Cancer: Causes and Therapy

From the National Cancer Institute

Inflammatory Breast Cancer

Key Points

Inflammatory breast cancer is a rare and very aggressive disease with symptoms that include redness, swelling, tenderness, and warmth in the breast.

Treatment for inflammatory breast cancer is usually more aggressive than treatment for most other types of breast cancer.

People with inflammatory breast cancer are encouraged to enroll in clinical trials that are testing new treatments.

What is inflammatory breast cancer?

Inflammatory breast cancer (IBC) is a rare and very aggressive disease in which cancer cells block lymph vessels in the skin of the breast. This type of breast cancer is called “inflammatory” because the breast often looks swollen and red, or “inflamed.”

Inflammatory breast cancer accounts for 1 to 5 percent of all breast cancers diagnosed in the United States. Most inflammatory breast cancers are invasive ductal carcinomas,

which means they developed from cells that line the milk ducts of the breast and then spread beyond the ducts.

Inflammatory breast cancer progresses rapidly, often in a matter of weeks or months. Inflammatory breast cancer is either stage III or IV at diagnosis, depending on whether cancer cells have spread only to nearby lymph nodes or to other tissues as well.

Additional features of inflammatory breast cancer include the following:

Compared with other types of breast cancer, inflammatory breast cancer tends to be diagnosed at younger ages (median age of 57 years, compared with a median age of 62 years for other types of breast cancer).

It is more common and diagnosed at younger ages in African American women than in white women. The median age at diagnosis in African American women is 54 years, compared with a median age of 58 years in white women.

Inflammatory breast tumors are frequently hormone receptor negative, which means that hormone therapies, such as tamoxifen, that interfere with the growth of cancer cells fueled by estrogen may not be effective against these tumors.

Inflammatory breast cancer is more common in obese women than in women of normal weight.

Like other types of breast cancer, inflammatory breast cancer can occur in men, but usually at an older age (median age at diagnosis of 66.5 years) than in women.

What are the symptoms of inflammatory breast cancer?

Symptoms of inflammatory breast cancer include swelling (edema) and redness (erythema) that affect a third or more of the breast. The skin of the breast may also appear pink, reddish purple, or bruised. In addition, the skin may have ridges or appear pitted, like the skin of an orange (called peau d'orange). These symptoms are caused by the buildup of fluid (lymph) in the skin of the breast. This fluid buildup occurs because cancer cells have blocked lymph vessels in the skin, preventing the normal flow of lymph through the tissue. Sometimes, the breast may contain a solid tumor that can be felt during a physical exam, but, more often, a tumor cannot be felt.

Other symptoms of inflammatory breast cancer include a rapid increase in breast size; sensations of heaviness, burning, or tenderness in the breast; or a nipple that is inverted (facing inward). Swollen lymph nodes may also be present under the arm, near the collarbone, or in both places.

It is important to note that these symptoms may also be signs of other diseases or conditions, such as an infection, injury, or

another type of breast cancer that is locally advanced. For this reason, women with inflammatory breast cancer often have a delayed diagnosis of their disease.

How is inflammatory breast cancer diagnosed?

Inflammatory breast cancer can be difficult to diagnose. Often, there is no lump that can be felt during a physical exam or seen in a screening mammogram. In addition, most women diagnosed with inflammatory breast cancer have non-fatty (dense) breast tissue, which makes cancer detection in a screening mammogram more difficult. Also, because inflammatory breast cancer is so aggressive, it can arise between scheduled screening mammograms and progress quickly. The symptoms of inflammatory breast cancer may be mistaken for those of mastitis, which is an infection of the breast, or another form of locally advanced breast cancer.

To help prevent delays in diagnosis and in choosing the best course of treatment, an international panel of experts published guidelines on how doctors can diagnose and stage inflammatory breast cancer correctly. Their recommendations are summarized below.

Minimum criteria for a diagnosis of inflammatory breast cancer include the following:

A rapid onset of erythema (redness), edema (swelling), and a peau d'orange appearance and/or abnormal breast warmth, with or without a lump that can be felt.

The above-mentioned symptoms have been present for less than 6 months.

The erythema covers at least a third of the breast.

Initial biopsy samples from the affected breast show invasive carcinoma.

Further examination of tissue from the affected breast should include testing to see if the cancer cells have hormone receptors (estrogen and progesterone receptors) or a mutation that causes them to make greater than normal amounts of the HER2 protein (HER2-positive breast cancer).

Imaging and staging tests should include the following:

A diagnostic mammogram and an ultrasound of the breast and regional (nearby) lymph nodes.

A PET scan or a CT scan and a bone scan to see if the cancer has spread to other parts of the body.

Proper diagnosis and staging of cancer helps doctors develop the best treatment plan and estimate the likely outcome of the disease, including the chances for recurrence and survival.

How is inflammatory breast cancer treated?

Inflammatory breast cancer is treated first with systemic chemotherapy to help shrink the tumor, then with surgery to remove the tumor, followed by radiation therapy. This approach to treatment is called a multimodal approach. Studies have found that women with inflammatory breast cancer who are treated with a multi-modal approach have better responses to therapy and longer survival. Treatments used in a multimodal approach may include those described below.

Neoadjuvant chemotherapy: This type of chemotherapy is given before surgery and usually includes both anthracycline and taxane drugs. At least six cycles of neoadjuvant chemotherapy given over the course of 4 to 6 months before attempting to remove the tumor has been recommended, unless the disease continues to progress during this time and doctors decide that surgery should not be delayed.

Targeted therapy: This type of treatment may be used if a woman’s biopsy samples show that her cancer cells have a

tumor marker that can be targeted with specific drugs. For example, inflammatory breast cancers often produce greater than normal amounts of the HER2 protein, which means they may respond positively to drugs, such as trastuzumab (Herceptin), that target this protein. Anti-HER2 therapy can be given as part of neoadjuvant therapy and after surgery (adjuvant therapy). Studies have shown that women with inflammatory breast cancer who received trastuzumab in addition to chemotherapy have better responses to treatment and better survival.

Hormone therapy: If a woman's biopsy samples show that her cancer cells contain hormone receptors, hormone therapy is another treatment option. For example, breast cancer cells that have estrogen receptors depend on the female hormone estrogen to promote their growth. Drugs such as tamoxifen, which prevent estrogen from binding to its receptor, and aromatase inhibitors such as letrozole, which block the body's ability to make estrogen, can cause estrogen-dependent cancer cells to stop growing and die.

Surgery: The standard surgery for inflammatory breast cancer is a modified radical mastectomy. This surgery involves removal of the entire affected breast and most or all of the lymph nodes under the adjacent arm. Often, the lining over the underlying chest muscles is also removed, but the chest muscles are

preserved. Sometimes, however, the smaller chest muscle (pectoralis minor) may be removed, too.

Radiation therapy: Post-mastectomy radiation therapy to the chest wall under the breast that was removed is a standard part of multi-modal therapy for inflammatory breast cancer. If a woman received trastuzumab before surgery, she may continue to receive it during postoperative radiation therapy. If breast reconstruction is planned, the sequencing of the radiation therapy and reconstructive surgery may be influenced by the method of breast reconstruction used. If a breast implant is to be used, the preferred approach is to delay radiation therapy until after the reconstructive surgery. If a woman's own tissues are going to be used in breast reconstruction, it is preferable to delay reconstructive surgery until after the radiation therapy has been completed.

Adjuvant therapy: Adjuvant systemic therapy may be given after surgery to reduce the chance of cancer recurrence. This therapy may include additional chemotherapy, antihormonal therapy, targeted therapy (such as trastuzumab), or some combination of these treatments.

Supportive/palliative care: The goal of supportive/palliative care is to improve the quality of life of patients who have a serious or life-threatening disease, such as cancer, and to provide support to their loved ones.

What is the prognosis of patients with inflammatory breast cancer?

The prognosis, or likely outcome, for a patient diagnosed with cancer is often viewed as the chance that the cancer will be treated successfully and that the patient will recover completely. Many factors can influence a cancer patient's prognosis, including the type and location of the cancer, the stage of the disease, the patient's age and overall general health, and the extent to which the patient's disease responds to treatment.

Because inflammatory breast cancer usually develops quickly and spreads aggressively to other parts of the body, women diagnosed with this disease, in general, do not survive as long as women diagnosed with other types of breast cancer. According to statistics from NCI's Surveillance, Epidemiology, and End Results (SEER) program, the 5-year relative survival for women diagnosed with inflammatory breast cancer during the period from 1988 through 2001 was 34 percent, compared with a 5-year relative survival of up to 87 percent among women diagnosed with other stages of invasive breast cancers.

It is important to keep in mind, however, that these survival statistics are based on large numbers of patients and that an individual woman's prognosis could be better or worse, depending on her tumor characteristics and medical history. Women who have inflammatory breast cancer are encouraged to talk with their doctor about their prognosis, given their particular situation.

Research has shown that the following factors are associated with a better prognosis for women with inflammatory breast cancer:

Stage of disease: Women with stage III disease have a better prognosis than women with stage IV disease. Among women who have stage III inflammatory breast cancer, about 40 percent survive at least 5 years after their diagnosis, whereas among women with stage IV inflammatory breast cancer, only about 11 percent survive for at least 5 years after their diagnosis.

Tumor grade: Women with grade I or grade II tumors have a better prognosis than those with grade III tumors. Tumor grade is a term that describes what cancer cells look like under a microscope, with a higher grade indicating a more abnormal

appearance and a more aggressive cancer that is likely to grow and spread. Among women who are diagnosed with grade I or grade II inflammatory breast cancer, 77 percent survived at least 2 years after their diagnosis, whereas among women who were diagnosed with grade III inflammatory breast cancer, 65 percent survived at least 2 years after their diagnosis.

Ethnicity: African American women who have inflammatory breast cancer generally have a worse prognosis than women of other racial and ethnic groups. Studies have found that around 53 percent of African American women who are diagnosed with inflammatory breast cancer survive at least 2 years after diagnosis, whereas 69 percent of women from other racial and ethnic groups survive at least 2 years after diagnosis.

Estrogen receptor status: Women with inflammatory breast whose cancer cells have estrogen receptors have a better prognosis than those whose cancer cells are estrogen receptor negative. The median survival for women with estrogen-receptor negative inflammatory breast cancer is 2 years, whereas the median survival for those with estrogen receptor-positive inflammatory breast cancer is 4 years.

Type of treatment: Multimodal treatment of inflammatory breast cancer improves a woman’s prognosis. Historically, among women who had only surgery, radiation therapy, or surgery and radiation therapy, fewer than 5 percent survived

longer than 5 years. However, when women are treated with neoadjuvant chemotherapy, mastectomy, adjuvant chemotherapy, and radiation therapy, their 5-year disease-free survival ranges from 24 to 49 percent. One long-term study found that 28 percent of women with inflammatory breast cancer survived 15 years or longer after they were treated with multimodal therapy.

Ongoing research, especially at the molecular level, will increase our understanding of how inflammatory breast cancer begins and progresses. This knowledge should enable the development of new treatments and more accurate prognoses for women diagnosed with this disease. It is important, therefore, that women who are diagnosed with inflammatory breast cancer talk with their doctor about the option of participating in a clinical trial.

What clinical trials are available for women with inflammatory breast cancer?

NCI sponsors clinical trials of new treatments for all types of cancer, as well as trials that test better ways to use existing treatments. Participation in clinical trials is a treatment option for many patients with inflammatory breast cancer, and all patients with this disease are encouraged to consider treatment in a clinical trial.

Below are links to clinical trials for inflammatory breast cancer patients. These clinical trials can be found in NCI's list of clinical trials. For information about how to search the list, see "Help Using the NCI Clinical Trials Search Form."

All inflammatory breast cancer trials

Treatment trials for inflammatory breast cancer

People interested in taking part in a clinical trial should talk with their doctor. Information about clinical trials is available from NCI's Cancer Information Service at 1–800–4–CANCER and in the NCI booklet Taking Part in Cancer Treatment Research Studies. Additional information about clinical trials is available at http://www.cancer.gov/clinicaltrials.

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Cancer Prevention

Antioxidants and Cancer Prevention
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Key Points

Antioxidants are chemicals that block the activity of other chemicals known as free radicals. Free radicals are highly reactive and have the potential to cause damage to cells, including damage that may lead to cancer.

Free radicals are formed naturally in the body. In addition, some environmental toxins may contain high levels of free radicals or stimulate the body's cells to produce more free radicals.

Some antioxidants are made naturally by the body. Others can only be obtained from external (exogenous) sources, including the diet and dietary supplements.

Laboratory and animal research has shown that exogenous antioxidants can help prevent the free radical damage associated with the development of cancer.

Research in humans has not demonstrated convincingly that taking antioxidant supplements can help reduce the risk of developing or dying from cancer, and some studies have even shown an increased risk of some cancers.

What are free radicals, and do they play a role in cancer development?

Free radicals are highly reactive chemicals that have the potential to harm cells. They are created when an atom or a molecule (a chemical that has two or more atoms) either gains or loses an electron (a small negatively charged particle found in atoms). Free radicals are formed naturally in the body and play an important role in many normal cellular processes (1,2). At high concentrations, however, free radicals can be hazardous to the body and damage all major components of cells, including DNA, proteins, and cell membranes. The damage to cells caused by free radicals, especially the damage to DNA, may play a role in the development of cancer and other health conditions (1,2).

Abnormally high concentrations of free radicals in the body can be caused by exposure to ionizing radiation and other environmental toxins. When ionizing radiation hits an atom or a molecule in a cell, an electron may be lost, leading to the formation of a free radical. The production of abnormally high levels of free radicals is the mechanism by which ionizing radiation kills cells. Moreover, some environmental toxins, such as cigarette smoke, some metals, and high-oxygen

atmospheres, may contain large amounts of free radicals or stimulate the body's cells to produce more free radicals.

Free radicals that contain the element oxygen are the most common type of free radicals produced in living tissue. Another name for them is "reactive oxygen species," or "ROS" (1,2).

What are antioxidants?

Antioxidants are chemicals that interact with and neutralize free radicals, thus preventing them from causing damage. Antioxidants are also known as "free radical scavengers."

The body makes some of the antioxidants it uses to neutralize free radicals. These antioxidants are called endogenous antioxidants. However, the body relies on external (exogenous) sources, primarily the diet, to obtain the rest of the antioxidants it needs. These exogenous antioxidants are commonly called dietary antioxidants. Fruits, vegetables, and grains are rich sources of dietary antioxidants. Some dietary antioxidants are also available as dietary supplements (1,3).

Examples of dietary antioxidants include beta-carotene, lycopene, and vitamins A, C, and E (alpha-tocopherol). The mineral element selenium is often thought to be a dietary antioxidant, but the antioxidant effects of selenium are most likely due to the antioxidant activity of proteins that have this element as an essential component (i.e., selenium-containing proteins), and not to selenium itself (4).

Can antioxidant supplements help prevent cancer?

In laboratory and animal studies, the presence of increased levels of exogenous antioxidants has been shown to prevent the types of free radical damage that have been associated with cancer development. Therefore, researchers have investigated whether taking dietary antioxidant supplements can help lower the risk of developing or dying from cancer in humans.

Many observational studies, including case–control studies and cohort studies, have been conducted to investigate whether the use of dietary antioxidant supplements is associated with reduced risks of cancer in humans. Overall, these studies have yielded mixed results (5). Because observational studies cannot adequately control for biases that might influence study

outcomes, the results of any individual observational study must be viewed with caution.

Randomized controlled clinical trials, however, lack most of the biases that limit the reliability of observational studies. Therefore, randomized trials are considered to provide the strongest and most reliable evidence of the benefit and/or harm of a health-related intervention. To date, nine randomized controlled trials of dietary antioxidant supplements for cancer prevention have been conducted worldwide. Many of the trials were sponsored by the National Cancer Institute. The results of these nine trials are summarized below.

Linxian General Population Nutrition Intervention Trial: This trial was the first large-scale randomized trial to investigate the effects of antioxidant supplements on cancer risk. In the trial, healthy Chinese men and women at increased risk of developing esophageal cancer and gastric cancer were randomly assigned to take a combination of 15 milligrams (mg) beta-carotene, 30 mg alpha-tocopherol, and 50 micrograms (µg) selenium daily for 5 years or to take no antioxidant supplements. The initial results of the trial showed that people who took antioxidant supplements had a lower risk of death from gastric cancer but not from esophageal cancer. However,

their risks of developing gastric cancer and/or esophageal cancer were not affected by antioxidant supplementation (6).

In 2009, 15-year results from this trial were reported (10 years after antioxidant supplementation ended). In the updated results, a reduced risk of death from gastric cancer was no longer found for those who took antioxidant supplements compared with those who did not (7).

Alpha-Tocopherol/Beta-Carotene Cancer Prevention Study (ATBC): This trial investigated whether the use of alpha-tocopherol and/or beta-carotene supplements for 5 to 8 years could help reduce the incidence of lung and other cancers in middle-aged male smokers in Finland. Initial results of the trial, reported in 1994, showed an increase in the incidence of lung cancer among the participants who took beta-carotene supplements (20 mg per day); in contrast, alpha-tocopherol supplementation (50 mg per day) had no effect on lung cancer incidence (8). Later results showed no effect of beta-carotene or alpha-tocopherol supplementation on the incidence of urothelial (bladder, ureter, or renal pelvis), pancreatic, colorectal, renal cell (kidney), or upper aerodigestive tract (oral/pharyngeal, esophageal, or laryngeal) cancers (9,10,11,12).

Carotene and Retinol Efficacy Trial (CARET): This U.S. trial examined the effects of daily supplementation with beta-carotene and retinol (vitamin A) on the incidence of lung cancer, other cancers, and death among people who were at high risk of lung cancer because of a history of smoking or exposure to asbestos. The trial began in 1983 and ended in late 1995, 2 years earlier than originally planned. Results reported in 1996 showed that daily supplementation with both 15 mg beta-carotene and 25,000 International Units (IU) retinol was associated with increased lung cancer and increased death from all causes (all-cause mortality) (13). A 2004 report showed that these adverse effects persisted up to 6 years after supplementation ended, although the elevated risks of lung cancer and all-cause mortality were no longer statistically significant (14). Additional results, reported in 2009, showed that beta-carotene and retinol supplementation had no effect on the incidence of prostate cancer (15).

Physicians' Health Study I (PHS I): This trial examined the effects of long-term beta-carotene supplementation on cancer incidence, cancer mortality, and all-cause mortality among U.S. male physicians. The results of the study, reported in 1996, showed that beta-carotene supplementation (50 mg every other day for 12 years) had no effect on any of these outcomes in smokers or nonsmokers (16).

Women's Health Study (WHS): This trial investigated the effects of beta-carotene supplementation (50 mg every other day), vitamin E supplementation (600 IU every other day), and aspirin (100 mg every other day) on the incidence of cancer and cardiovascular disease in U.S. women ages 45 and older. The results, reported in 1999, showed no benefit or harm associated with 2 years of beta-carotene supplementation (17). In 2005, similar results were reported for vitamin E supplementation (18).

Supplémentation en Vitamines et Minéraux Antioxydants (SU.VI.MAX) Study: This trial investigated the effects of daily supplementation with a combination of antioxidants and minerals on the incidence of cancer and cardiovascular disease in French men and women. The initial results of the study, reported in 2004, showed that daily supplementation with vitamin C (120 mg), vitamin E (30 mg), beta-carotene (6 mg), and the minerals selenium (100 µg) and zinc (20 mg) for a median of 7.5 years had no effect on the incidence of cancer or cardiovascular disease or on all-cause mortality (19). However, when the data for men and women were analyzed separately, antioxidant and mineral supplementation was associated with lower total cancer incidence and all-cause mortality among men but not among women, and with an increase in skin cancer incidence, including melanoma, among women but not among men (19,20). The beneficial effects of the supplements for men

disappeared within 5 years of ending supplementation, as did the increased risk of skin cancer among women (21,22).

Heart Outcomes Prevention Evaluation–The Ongoing Outcomes (HOPE–TOO) Study: This international trial examined the effects of alpha-tocopherol supplementation on cancer incidence, death from cancer, and the incidence of major cardiovascular events (heart attack, stroke, or death from heart disease) in people diagnosed with cardiovascular disease or diabetes. The results, reported in 2005, showed no effect of daily supplementation with alpha-tocopherol (400 IU) for a median of 7 years on any of the outcomes (23).

Selenium and Vitamin E Cancer Prevention Trial (SELECT): This U.S. trial investigated whether daily supplementation with selenium (200 µg), vitamin E (400 IU), or both would reduce the incidence of prostate cancer in men ages 50 and older. The study began in 2001 and was stopped in 2008, approximately 5 years earlier than originally planned. Results reported in late 2008 showed that the use of these supplements for a median duration of 5.5 years did not reduce the incidence of prostate or other cancers (24). Updated findings from the study, reported in 2011, showed that, after an average of 7 years (5.5 years on supplements and 1.5 years off supplements), there were 17 percent more cases of prostate cancer among men taking vitamin E alone than among men taking a placebo (25).

No increase in prostate risk was observed for men assigned to take selenium alone or vitamin E plus selenium compared with men assigned to take a placebo (24).

Physicians' Health Study II (PHS II): This trial examined whether supplementation with vitamin E, vitamin C, or both would reduce the incidence of cancer in male U.S. physicians ages 50 years and older. The results, reported in 2009, showed that the use of these supplements (400 IU vitamin E every other day, 500 mg vitamin C every day, or a combination of the two) for a median of 7.6 years did not reduce the incidence of prostate cancer or other cancers, including lymphoma, leukemia, melanoma, and cancers of the lung, bladder, pancreas, and colon and rectum (26).

Overall, these nine randomized controlled clinical trials did not provide evidence that dietary antioxidant supplements are beneficial in primary cancer prevention. In addition, a systematic review of the available evidence regarding the use of vitamin and mineral supplements for the prevention of chronic diseases, including cancer, conducted for the United States Preventive Services Task Force (USPSTF) likewise found no clear evidence of benefit in preventing cancer (27).

It is possible, however, that the lack of benefit in clinical studies can be explained by differences in the effects of the tested

antioxidants when they are consumed as purified chemicals as opposed to when they are consumed in foods, which contain complex mixtures of antioxidants, vitamins, and minerals (3). Therefore, acquiring a more complete understanding of the antioxidant content of individual foods, how the various antioxidants and other substances in foods interact with one another, and factors that influence the uptake and distribution of food-derived antioxidants in the body are active areas of ongoing cancer prevention research.

Should people already diagnosed with cancer take antioxidant supplements?

Several randomized controlled trials, some including only small numbers of patients, have investigated whether taking antioxidant supplements during cancer treatment alters the effectiveness or reduces the toxicity of specific therapies (28). Although these trials had mixed results, some found that people who took antioxidant supplements during cancer therapy had worse outcomes, especially if they were smokers.

Additional large randomized controlled trials are needed to provide clear scientific evidence about the potential benefits or harms of taking antioxidant supplements during cancer treatment. Until more is known about the effects of antioxidant supplements in cancer patients, these supplements should be used with caution. Cancer patients should inform their doctors about their use of any dietary supplement.

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Mammograms
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Key Points

A mammogram is an x-ray picture of the breast. Screening mammograms are used to check for breast cancer in women who have no signs or symptoms of the disease. Diagnostic mammograms are used to check for breast cancer after a lump or other sign or symptom of the disease has been found.

Screening mammography can help reduce the number of deaths from breast cancer among women ages 40 to 74.

Potential limitations of screening mammography include false-positive results, overdiagnosis and overtreatment, false-negative results, and radiation exposure.

What is a mammogram?

A mammogram is an x-ray picture of the breast.

Mammograms can be used to check for breast cancer in women who have no signs or symptoms of the disease. This type of mammogram is called a screening mammogram. Screening mammograms usually involve two x-ray pictures, or images, of each breast. The x-ray images make it possible to detect tumors that cannot be felt. Screening mammograms can

also find microcalcifications (tiny deposits of calcium) that sometimes indicate the presence of breast cancer.

Mammograms can also be used to check for breast cancer after a lump or other sign or symptom of the disease has been found. This type of mammogram is called a diagnostic mammogram. Besides a lump, signs of breast cancer can include breast pain, thickening of the skin of the breast, nipple discharge, or a change in breast size or shape; however, these signs may also be signs of benign conditions. A diagnostic mammogram can also be used to evaluate changes found during a screening mammogram or to view breast tissue when it is difficult to obtain a screening mammogram because of special circumstances, such as the presence of breast implants (see Question 11).

How are screening and diagnostic mammograms different?

Diagnostic mammography takes longer than screening mammography because more x-rays are needed to obtain views of the breast from several angles. The technician may

magnify a suspicious area to produce a detailed picture that can help the doctor make an accurate diagnosis.

What are the benefits of screening mammograms?

Early detection of breast cancer with screening mammography means that treatment can be started earlier in the course of the disease, possibly before it has spread. Results from randomized clinical trials and other studies show that screening mammography can help reduce the number of deaths from breast cancer among women ages 40 to 74, especially for those over age 50 (1). However, studies to date have not shown a benefit from regular screening mammography in women under age 40 or from baseline screening mammograms (mammograms used for comparison) taken before age 40.

What are some of the potential limitations of screening mammograms?

False-positive results. False-positive results occur when radiologists decide mammograms are abnormal but no cancer is actually present. All abnormal mammograms should be followed up with additional testing (diagnostic mammograms, ultrasound, and/or biopsy) to determine whether cancer is present.

False-positive results are more common for younger women, women who have had previous breast biopsies, women with a family history of breast cancer, and women who are taking estrogen (for example, menopausal hormone therapy).

False-positive mammogram results can lead to anxiety and other forms of psychological distress in affected women. The additional testing required to rule out cancer can also be costly and time consuming and can cause physical discomfort.

Overdiagnosis and overtreatment. Screening mammograms can find cancers and cases of ductal carcinoma in situ (DCIS, a noninvasive tumor in which abnormal cells that may become cancerous build up in the lining of breast ducts) that need to be treated. However, they can also find cancers and cases of DCIS that will never cause symptoms or threaten a woman’s life,

leading to "overdiagnosis" of breast cancer. Treatment of these latter cancers and cases of DCIS is not needed and leads to "overtreatment." Overtreatment exposes women unnecessarily to the adverse effects associated with cancer therapy.

Because doctors often cannot distinguish cancers and cases of DCIS that need to be treated from those that do not, they are all treated.

False-negative results. False-negative results occur when mammograms appear normal even though breast cancer is present. Overall, screening mammograms miss about 20 percent of breast cancers that are present at the time of screening.

The main cause of false-negative results is high breast density. Breasts contain both dense tissue (i.e., glandular tissue and connective tissue, together known as fibroglandular tissue) and fatty tissue. Fatty tissue appears dark on a mammogram, whereas fibroglandular tissue appears as white areas. Because fibroglandular tissue and tumors have similar density, tumors can be harder to detect in women with denser breasts.

False-negative results occur more often among younger women than among older women because younger women are more likely to have dense breasts. As a woman ages, her breasts usually become more fatty, and false-negative results become less likely. False-negative results can lead to delays in treatment and a false sense of security for affected women.

Some of the cancers missed by screening mammograms can be detected by clinical breast exams (physical exams of the breast done by a health care provider).

Finding cancer early does not always reduce a woman's chance of dying from breast cancer. Even though mammograms can detect malignant tumors that cannot be felt, treating a small tumor does not always mean that the woman will not die from the cancer. A fast-growing or aggressive cancer may have already spread to other parts of the body before it is detected. Women with such tumors live a longer period of time knowing that they likely have a fatal disease.

In addition, screening mammograms may not help prolong the life of a woman who is suffering from other, more life-threatening health conditions.

Radiation exposure. Mammograms require very small doses of radiation. The risk of harm from this radiation exposure is extremely low, but repeated x-rays have the potential to cause cancer. The benefits of mammography, however, nearly always outweigh the potential harm from the radiation exposure. Nevertheless, women should talk with their health care providers about the need for each x-ray. In addition, they should always let their health care provider and the x-ray technician know if there is any possibility that they are pregnant, because radiation can harm a growing fetus.

Where can I find current recommendations for screening mammography?

Many organizations and professional societies, including the United States Preventive Services Task Force (which is convened by the Agency for Healthcare Research and Quality, a federal agency), have developed guidelines for mammography screening. All recommend that women should talk with their doctor about the benefits and harms of mammography, when to start screening, and how often to be screened.

Although NCI does not issue guidelines for cancer screening, it conducts and facilitates basic and translational research that informs standard clinical practice and medical decision making that other organizations may use to develop their guidelines.

What is the best method of detecting breast cancer as early as possible?

Getting a high-quality screening mammogram and having a clinical breast exam on a regular basis are the most effective ways to detect breast cancer early.

Checking one's own breasts for lumps or other unusual changes is called a breast self-exam, or BSE. This type of exam cannot replace regular screening mammograms or clinical breast exams. In clinical trials, BSE alone was not found to help reduce the number of deaths from breast cancer.

Although regular BSE is not specifically recommended for breast cancer screening, many women choose to examine their own breasts. Women who do so should remember that breast

changes can occur because of pregnancy, aging, or menopause; during menstrual cycles; or when taking birth control pills or other hormones. It is normal for breasts to feel a little lumpy and uneven. Also, it is common for breasts to be swollen and tender right before or during a menstrual period. If a woman notices any unusual changes in her breasts, she should contact her health care provider.

What is the Breast Imaging Reporting and Database System (BI-RADS®)?

The American College of Radiology (ACR) has established a uniform way for radiologists to describe mammogram findings. The system, called BI-RADS, includes seven standardized categories, or levels. Each BI-RADS category has a follow-up plan associated with it to help radiologists and other physicians appropriately manage a patient's care.

Breast Imaging Reporting and Database System (BI-RADS)

Category Assessment Follow-up

0 Need additional imaging evaluation -Additional imaging needed before a category can be assigned

1 Negative - Continue regular screening mammograms (for women over age 40)

2 Benign (noncancerous) finding - Continue regular screening mammograms (for women over age 40)

3 Probably benign - Receive a 6-month follow-up mammogram

4 Suspicious abnormality - May require biopsy

5 Highly suggestive of malignancy (cancer)- Requires biopsy

6 Known biopsy-proven malignancy (cancer) - Biopsy confirms presence of cancer before treatment begins

How much does a mammogram cost?

For most women with private insurance, the cost of screening mammograms is covered without copayments or deductibles, but women should contact their mammography facility or health insurance company for confirmation of the cost and coverage.

Medicare pays for annual screening mammograms for all female Medicare beneficiaries who are age 40 or older. Medicare will also pay for one baseline mammogram for female beneficiaries between the ages of 35 and 39. There is no

deductible requirement for this benefit. Information about coverage is available on the Medicare website or through the Medicare Hotline at 1–800–MEDICARE (1–800–633–4227). For the hearing impaired, the telephone number is 1–877–486–2048.

How can uninsured or low-income women obtain a free or low-cost screening mammogram?

Some state and local health programs and employers provide mammograms free or at low cost. For example, the Centers for Disease Control and Prevention (CDC) coordinates the National Breast and Cervical Cancer Early Detection Program. This program provides screening services, including clinical breast exams and mammograms, to low-income, uninsured women throughout the United States and in several U.S. territories. Contact information for local programs is available on the CDC website or by calling 1–800–CDC–INFO (1–800–232–4636).

Information about free or low-cost mammography screening programs is also available from NCI's Cancer Information Service at 1–800–4–CANCER (1–800–422–6237) and from local hospitals, health departments, women's centers, or other community groups.

Where can women get high-quality mammograms?

Women can get high-quality mammograms in breast clinics, hospital radiology departments, mobile vans, private radiology offices, and doctors' offices.

The Mammography Quality Standards Act (MQSA) is a Federal law that requires mammography facilities across the nation to meet uniform quality standards. Under the law, all mammography facilities must: 1) be accredited by an FDA-approved accreditation body; 2) be certified by the FDA, or an agency of a state that has been approved by the FDA, as meeting the standards; 3) undergo an annual MQSA inspection; and 4) prominently display the certificate issued by the agency. More information about MQSA is available from the FDA.

Women can ask their doctors or staff at a local mammography facility about FDA certification before making an appointment. Women should look for the MQSA certificate at the mammography facility and check its expiration date. MQSA regulations also require that mammography facilities give patients an easy-to-read report of their mammogram results.

Information about local FDA-certified mammography facilities is available through NCI's Cancer Information Service at 1–800–4–CANCER (1–800–422–6237). Also, a searchable list of these facilities can be found on the FDA website.

What should women with breast implants do about screening mammograms?

Women with breast implants should continue to have mammograms. (A woman who had an implant following a mastectomy should ask her doctor whether a mammogram of the reconstructed breast is necessary.) It is important to let the mammography facility know about breast implants when scheduling a mammogram. The technician and radiologist must be experienced in performing mammography on women who have breast implants. Implants can hide some breast tissue, making it more difficult for the radiologist to detect an abnormality on the mammogram. If the technician performing the procedure is aware that a woman has breast implants, steps can be taken to make sure that as much breast tissue as possible can be seen on the mammogram. A special technique called implant displacement views may be used.

What is digital mammography? How is it different from conventional (film) mammography?

Digital and conventional mammography both use x-rays to produce an image of the breast; however, in conventional mammography, the image is stored directly on film, whereas, in digital mammography, an electronic image of the breast is stored as a computer file. This digital information can be enhanced, magnified, or manipulated for further evaluation more easily than information stored on film.

Because digital mammography allows a radiologist to adjust, store, and retrieve digital images electronically, digital mammography may offer the following advantages over conventional mammography:

Health care providers can share image files electronically, making long-distance consultations between radiologists and breast surgeons easier.

Subtle differences between normal and abnormal tissues may be more easily noted.

Fewer follow-up procedures may be needed.

Fewer repeat images may be needed, reducing the exposure to radiation.

To date, there is no evidence that digital mammography helps to reduce a woman's risk of dying from breast cancer compared with film mammography. Results from a large NCI-sponsored clinical trial that compared digital mammography with film mammography found no difference between digital and film mammograms in detecting breast cancer in the general population of women in the trial; however, digital mammography appeared to be more accurate than conventional film mammography in younger women with dense breasts (2). A subsequent analysis of women aged 40 through 79 who were undergoing screening in U.S. community-based imaging facilities also found that digital and film mammography had similar accuracy in most women. Digital screening had higher sensitivity in women with dense breasts (3).

Some health care providers recommend that women who have a very high risk of breast cancer, such as those with a known mutation in either the BRCA1 or BRCA2 gene or extremely dense breasts, have digital mammograms instead of conventional mammograms; however, no studies have shown

that digital mammograms are superior to conventional mammograms in reducing the risk of death for these women.

Digital mammography can be done only in facilities that are certified to practice conventional mammography and have received FDA approval to offer digital mammography. The procedure for having a mammogram with a digital system is the same as with conventional mammography.

What is 3D mammography?

Three-dimensional (3D) mammography, also known as breast tomosynthesis, is a type of digital mammography in which x-ray machines are used to take pictures of thin slices of the breast from different angles and computer software is used to reconstruct an image. This process is similar to how a computed tomography (CT) scanner produces images of structures inside of the body. 3D mammography uses very low dose x-rays, but, because it is generally performed at the same time as standard two-dimensional (2D) digital mammography, the radiation dose is slightly higher than that of standard mammography. The accuracy of 3D mammography has not been compared with that of 2D mammography in randomized studies. Therefore, researchers do not know whether 3D

mammography is better or worse than standard mammography at avoiding false-positive results and identifying early cancers.

What other technologies are being developed for breast cancer screening?

NCI is supporting the development of several new technologies to detect breast tumors. This research ranges from methods being developed in research labs to those that are being studied in clinical trials. Efforts to improve conventional mammography include digital mammography, magnetic resonance imaging (MRI), positron emission tomography (PET) scanning, and diffuse optical tomography, which uses light instead of x-rays to create pictures of the breast.

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Biological Therapies for Cancer

Key Points

Biological therapy uses living organisms, substances derived from living organisms, or synthetic versions of such substances to treat cancer.

Some types of biological therapy exploit the immune system's natural ability to detect and kill cancer cells, whereas other types target cancer cells directly.

Biological therapies include monoclonal antibodies, cytokines, therapeutic vaccines, the bacterium bacillus Calmette-Guérin, cancer-killing viruses, gene therapy, and adoptive T-cell transfer.

The side effects of biological therapies can differ by treatment type, but reactions at the site of administration are fairly common with these treatments.

What is biological therapy?

Biological therapy involves the use of living organisms, substances derived from living organisms, or laboratory-produced versions of such substances to treat disease. Some biological therapies for cancer use vaccines or bacteria to stimulate the body's immune system to act against cancer cells. These types of biological therapy, which are sometimes referred to collectively as "immunotherapy" or "biological response modifier therapy," do not target cancer cells directly. Other biological therapies, such as antibodies or segments of genetic material (RNA or DNA), do target cancer cells directly. Biological therapies that interfere with specific molecules involved in tumor growth and progression are also referred to as targeted therapies. (For more information, see Targeted Cancer Therapies.)

For patients with cancer, biological therapies may be used to treat the cancer itself or the side effects of other cancer treatments. Although many forms of biological therapy have been approved by the U.S. Food and Drug Administration (FDA), others remain experimental and are available to cancer patients principally through participation in clinical trials (research studies involving people).

What is the immune system and what role does it have in biological therapy for cancer?

The immune system is a complex network of organs, tissues, and specialized cells. It recognizes and destroys foreign invaders, such as bacteria or viruses, as well as some damaged, diseased, or abnormal cells in the body, including cancer cells. An immune response is triggered when the immune system encounters a substance, called an antigen, it recognizes as "foreign."

White blood cells are the primary players in immune system responses. Some white blood cells, including macrophages and natural killer cells, patrol the body, seeking out foreign invaders and diseased, damaged, or dead cells. These white blood cells provide a general—or nonspecific—level of immune protection.

Other white blood cells, including cytotoxic T cells and B cells, act against specific targets. Cytotoxic T cells release chemicals that can directly destroy microbes or abnormal cells. B cells make antibodies that latch onto foreign intruders or abnormal cells and tag them for destruction by another component of the immune system. Still other white blood cells, including dendritic

cells, play supporting roles to ensure that cytotoxic T cells and B cells do their jobs effectively.

It is generally believed that the immune system's natural capacity to detect and destroy abnormal cells prevents the development of many cancers. Nevertheless, some cancer cells are able to evade detection by using one or more strategies. For example, cancer cells can undergo genetic changes that lead to the loss of cancer-associated antigens, making them less "visible" to the immune system. They may also use several different mechanisms to suppress immune responses or to avoid being killed by cytotoxic T cells (1).

The goal of immunotherapy for cancer is to overcome these barriers to an effective anticancer immune response. These biological therapies restore or increase the activities of specific immune-system components or counteract immunosuppressive signals produced by cancer cells.

What are monoclonal antibodies, and how are they used in cancer treatment?

Monoclonal antibodies, or MAbs, are laboratory-produced antibodies that bind to specific antigens expressed by cancer cells, such as a protein that is present on the surface of cancer cells but is absent from (or expressed at lower levels by) normal cells.

To create MAbs, researchers inject mice with an antigen from human cancer cells. They then harvest the antibody-producing cells from the mice and individually fuse them with a myeloma cell (cancerous B cell) to produce a fusion cell known as a hybridoma. Each hybridoma then divides to produce identical daughter cells or clones—hence the term “monoclonal”—and antibodies secreted by different clones are tested to identify the antibodies that bind most strongly to the antigen. Large quantities of antibodies can be produced by these immortal hybridoma cells. Because mouse antibodies can themselves elicit an immune response in humans, which would reduce their effectiveness, mouse antibodies are often “humanized” by replacing as much of the mouse portion of the antibody as possible with human portions. This is done through genetic engineering.

Some MAbs stimulate an immune response that destroys cancer cells. Similar to the antibodies produced naturally by B cells, these MAbs “coat” the cancer cell surface, triggering its destruction by the immune system. FDA-approved MAbs of this type include rituximab, which targets the CD20 antigen found on non-Hodgkin lymphoma cells, and alemtuzumab, which targets the CD52 antigen found on B-cell chronic lymphocytic leukemia (CLL) cells. Rituximab may also trigger cell death (apoptosis) directly.

Another group of MAbs stimulates an anticancer immune response by binding to receptors on the surface of immune cells and inhibiting signals that prevent immune cells from attacking the body’s own tissues, including cancer cells. One such MAb, ipilimumab, has been approved by the FDA for treatment of metastatic melanoma, and others are being investigated in clinical studies (2).

Other MAbs interfere with the action of proteins that are necessary for tumor growth. For example, bevacizumab targets vascular endothelial growth factor (VEGF), a protein secreted by tumor cells and other cells in the tumor’s microenvironment that promotes the development of tumor blood vessels. When bound to bevacizumab, VEGF cannot interact with its cellular

receptor, preventing the signaling that leads to the growth of new blood vessels.

Similarly, cetuximab and panitumumab target the epidermal growth factor receptor (EGFR), and trastuzumab targets the human epidermal growth factor receptor 2 (HER-2). MAbs that bind to cell surface growth factor receptors prevent the targeted receptors from sending their normal growth-promoting signals. They may also trigger apoptosis and activate the immune system to destroy tumor cells.

Another group of cancer therapeutic MAbs are the immunoconjugates. These MAbs, which are sometimes called immunotoxins or antibody-drug conjugates, consist of an antibody attached to a cell-killing substance, such as a plant or bacterial toxin, a chemotherapy drug, or a radioactive molecule. The antibody latches onto its specific antigen on the surface of a cancer cell, and the cell-killing substance is taken up by the cell. FDA-approved conjugated MAbs that work this way include 90Y-ibritumomab tiuxetan, which targets the CD20 antigen to deliver radioactive yttrium-90 to B-cell non-Hodgkin lymphoma cells, and ado-trastuzumab emtansine, which targets the HER-2 molecule to deliver the drug DM1, which

inhibits cell proliferation, to HER-2 expressing metastatic breast cancer cells.

What are cytokines, and how are they used in cancer treatment?

Cytokines are signaling proteins that are produced by white blood cells. They help mediate and regulate immune responses, inflammation, and hematopoiesis (new blood cell formation). Two types of cytokines are used to treat patients with cancer: interferons (INFs) and interleukins (ILs). A third type, called hematopoietic growth factors, is used to counteract some of the side effects of certain chemotherapy regimens.

Researchers have found that one type of INF, INF-alfa, can enhance a patient's immune response to cancer cells by activating certain white blood cells, such as natural killer cells and dendritic cells (3). INF-alfa may also inhibit the growth of cancer cells or promote their death (4,5). INF-alfa has been approved for the treatment of melanoma, Kaposi sarcoma, and several hematologic cancers.

Like INFs, ILs play important roles in the body's normal immune response and in the immune system's ability to respond to cancer. Researchers have identified more than a dozen distinct ILs, including IL-2, which is also called T-cell growth factor. IL-2 is naturally produced by activated T cells. It increases the proliferation of white blood cells, including cytotoxic T cells and natural killer cells, leading to an enhanced anticancer immune response (6). IL-2 also facilitates the production of antibodies by B cells to further target cancer cells. Aldesleukin, IL-2 that is made in a laboratory, has been approved for the treatment of metastatic kidney cancer and metastatic melanoma. Researchers are currently investigating whether combining aldesleukin treatment with other types of biological therapies may enhance its anticancer effects.

Hematopoietic growth factors are a special class of naturally occurring cytokines. All blood cells arise from hematopoietic stem cells in the bone marrow. Because chemotherapy drugs target proliferating cells, including normal blood stem cells, chemotherapy depletes these stem cells and the blood cells that they produce. Loss of red blood cells, which transport oxygen and nutrients throughout the body, can cause anemia. A decrease in platelets, which are responsible for blood clotting, often leads to abnormal bleeding. Finally, lower white

blood cell counts leave chemotherapy patients vulnerable to infections.

Several growth factors that promote the growth of these various blood cell populations have been approved for clinical use. Erythropoietin stimulates red blood cell formation, and IL-11 increases platelet production. Granulocyte-macrophage colony-stimulating factor (GM-CSF) and granulocyte colony-stimulating factor (G-CSF) both increase the number of white blood cells, reducing the risk of infections. Treatment with these factors allows patients to continue chemotherapy regimens that might otherwise be stopped temporarily or modified to reduce the drug doses because of low blood cell numbers.

G-CSF and GM-CSF can also enhance the immune system's specific anticancer responses by increasing the number of cancer-fighting T cells. Thus, GM-CSF and G-CSF are used in combination with other biological therapies to strengthen anticancer immune responses.

What are cancer treatment vaccines?

Cancer treatment vaccines are designed to treat cancers that have already developed rather than to prevent them in the first place. Cancer treatment vaccines contain cancer-associated antigens to enhance the immune system's response to a patient's tumor cells. The cancer-associated antigens can be proteins or another type of molecule found on the surface of or inside cancer cells that can stimulate B cells or killer T cells to attack them.

Some vaccines that are under development target antigens that are found on or in many types of cancer cells. These types of cancer vaccines are being tested in clinical trials in patients with a variety of cancers, including prostate, colorectal, lung, breast, and thyroid cancers. Other cancer vaccines target antigens that are unique to a specific cancer type (7-14). Still other vaccines are designed against an antigen specific to one patient's tumor and need to be customized for each patient. The one cancer treatment vaccine that has received FDA approval, sipuleucel-T, is this type of vaccine.

Because of the limited toxicity seen with cancer vaccines, they are also being tested in clinical trials in combination with other forms of therapy, such as hormonal therapy, chemotherapy,

radiation therapy, and targeted therapies. (For more information see Cancer Vaccines.)

What is bacillus Calmette-Guérin therapy?

Bacillus Calmette-Guérin (BCG) was the first biological therapy to be approved by the FDA. It is a weakened form of a live tuberculosis bacterium that does not cause disease in humans. It was first used medically as a vaccine against tuberculosis. When inserted directly into the bladder with a catheter, BCG stimulates a general immune response that is directed not only against the foreign bacterium itself but also against bladder cancer cells. How and why BCG exerts this anticancer effect is not well understood, but the efficacy of the treatment is well documented. Approximately 70 percent of patients with early-stage bladder cancer experience a remission after BCG therapy (15).

BCG is also being studied in the treatment of other types of cancer (16-18).

What is oncolytic virus therapy?

Oncolytic virus therapy is an experimental form of biological therapy that involves the direct destruction of cancer cells. Oncolytic viruses infect both cancer and normal cells, but they have little effect on normal cells. In contrast, they readily replicate, or reproduce, inside cancer cells and ultimately cause the cancer cells to die. Some viruses, such as reovirus, Newcastle disease virus, and mumps virus, are naturally oncolytic, whereas others, including measles virus, adenovirus, and vaccinia virus, can be adapted or modified to replicate efficiently only in cancer cells. In addition, oncolytic viruses can be genetically engineered to preferentially infect and replicate in cancer cells that produce a specific cancer-associated antigen, such as EGFR or HER-2 (19).

One of the challenges in using oncolytic viruses is that they may themselves be destroyed by the patient's immune system before they have a chance to attack the cancer. Researchers have developed several strategies to overcome this challenge, such as administering a combination of immune-suppressing chemotherapy drugs like cyclophosphamide along with the virus or "cloaking" the virus within a protective envelope. But an immune reaction in the patient may actually have benefits: although it may hamper oncolytic virus therapy at the time of

viral delivery, it may enhance cancer cell destruction after the virus has infected the tumor cells (20-23).

No oncolytic virus has been approved for use in the United States, although H101, a modified form of adenovirus, was approved in China in 2006 for the treatment of patients with head and neck cancer. Several oncolytic viruses are currently being tested in clinical trials. Researchers are also investigating whether oncolytic viruses can be combined with other types of cancer therapies or can be used to sensitize patients' tumors to additional therapy.

What is gene therapy?

Still an experimental form of treatment, gene therapy attempts to introduce genetic material (DNA or RNA) into living cells. Gene therapy is being studied in clinical trials for many types of cancer.

In general, genetic material cannot be inserted directly into a person's cells. Instead, it is delivered to the cells using a carrier, or "vector." The vectors most commonly used in gene therapy are viruses, because they have the unique ability to recognize certain cells and insert genetic material into them. Scientists

alter these viruses to make them more safe for humans (e.g., by inactivating genes that enable them to reproduce or cause disease) and/or to improve their ability to recognize and enter the target cell. A variety of liposomes (fatty particles) and nanoparticles are also being used as gene therapy vectors, and scientists are investigating methods of targeting these vectors to specific cell types.

Researchers are studying several methods for treating cancer with gene therapy. Some approaches target cancer cells, to destroy them or prevent their growth. Others target healthy cells to enhance their ability to fight cancer. In some cases, researchers remove cells from the patient, treat the cells with the vector in the laboratory, and return the cells to the patient. In others, the vector is given directly to the patient. Some gene therapy approaches being studied are described below.

Replacing an altered tumor suppressor gene that produces a nonfunctional protein (or no protein) with a normal version of the gene. Because tumor suppressor genes (e.g., TP53) play a role in preventing cancer, restoring the normal function of these genes may inhibit cancer growth or promote cancer regression.

Introducing genetic material to block the expression of an oncogene whose product promotes tumor growth. Short RNA or DNA molecules with sequences complementary to the gene's messenger RNA (mRNA) can be packaged into vectors or given to cells directly. These short molecules, called oligonucleotides, can bind to the target mRNA, preventing its translation into protein or even causing its degradation.

Improving a patient's immune response to cancer. In one approach, gene therapy is used to introduce cytokine-producing genes into cancer cells to stimulate the immune response to the tumor.

Inserting genes into cancer cells to make them more sensitive to chemotherapy, radiation therapy, or other treatments

Inserting genes into healthy blood-forming stem cells to make them more resistant to the side effects of cancer treatments, such as high doses of anticancer drugs

Introducing "suicide genes" into a patient's cancer cells. A suicide gene is a gene whose product is able to activate a "pro-drug" (an inactive form of a toxic drug), causing the toxic drug to be produced only in cancer cells in patients given the pro-drug. Normal cells, which do not express the suicide genes, are not affected by the pro-drug.

Inserting genes to prevent cancer cells from developing new blood vessels (angiogenesis)

Proposed gene therapy clinical trials, or protocols, must be approved by at least two review boards at the researchers' institution before they can be conducted. Gene therapy protocols must also be approved by the FDA, which regulates all gene therapy products. In addition, gene therapy trials that are funded by the National Institutes of Health must be registered with the NIH Recombinant DNA Advisory Committee.

What is adoptive T-cell transfer therapy?

Adoptive cell transfer is an experimental anticancer therapy that attempts to enhance the natural cancer-fighting ability of a patient's T cells. In one form of this therapy, researchers first harvest cytotoxic T cells that have invaded a patient's tumor. They then identify the cells with the greatest antitumor activity and grow large populations of those cells in a laboratory. The patients are then treated to deplete their immune cells, and the laboratory-grown T cells are infused into the patients.

In another, more recently developed form of this therapy, which is also a kind of gene therapy, researchers isolate T cells from a small sample of the patient's blood. They genetically

modify the cells by inserting the gene for a receptor that recognizes an antigen specific to the patient's cancer cells and grow large numbers of these modified cells in culture. The genetically modified cells are then infused into patients whose immune cells have been depleted. The receptor expressed by the modified T cells allows these cells to attach to antigens on the surface of the tumor cells, which activates the T cells to attack and kill the tumor cells.

Adoptive T-cell transfer was first studied for the treatment of metastatic melanoma because melanomas often cause a substantial immune response, with many tumor-invading cytotoxic T cells. Adoptive cell transfer with genetically modified T cells is also being investigated as a treatment for other solid tumors, as well as for hematologic cancers (24-29).

What are the side effects of biological therapies?

The side effects associated with various biological therapies can differ by treatment type. However, pain, swelling, soreness, redness, itchiness, and rash at the site of infusion or injection are fairly common with these treatments.

Less common but more serious side effects tend to be more specific to one or a few types of biological therapy. For example, therapies intended to prompt an immune response against cancer can cause an array of flu-like symptoms, including fever, chills, weakness, dizziness, nausea or vomiting, muscle or joint aches, fatigue, headache, occasional breathing difficulties, and lowered or heightened blood pressure. Biological therapies that provoke an immune system response also pose a risk of severe or even fatal hypersensitivity (allergic) reactions.

Potential serious side effects of specific biological therapies are as follows:

MAbs

Flu-like symptoms

Severe allergic reaction

Lowered blood counts

Changes in blood chemistry

Organ damage (usually to heart, lungs, kidneys, liver or brain)

Cytokines (interferons, interleukins, hematopoietic growth factors)

Flu-like symptoms

Severe allergic reaction

Lowered blood counts

Changes in blood chemistry

Organ damage (usually to heart, lungs, kidneys, liver or brain)

Treatment vaccines

Flu-like symptoms

Severe allergic reaction

BCG

Flu-like symptoms

Severe allergic reaction

Urinary side effects

Pain or burning sensation during urination

Increased urgency or frequency of urination

Blood in the urine

Oncolytic viruses

Flu-like symptoms

Tumor lysis syndrome: severe, sometimes life-threatening alterations in blood chemistry following the release of materials formerly contained within cancer cells into the bloodstream

Gene therapy

Flu-like symptoms

Secondary cancer: techniques that insert DNA into a host cell chromosome can cause cancer to develop if the insertion inhibits expression of a tumor suppressor gene or activates an oncogene; researchers are working to minimize this possibility

Mistaken introduction of a gene into healthy cells, including reproductive cells

Overexpression of the introduced gene may harm healthy tissues

Virus vector transmission to other individuals or into the environment

How can people obtain information about clinical trials of biological therapies for cancer?

Both FDA-approved and experimental biological therapies for specific types of cancer are being studied in clinical trials. The names of the biological therapy types listed below are links to descriptions of ongoing clinical trials that are testing those types of biological therapies in cancer patients. These trial descriptions can also be accessed by searching NCI's list of cancer clinical trials on the NCI website. NCI's list of cancer clinical trials includes all NCI-funded clinical trials as well as studies conducted by investigators at hospitals and medical centers throughout the United States and around the world.

Monoclonal antibodies

Cytokine therapy

Vaccine therapy

Adoptive T-cell therapy

Oncolytic virus therapy

Gene therapy

DNA oligonucleotide therapy

RNA oligonucleotide therapy

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