, which has so far proved to be the best available. And if the new agent shows promise, the participant may be among the first to benefit from it. Risks can include experiencing adverse effects that were not noted in prior studies or are worse than those found in standard treatment and receiving a new agent that turns out to be less effective than the standard treatment. Accrual for phase III trials can take from three to four years.

Patient Participation
After receiving a thorough explanation of the possible risks and benefits of the treatment being studied, the patient should always be the one to decide whether he or she will participate in a clinical trial. It is the responsibility of each research center’s Institutional Review Board to ensure that all clinical trials include treatments that are at least as good as standard care. Patients who choose to take part in clinical trials may or may not receive a benefit beyond what they would have received with standard care, but their participation will add to what is known about their disease and perhaps lead to a cure.

For more information about clinical trials, speak to your physician or call the Cancer Information Service at 1-800-4-CANCER (1-800-422-6237).

For more information, contact your physician or contact the M. D. Anderson Information Line:
(800) 392-1611 within the United States, or
(713) 792-6161 in Houston and outside the United States.

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Bigger than a Blood Test: Ethical Cautions about Genetic Testing

Martin L. Smith, S.T.D., and Anne L. Flamm, J.D.

A cholesterol test is routine and quite simple. Most patients are likely to consent readily because high levels of cholesterol can be treated and the morbidity and risks associated with the test are minimal. The results are clear and easily understood by most patients and therefore can usually be communicated to the patient over the telephone or in a letter.

But having blood drawn for a genetic test is a different story. Genetic testing raises many complex ethical issues, not only for the individual being tested but also for that person’s family.

Genetic testing is done for a variety of reasons, including pre-implantation and prenatal diagnosis in embryos, newborn screening, carrier testing, diagnosis of disease, and predictive testing. Many ethical questions arise from the uncertainty of the results, as well as from their implications: Is the test sensitive enough to detect the presence or absence of a genetic mutation? Does a positive result identify disease or merely the propensity for disease? Are preventive measures or an effective treatment available for an identified disorder? Is the individual being tested prepared for the psychosocial impact of the information imparted by the test? What might that individual’s test results reveal about members of his or her family?

An essential component of genetic testing is a thorough and effective informed consent process. The reductionist model of informed consent that focuses on simply getting the patient’s signature on a consent form is inadequate. Rather, a truly informative and educational process addresses what the test results will and will not mean, the possibility and percentages (if known) of false-positive and false-negative test results, who will have access to the test results, whether treatment or preventive measures are available if the test results are conclusively positive, and the implications the results may have for the patient’s family members, now and in the future. As is true for any informed consent process, simply providing information is not enough; the patient must understand the information.

Because of the great complexity of genetics in general and genetic testing in particular, educating patients and communicating test results requires the assistance of trained professionals, such as genetic counselors. When, in their professional judgment, testing offers a benefit, physicians should advise and encourage patients to pursue genetic testing. However, they should not pressure a patient to undergo testing if, after a thorough educational process, the patient refuses the test. Finally, physicians should communicate genetic test results to patients in person, allowing sufficient time to respond to the questions and concerns that patients will undoubtedly have.
CLINICAL PRACTICE GUIDELINES
Quarterly Supplement to OncoLog
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About These Clinical Practice Guidelines

This guideline may assist in the diagnostic evaluation and treatment of patients with clinical symptoms or positive screening tests (if such testing exists). The clinician is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care.

M. D. Anderson Cancer Center's Practice Guidelines are continually updated as new information becomes available and are being expanded to include the entire spectrum of cancer management. New guidelines for screening and diagnosis are under development. Access the most current version of all M. D. Anderson Practice Guidelines from M. D. Anderson's Home Page at http://www.mdanderson.org.

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Synopsis & Highlights

Although they are not the only ways that gynecologic cancers are discovered, an abnormal mass found during clinical examination or the presence of abnormal vaginal bleeding should initiate an evaluation for a possible ovarian, cervical, or uterine malignancy.

In this discussion, it is assumed that a complete medical history, including determining whether the patient is menopausal or pregnant, and a Pap test are performed as standard practice in any thorough evaluation of the female genital tract and are repeated at appropriate times in the diagnostic process.

Abnormal Vaginal Bleeding

A patient whose pregnancy test is positive should be referred to an obstetrician/gynecologist for further evaluation and follow-up to include the investigation of possible obstetric causes of bleeding. (Although it is rare, the possibility of gestational...)

(Continued on next page)
trophoblastic disease should be considered.) For all other patients, further diagnostic assessment is based on cytologic examination of tissue samples from an endometrial biopsy and an endocervical curettage. “It would also be standard practice to repeat the Pap test at this time,” says Dr. Bodurka.

Where biopsy results are negative for a malignancy, further evaluation or treatment may be pursued. In patients who are not pregnant, noncancerous causes of abnormal bleeding include anovulatory menstrual cycles, uterine leiomyoma or polyps, endometrial hyperplasia, and certain medications.

If a malignancy is confirmed by biopsy results, the clinician should refer to the appropriate treatment guideline. Referral to a gynecologic oncologist is recommended. A pathologic finding of complex hyperplasia with atypia must be treated. Our experts recommend consultation with a gynecologic oncologist, as this finding is associated with a significant (25% to 30%) risk of progression to endometrial cancer. Management of complex hyperplasia with atypia is directed by considerations of the patient’s age and desire for fertility. A medical approach may be possible for patients who desire preservation of fertility; for postmenopausal patients, a simple hysterectomy is recommended.

This procedure may be performed via an abdominal, vaginal, or laparoscopic approach, with frozen-section evaluation of the uterus to detect endometrial carcinoma. If present, this indicates the need for a staging procedure that requires the expertise of a gynecologic oncologist.

Pelvic Mass
Upon the discovery of an adnexal or pelvic mass, the possibility of pregnancy should be considered and either confirmed or ruled out. Patients with positive pregnancy tests may be referred to an obstetrician/gynecologist for further evaluation. All other patients should undergo evaluation for ovarian cancer using transvaginal ultrasonography and serum CA 125 level measurement.

It should be noted that an elevated CA 125 level is not diagnostic by itself; CA 125 is not specific to ovarian cancer and can be elevated in several noncancerous conditions, particularly in endometriosis, uterine leiomyoma, and benign ovarian cysts, as well as in inflammatory processes such as cholecystitis, pancreatitis, appendicitis, and pericarditis and in other malignancies, including cancers of the stomach, colon, liver, and pancreas. Furthermore, ovarian cancer may be present in patients whose CA 125 level is normal. Alongside other diagnostic tests, however, it is a useful tool.

Ascites
When clinical examination or ultrasonography confirms the presence of ascites, our experts recommend that the clinician refer to treatment guidelines for ovarian cancer before pursuing any other course of action. The next probable step will be an exploratory laparotomy, ideally performed by a gynecologic oncologist, for which there are specific recommended parameters. It is especially important in this situation that, to avoid disseminating cancer cells, invasive diagnostic procedures such as biopsies or laparoscopic procedures not be used. According to Dr. Bodurka, needle and trocar sites create possible foci of implantation for tumor cells.

Nature of the Mass
Masses that are noted during clinical examination to be nodular, firm, or fixed are suspicious for a malignant process, but the next steps in diagnosis should be determined by the results of transvaginal ultrasonography. If a mass is complex in nature—septations, excrescences, high blood flow, and low resistance are suggestive of malignancy—or large (8 cm or more), and CA 125 measurement is elevated (> 35 U/ml), suspicion of an ovarian malignancy should be quite high. “Beyond this point, the only way to confirm this diagnosis is by examination of (Continued on next page)
Suspicion of Gynecologic Cancer

CLINICAL PRESENTATION

- Adnexal or pelvic mass
  - Patient premenopausal?
    - Yes
      - Pregnancy test positive?
        - Yes
          - Refer patient to Ob/Gyn for follow-up or consultation (including testing for gestational trophoblastic disease)
        - No
          - Mass with ascites
            - Complex mass or
              - Cyst ≥ 8 cm or
              - CA 125 > 35 U/ml
              - Colon cancer ruled out?
                - Yes
                  - Refer to Colon Cancer Practice Guideline (available on the Internet)
                - No
                  - Other individualized treatment
            - Mass without ascites
              - Left adnexal mass > 5 cm fixed to sigmoid colon
                - Reference
              - Simple cyst < 8 cm or
                - Pelvic inflammatory disease or
                - Uterine leiomyoma
                  - Refer patient to Ob/Gyn for follow-up or consultation (including testing for gestational trophoblastic disease)
                  - Other individualized evaluation, treatment, or both
  - No
    - Pelvic exam, transvaginal ultrasound, and CA 125 measurement

- Abnormal vaginal bleeding
  - Patient premenopausal?
    - Yes
      - Pregnancy test positive?
        - Yes
          - Endometrial biopsy with endocervical curettage
            - Positive
              - Cancer
              - Atypical hyperplasia
                - Refer to appropriate Gynecologic Cancer Practice Guideline (available on the Internet)
                - Follow-up with gynecologic oncologist
            - Negative
              - Other individualized evaluation, treatment, or both
        - No
          - Positive
            - Other individualized evaluation, treatment, or both
          - Negative
            - Other individualized evaluation, treatment, or both
    - No
      - Other individualized evaluation, treatment, or both

M. D. Anderson's Practice Guidelines were developed by multidisciplinary teams of physicians and nurses and are intended to represent evidence-based cancer care with consensus of opinion used secondarily.
tissue derived from surgical excision," says Dr. Ramirez. Such a mass should be removed intact during an exploratory laparotomy as described above. Needle biopsy and laparoscopic exploration are not appropriate in this circumstance, for reasons previously cited.

According to the guideline, if a left adnexal mass larger than 5 cm and fixed to the sigmoid colon is discovered, the possibility of colorectal cancer should be considered and investigated. But Dr. Ramirez says that a mass of any size that is fixed to the colon should arouse suspicion of colorectal cancer. "Similarly," he adds, "right adnexal masses fixed to the cecum should be investigated for cecal or appendiceal cancer."

For masses confirmed to be noncancerous, such as simple cysts, leiomyoma, or hydrosalpinx secondary to previous or current pelvic inflammatory disease, appropriate subsequent evaluation or treatment may commence.

Sometimes a mass is discovered during a surgical procedure. "In such cases, an intraoperative consultation with a gynecologic oncologist may be considered," says Dr. Bevers, who directs M. D. Anderson's Gynecologic Outreach Program, which offers consultations to community physicians. "We're often called preoperatively or intraoperatively but are available at any point in the process where a physician feels it to be appropriate," he says. Many physicians use this service because it enables them to continue in their role as primary caregiver to a patient, while offering her specialty support from M. D. Anderson physicians. "For many patients and their physicians, it works better than a direct referral," says Dr. Bevers. "It's one more way that we can be available to help provide a continuum of cancer care."

**Clinical Perspectives**

- It is a common misconception that a cancer diagnosis must be confirmed before referring a patient to a specialty cancer center. This misconception is especially important in the setting of suspected gynecologic cancer, as it is sometimes leads to biopsies or laparoscopic procedures that are intended to confirm or document a cancer diagnosis but can cause delays in appropriate treatment as well as the complications noted earlier. In these cases, experts recommend referring the patient to a cancer center for confirmation of the diagnosis or consulting with a gynecologic oncologist during the diagnostic process.

- Don't dismiss cancer as a possibility until it is ruled out, and always keep it on the list of differential diagnoses. Ovarian cancer in particular is a deadly disease because its symptoms are so subtle and it is often in an advanced stage before it is discovered. In many cases of ovarian cancer, attempts have been made to treat the symptoms (hormone adjustments for bloating complaints, for example) or the patient has been referred to a nononcologic gastrointestinal specialist before cancer is considered.

- If the tests aren't making sense, keep pursuing a diagnosis. It is very important to continue testing until all findings and test results are concordant with a specific diagnosis.

**References & Suggested Reading**
