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LETTER FROM THE EDITOR

Dear Reader:

In this issue we present articles on breast cancer and a review of Type 1 Diabetes Mellitus. We also introduce a new contributor, Jeanne Mariani, a member of the RGA® Underwriting Group.

In recent years, breast cancer statistics have shown a very gradual reduction in mortality in populations around the world. The mortality remains high in most countries in the Northern Hemisphere while in countries such as Japan and China the mortality rate remains quite low. These changes have been attributed to early diagnosis, improvement in therapy and possibly, lifestyle changes. As a result of these changes, we are likely to see increasing numbers of applications from women with breast-cancer histories. The challenge will be to stratify these applicants appropriately. In cases of early disease (carcinoma in situ and early Stage 1 disease) the majority of these women may approach close to standard mortality. More advanced disease is associated with 10-year survival rates, ranging from 66 percent with Stage II disease to 7 percent with Stage IV disease.

These statistics confirm that even Stage II disease remains a chronic disease with significant underwriting implications. Permanent ratings may be appropriate for many years after the completion of treatment.

Breast cancer's complexity precludes a discussion of all its facets. In this issue we will address genetic factors, treatment, and hormonal manipulation.

In the review of Type 1 Diabetes Mellitus we have attempted to demonstrate how improvements in treatment and management have increased survival, allowing for more accurate underwriting decisions for consistently compliant applicants.

Comments and questions, as well as suggestions for future issues, should be addressed to J. Carl Holowaty, M.D. at e-mail: cholowaty@rgare.com.

Sincerely,
Norma E. Davis, M.D.

GENETICS AND NEW TREATMENTS IN BREAST CANCER

Approximately 180,000 women in the U.S. alone are diagnosed with breast cancer each year. Considering that breast cancer accounts for 29 percent of all cancers in women, it's no wonder that we, as underwriters, are faced with numerous applications from breast-cancer survivors. What follows are a few topics of interest on the genetics and treatment of breast cancer.

Genetics of Cancer

There are two types of genetic lesions that can lead to the development of cancer: mutations in tumor suppressor genes and mutations in oncogenes. The protein products of tumor suppressor genes function in normal cells to control cell growth and apoptosis (programmed cell death). Mutations in these types of genes lead to the loss of this control function, resulting in unchecked cell growth (i.e. tumor formation). The protein products of mutated oncogenes are usually produced in small amounts in the cell, if at all, and function to control normal cell growth. A mutation in one of these genes can lead to an overexpression of the protein, >>>

>>> or a different form of the protein, either of which can also lead to the unsuppressed growth seen in tumors. A genetic mutation can either be specific for a certain tumor type or may occur in many types of cancers. HER2 (see below) is an oncogene, the protein product that is found to be overexpressed in some breast cancers. P53 is a tumor suppressor gene, mutations of which are found in many tumor types, including breast cancer.

BRCA1 and BRCA2

The BRCA1 and BRCA2 genes are tumor suppressor genes associated with a predisposition to develop breast cancer. A woman with a mutation in one of these genes may have up to a 60-percent chance of developing breast cancer in her lifetime. The original genetic testing for mutations in these genes was done solely on high-risk women with a strong family history of breast cancer. The general population may have a lower incidence of disease associated with these mutations.

For all the publicity BRCA1 and BRCA2 have received in the media, a mutation in one of these genes is found in only 5-10 percent of women diagnosed with breast cancer. The majority of women with breast cancer do not carry a mutation in these genes. However, women who do carry one of these mutations and go on to develop cancer are likely to present with high grade, estrogen receptor negative tumors. In addition, they are more likely to relapse after treatment and have a worse overall prognosis than women who do not carry BRCA mutations. Mutations in these genes have also been associated with the development of ovarian, prostate, and colorectal cancers.

Prophylactic Mastectomies

A 1999 article in The New England Journal of Medicine discussed a study of prophylactic mastectomies in women with a high to moderate risk of breast cancer. These women had strong family histories of breast cancer, but were not genetically tested for the BRCA mutations. It was found that prophylactic mastectomies could reduce the incidence of breast cancer by at least 90 percent. In this type of operation, it is not possible to remove all of the breast tissue, so the operation does not guarantee that cancer will not develop. In addition, it is a major, disfiguring operation, and although these results are optimistic, many of the women operated on would not have developed cancer anyway. However, prophylactic mastectomy is an option many women have chosen when faced with a positive test for a BRCA mutation, and an even greater risk of developing the disease.

HER2

Within the last year, the media has reported on a new test for women who have already been diagnosed with breast cancer. The test, called the "Inform Gene Detection System Test," developed by Oncor Inc., examines tumor tissue for overexpression of the HER2 gene product. This protein, the product of the HER2 gene, is found on the surface of some cells, and plays a role in regulating growth by acting as a receptor for growth factors. Breast cancers that overexpress the protein product of this gene are associated with a poor prognosis. A positive test indicates that the tumor has a high likelihood of recurring. In node-negative women, this test may help determine whether chemotherapy will be beneficial or even necessary. It appears that this testing may become as routine as estrogen and progesterone receptor testing in the future, and may therefore, be another valuable tool for prediction in underwriting.

In 1998, the FDA approved the drug, Herceptin (Trastuzumab), an antibody against HER2. Herceptin, when given to women with overexpression of HER2, binds to the protein on the cell surface, slowing the tumor growth. Initial studies indicate treatment with Herceptin, combined with traditional chemotherapy, slowed disease progression and increased response rates.

p53

The p53 gene produces a protein that is thought to regulate the growth of normal cells by suppressing cell division or inducing apoptosis (programmed cell death). A mutation in the p53 gene can cause a loss of this function, which can lead to unchecked cell growth and tumorigenesis. Several studies have indicated that abnormal p53 in breast cancers is a marker for aggressive tumors and recurrent disease. Alterations in p53 are the most common genetic mutation found in all human cancers.

Several additional gene mutations and abnormal gene products, such as UPA, PAI-1 and CtIP, are under investigation to determine their usefulness as predictors of the outcome of breast cancer. Genetic tests may eventually play an important role in the choice and type of therapies for this disease as well as more accurately predicting the course of the disease.

Jeanne Mariani

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TYPE 1 DIABETES MELLITUS — AN OVERVIEW

Type I Diabetes Mellitus (*insulin-dependent diabetes mellitus, juvenile diabetes*) varies in frequency from country to country as well as within regions of the same country. It is an autoimmune disease that usually affects persons under 20 years of age. However, it can occur at any age and does demonstrate a small peak in midlife. With advances in treatment, the mortality and morbidity associated with this impairment have improved significantly during the past 40 years, resulting in an estimated 15-year increase in life expectancy.

The incidence of Type I Diabetes varies from less than one per 100,000 in Korea to greater than 40 per 100,000 in certain parts of Finland. The disease is rare among Asians, Native Americans and Black Africans while the incidence in Europe increases as one travels north from the Mediterranean region. In the United States, the incidence varies from 10 per 100,000 in San Diego to nearly 20 per 100,000 in North Dakota.

The reasons for these variations appear to be multifactorial. Genetic predisposition is well recognized, as is the autoimmune process. These are represented by insulitis (lymphocytic infiltration of the islets) and the presence of antibodies to islet cells, insulin and glutamic acid decarboxylase, which appear before the onset of symptoms. The presence of autoimmune antibodies does not, however, always result in the development of diabetes, suggesting that environmental factors contribute to its evolution. This is further enhanced by the following observations:

- Regional differences in prevalence occur in fairly homogeneous populations.
- Seasonal variations exist in rates of appearance with statistically significant increases in late fall and early winter.
- Only 33 percent of identical twins of the index patients will develop the disease.
- The frequency of Type I Diabetes is higher among children who were not breast fed.
- The incidence has been increasing in several countries during the past three decades.
- Reports of Type I Diabetes among siblings, twins, single-family members and children under three years of age support a hypothesis that enteroviruses are etiologic agents.
- There appears to be an increased incidence in children who are exposed to cow milk before six months of age.

In addition to the group with autoimmune disease, approximately 10 percent of diabetics present with an abrupt onset of symptoms but have no evidence of insulitis and no diabetes-related antibodies. This group frequently has normal hemoglobin A_1c levels and elevated pancreatic enzyme (amylase and elastase) at diagnosis, features not observed in antibody-positive diabetics. Based on the prevalence of this group, the American Diabetes Association and the World Health Organization have proposed that Type I Diabetes be subdivided into:

Type IA — Autoimmune Diabetes
Type IB — Idiopathic Diabetes

Historically, Type I Diabetes was associated with significantly increased mortality and morbidity compared with Type II Diabetes. The comparison was even more dramatic due to the younger average age at onset and the apparent accelerated rate at which vascular and neurologic complications occurred. Researchers recognized that the complications resulted from the inability to maintain stable blood-sugar levels at close to normal range. As a result, studies were developed to assess the effects of different treatment protocols on blood sugar control. The most widely known study, the Diabetes Control and Complication Trial Research Group (DCCT Study), followed over 1,400 individuals for an average of 6.5 years.

Two groups were assessed at baseline and at regular intervals during the study to assess their responses to different treatment regimens as follows:

Group 1: Conventional Therapy - consisted of one or two daily injections of a mixture of intermediate and rapid-acting insulins, instructions on diet and exercise. Members of this group monitored their blood or urine glucose daily, but did not adjust insulin dosages daily.
Group 2: Intensive Therapy - received three or more doses of insulin daily by injection or using the insulin pump. Blood glucose was measured at least four times daily. Special attention was paid to dietary intake and level of exercise.

While the members of the conventional group were examined every three months, the intensive therapy group was examined monthly and contacted frequently to adjust insulin dosage to assure tight control of blood sugar and glycosylated hemoglobin levels.

At the end of the study period, the benefits of intensive treatment were obvious. The risk of developing microvascular complications, such as nephropathy, and retinopathy and neuropathy were dramatically reduced. Subjects who had evidence of early retinopathy on entering the study showed reversal of the changes. When the hemoglobin A_1c is maintained at 7 percent or less, the risk of persistent albuminuria, a marker for progression to end-stage renal disease, is significantly reduced. Further, the effects of intensive therapy persisted for at least four years after the study ended, even in the presence of rising blood sugars.

There are some negative effects of intensive therapy, including weight gain and increased hypoglycemic episodes. The tendency to excessive weight gain has resulted in increased incidence of eating disorders among adolescent girls with Type I Diabetes and hypoglymcemic episodes are a concern, especially when they occur during sleep.

As a result of the DCCT and other studies, intensive therapy has become the treatment of choice. The burden to patients is being lessened by the increasing availability of insulin pumps, which are continually being improved in design.

Along with tight glycemic control, it appears that blood-pressure control is important in delaying or preventing nephropathy and retinopathy, which parallel each other. In a study of Type I Diabetics with diagnosed nephropathy, followed over a 10-year period, Trocha et al observed that an intensive antihypertensive therapy not only reduced the long-term mortality due to end-stage renal disease but also reduced the mortality and morbidity associated with macrovascular disease, i.e. coronary artery disease and peripheral vascular disease. Although this study included only 91 subjects, the end points comparing the intensive antihypertensive treatment group with the routine therapy group were statistically significant. While the death rate was 16 percent in the intensive group at the end of 10 years, it was 48 percent in the routine therapy group. Seven percent in the intensive group required amputation, compared with 25 percent in the other group. Fourteen percent developed blindness, compared with 35 percent in the intensive and routine treatment groups, respectively. This evidence strongly suggests that tight control of blood pressure should be an integral part of the management of Type I Diabetics.

Many of the factors contributing to the development of Type I Diabetes have been identified. Currently there are several studies in progress to develop treatments to:

- abort or delay beta islet cell loss
- prevent the development of diabetes in genetically predisposed individuals.

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THE TREATMENT OF BREAST CANCER

The treatment of breast cancer is most dependent on the stage of the tumor. Secondary factors are the type and estrogen receptor status of the tumor, and age and menopausal status of the patient. Thus, the various types of cancers will be discussed, grouped by stages, with important treatment options based on other variables when appropriate.

Breast Cancer in Situ

Breast cancer in situ is defined as carcinoma arising from the epithelium of the ductal system—ductal carcinoma in situ (DCIS), or of the lobules—lobular carcinoma in situ (LCIS). Due to the increased use of screening mammography, these noninvasive cancers are being diagnosed with increasing frequency, and now account for up to 20 percent of all breast cancers. Of the histologic subtypes, comedocarcinoma is the most aggressive and most likely to lead to microinvasion.

DCIS

The traditional treatment for DCIS was mastectomy, with a recurrence rate of 2 percent. The recent trend towards breast-conserving surgery leads to recurrence rates of up to 21 percent, but these recurrences are usually amenable to mastectomy with survival rates equal to those of the traditional therapy. Thus, breast-conserving therapy is a reasonable approach. The National Surgical Adjuvant Breast and Bowel Project (NSABP) found that breast-conserving surgery and adjuvant radiation is an acceptable option, with an invasive cancer recurrence rate of 3.9 percent in those treated with surgery and radiation, as opposed to 13.4 percent in those treated with surgery alone. There is no defined role for chemotherapy in DCIS, and the role of hormonal manipulation (e.g. Tamoxifen) is currently under investigation.

LCIS

LCIS (or lobular neoplasia) is typically a bilateral, diffuse process. Most feel that LCIS is a risk factor for invasive cancer, with a 2.2 percent incidence of invasive breast cancer within five years. The treatment of LCIS is controversial, with options ranging from observation to bilateral radical mastectomy. The trend is towards periodic examination and mammography. Tamoxifen was found to reduce the incidence of invasive breast cancer by 49 percent over four years.

Stage I Breast Cancer

Stage I breast cancer can be treated with various surgical procedures, ranging from local resection to mastectomy. Surgery alone, though, can lead to a recurrence rate of up to 20 percent at 10 years. It is now felt that limited surgery (lumpectomy, quadrantectomy or segmental mastectomy) combined with radiation therapy will lead to long-term survival equivalent to that of more extensive surgery. The surgical approach depends on the location and size of the tumor, the mammographic appearance, the size of the breast and the patient's age. The patient's willingness to accept a greater risk of cancer recurrence in order to preserve the breast is paramount in the decision-making process. The proper adjunctive therapy requires that the tumor be evaluated for the presence of estrogen receptors (an "ER positive" tumor).

The treatment also changes with metastasis, thus an axillary lymph node dissection or a sentinel lymph node biopsy is required. New data suggest that a bone marrow biopsy with special stains to detect epithelial cancer cells is a very sensitive method to detect metastasis. Any evidence of metastasis requires additional treatment (see Stage II with positive nodes) and helps predict long-term survival. The ER status and measures of tumor cell proliferation (flow cytometry, S-phase measurement and ploidy) are also helpful in the estimation of relapse for these cancers.

A significant percentage of women with Stage I, node-negative breast cancer will have recurrence, and several large studies have addressed this issue. An NSABP trial found significant improvement in five-year survival (disease free) for ER negative patients treated with adjuvant chemotherapy and for ER positive patients treated with Tamoxifen. Another study compared Tamoxifen alone to Tamoxifen and chemotherapy, and found 96 percent overall five-year survival in the latter group, marginally better than from Tamoxifen alone.

Tamoxifen was found to be protective in The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) random study of 75,000 women with Stage I and II cancer. Postmenopausal women with ER positive tumors who received daily Tamoxifen for two years had less recurrent disease and increased survival. Furthermore, these benefits lasted at least 10 years. Tamoxifen was also found to benefit women with ER negative tumors via a decreased incidence of contralateral recurrence. A 1998 study of 37,000 women showed that the benefits of Tamoxifen increased with longer treatment (1 year v. 2 years v. 5 years). Five years of Tamoxifen decreased mortality by 26 percent, compared with no hormonal therapy. Improvement in 10-year survival was 10.9 percent in metastatic disease and 5.6 percent in node-negative cancer, both for pre- and post-menopausal women. There has been no evidence that Tamoxifen treatment beyond five years adds any benefit. Some have advocated Tamoxifen treatment alone for elderly women. This approach has an unacceptable rate of recurrence and should not be looked upon as first-line therapy. This may be a reasonable option for those who could not otherwise tolerate surgery or refuse more involved treatment.

An NSABP trial compared preoperative versus postoperative chemotherapy in the treatment of Stage I

and II tumors. More women in the preoperative group were able to have breast-conserving procedures as opposed to the postoperative chemotherapy arm (68 percent v. 60 percent). There was no difference in overall recurrence of survival in these two groups. The sequence of radiation and chemotherapy has also been studied. Five-year survival is improved with chemotherapy prior to radiation. Furthermore, postponing radiation for several months after breast-conserving therapy until the completion of chemotherapy does not affect survival and reduces the morbidity of each therapy.

Thus, Stage I tumors can be treated with limited surgery and adjuvant chemotherapy. Chemotherapy first may allow more conservative surgery. Patients must be assessed for metastasis via lymph node analysis, and those patients who have evidence of metastasis should be offered radiation therapy after completion of chemotherapy and recovery from surgery. Hormonal therapy with Tamoxifen is beneficial to both ER positive and negative women. Regular follow-up is essential for the timely diagnosis of any tumor recurrence.

Stage II Breast Cancer

Stage II breast cancer is also treatable with a variety of surgical procedures. As with Stage I, conservative surgery (lumpectomy) and radiation provide survival rates to modified radical mastectomy alone. Preoperative chemotherapy may allow conservative surgery via reduction in tumor size. Treatment is dependent on characteristics of the tumor as well as the patient's attitude towards surgery and breast conservation. Axillary lymph node dissection or sentinel node biopsy is required for proper staging.

For those patients with Stage II and positive nodes, adjuvant chemotherapy increases survival. This therapy is combined with Tamoxifen in ER positive tumors. The NSABP found that chemotherapy also increased 10-year survival in women with ER positive, Stage II, node negative tumors. The data did not show any difference in such treatment for similar ER negative tumors. Tamoxifen alone is not acceptable, even in elderly patients. The timing of Tamoxifen and chemotherapy is currently being investigated; simultaneous use increases side effects of each. As with Stage I tumors, better results were found when radiation therapy was delayed until surgical recovery and completion of chemotherapy (similar survival with fewer complications).

In Stage II, node-positive cancers, the EBCTCG found no clear advantage with the routine use of chest-wall radiation therapy after surgery. Radiation should be considered for women who are at high risk for local or regional recurrence, e.g. those with four or more positive nodes, extracapsular extension or margins that are not clearly free of cancer.

Regular follow-up with annual physical examination and mammography is essential.

Stage III Breast Cancer

Stage III locally advanced breast cancer is divided into IIIA or IIIB, depending on the number of nodes involved and the tumor size. Standard IIIA treatment consists of modified radical mastectomy and radiation therapy. Chemotherapy is also utilized; it can be given prior to surgery to shrink tumors otherwise not amenable to surgery. Tamoxifen is given to women with ER positive tumors.

The role of preoperative chemotherapy to allow conservative surgery and breast conservation is being evaluated, as is the role of high-dose chemotherapy combined with bone-marrow transplant.

Stage IIIB breast cancers are treated in the same manner as Stage IV tumors.

Stage IV Breast Cancer

Stage IV (and IIIB) tumors are responsive to treatment, but long-term remission is less than 20 percent. Surgical treatment is limited to biopsy to assess tumor type and ER status. Radiation is used to control local symptoms and bone pain from metastatic disease. Aggressive chemotherapy regimens lead to 50-60 percent response rate, but toxic effects are significant and long-term survival is poor. Hormonal therapy (Tamoxifen) is an excellent first choice in ER positive tumors. High-dose chemotherapy with bone-marrow transplant is being investigated.

Summary

Significant progress in the treatment of breast cancer has been made in the last decade. Women today are being successfully treated with less-aggressive surgical procedures, which combined with radiation, chemotherapy and hormonal manipulation, allow patients to survive longer and have a better quality of life than patients of previous generations. Despite these advances, however, mortality is still significant and recurrence of disease can occur years to decades after completion of therapy. When underwriting, one should consider breast cancer a chronic disease, often warranting a permanent flat-extra rating.

The Reader is referred to http://cancernet.nci.nih.gov for the National Institute of Health's current (2/2000) recommendations on the treatment of breast cancer and an excellent review of relevant literature.

Robert J. Profumo, M.D.

>>> As the results of these studies become available and lead to refinements in both prophylactic and therapeutic treatment regimens, the mortality and morbidity associated with this disease will continue to improve.

During the past 40 years the incidence of diabetic nephropathy, the most common cause of death among Type I Diabetics, has decreased significantly. This is due to improvements in glycemic control as well as control of hypertension. The incidence of persistent albuminuria, the precursor to end-stage renal disease, was as high as 30 percent after 25 years of disease in individuals who developed diabetes prior to 1965. This phenomenon has steadily decreased in frequency and has been reported to be as low as 5.8 percent in those who developed the disease between 1971 and 1975. The downward trend in incidence continues to be observed in ongoing studies.

In individuals who are able to maintain good glycemic control, good blood pressure control, and avoid the risk factors associated with macrovascular disease such as hyperlipidemia and hypertriglycerdemia, the mortality risk is greatly improved. As a result, in underwriting the Type I Diabetic we should be asking the following questions:

> How long has the applicant had diabetes?
> Is there evidence of consistent, good glycemic control over the history of the patient's disease?
> Does the applicant have persistent albuminuria?
> Is there a history of smoking? Is there excess alcohol consumption?
> Is there a history of hypertension? Has the blood pressure been consistently well controlled?
> Is the total cholesterol within normal range? Is the cholesterol/HDL ratio normal? Is the LDL within normal range?
> Are the triglycerides normal?
> Does the applicant pursue a regular exercise program?

The more positive answers there are, the better the risk. Evaluating Type I Diabetics in this manner could help to effectively stratify this group and allow for appropriate selection in a challenging group of possible insureds.

Norma E. Davis, M.D.

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TAMOXIFEN

It is imperative for underwriters to keep current in their understanding of changing uses of medications. Occasionally, medications listed on a non-medical insurance form are the only means of making inferences about an applicant's health, as the following information on the use of Tamoxifen illustrates.

Tamoxifen (Novaldex/Tamoxifen Citrate) is an oral medication that has been used for more than 20 years for the treatment of breast cancer. In this article, I will discuss the way in which the use of Tamoxifen has changed during this period. This information should provide insight into the implications of noticing the use of Tamoxifen on an insurance applicant's nonmedical form.

Tamoxifen is a synthetic hormone, classified as a nonsteroidal antiestrogen, which has both estrogen agonist and antagonist activity. Prolonged exposure to estrogen can promote the growth of breast cancer cells. The antiestrogen (antagonist) effect of Tamoxifen is to counteract the effect of estrogen on these cells, slowing or even stopping their growth. When Tamoxifen was first introduced more than 20 years ago, it was primarily given to postmenopausal women with breast cancer who had axillary lymph-node involvement. Subsequent studies suggested the advantage of using Tamoxifen as an adjuvant therapy for the treatment of breast cancer in all stages. This advantage seems to be most evident for the first five years of treatment and is independent of nodal or menopausal status. Use of this medication for more than five years seems to be more beneficial in those with node positive, particularly estrogen receptor positive disease, than those without nodal involvement.

In 1998, the preliminary results of the National Surgical Adjuvant Breast and Bowel Project P-1 (NSABP study) suggested that the medication Tamoxifen reduced the risk of developing breast cancer by 45 percent in women considered to be at high risk for the disease. This caused great excitement because it opened a new potential use for Tamoxifen, that being as a chemoprophylactic agent in the battle against breast cancer. Those women felt to be at highest risk are those over the age of 60, and those under the age of 60 with strong family histories of breast cancer. As with most preliminary studies, the conclusions reached are not without controversy. Further trials published in "The Lancet" in Great Britain indicated they did not find the same benefits of Tamoxifen use in preventing breast cancer. On closer analysis of the available data, it appears that Tamoxifen may at the very least delay the onset of the disease, but it is indeed too early to know if it will actually ultimately prevent the occurrence of breast cancer. Nevertheless, the FDA's Oncologic Drugs Advisory Committee has approved Tamoxifen as a chemotherapeutic agent for women at high risk for developing breast cancer.

On the positive side, Tamoxifen slows bone loss, preserving bone density, and lowers serum cholesterol and low-density lipoprotein. On the negative side, however, it has an adverse effect on the endometrium. In the NSABP study, endometrial cancer occurred at the rate of 13 per 1,000 women, indicating the need for careful monitoring of women on the drug. Because the women were being followed, the lesions were detected at early stages, treated appropriately and there were no deaths.

As in prescribing all medications, physicians must weigh the potential benefits against the potential side effects. For some users, side effects may include weight gain, hot flashes, dysmenorrhea, headaches, nausea, and vomiting. Some of the less frequent but serious side effects include: thromboembolic events, including pulmonary embolism, hepatic toxicity, and the previously mentioned endometrial cancer.

While Tamoxifen is a well-publicized medication, it is not the only drug that may benefit women at risk of developing breast cancer. Another medication called raloxifene hydrochloride (Evista) has also been studied and may provide the same benefits as Tamoxifen. This drug is a selective estrogen receptor modifier. It was first used for the prevention of osteoporosis, but is now being further studied to see if it will help prevent breast cancer. Currently, the second-line hormonal treatment for receptor positive breast cancer is megestrol (Megace). Recent studies indicate that the aromatase inhibitors anastrazole (Arimidex) and letrozole (Femara) may offer survival advantages over megestrol.

Although Tamoxifen use has traditionally been associated with breast-cancer therapy, and to a lesser degree osteoporosis, it is occasionally selectively used to treat other medical conditions. These conditions are pancreatic cancer, gynecomastia, and mastalgia.

In the past, admission to the use of Tamoxifen implied that the applicant had breast cancer, and quite possibly metastatic breast cancer. Now, as I have indicated, we can expect to see this drug being used in a much larger population of women merely at risk of developing breast cancer, rather than already having clinical evidence of this disease. Underwriting caution, as usual, will be needed to separate those with a history of breast cancer, from those who are using the medication for either a predisposition to breast cancer, or other unrelated indications. **J.C. Holowaty, M.D.**

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