National Cancer Institute

Mesothelioma

Research Report

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Contents

This publication describes current knowledge of the causes and prevention, symptoms, diagnosis, and treatment of mesothelioma. The information presented here was gathered from medical textbooks, recent articles in the scientific literature, researchers at the National Cancer Institute (NCI), and scientific meetings.

Knowledge about cancer is increasing steadily. Up-to-date information on mesothelioma and other cancer-related subjects is available from the toll-free Cancer Information Service at 1-800-4-CANCER.

Description and Function of the Mesothelium

The mesothelium is a membrane that covers and protects internal organs of the body. It is composed of two layers of flat cells: the visceral membrane that immediately surrounds an organ and the parietal membrane that forms a sac around an organ. The mesothelium produces a lubricating fluid that is released between these two membrane layers, allowing moving organs (such as the beating heart and the expanding and contracting lungs) to glide easily against adjacent structures.

The mesothelium surrounding the lungs is called the pleural mesothelium (pleura). The peritoneal mesothelium (peritoneum) encases the digestive organs in the abdominal cavity, and the pericardial mesothelium (pericardium) covers the heart. Mesothelial membranes also surround the reproductive organs, such as the ovaries and testes.

Normally the cells of mesothelial tissue, like all cells, divide and reproduce in an orderly way to repair worn-out or injured tissues and to allow for growth. When cell division becomes disordered and uncontrolled, too many cells are produced, abnormal growth takes place, and masses of tissue known as tumors are formed. Tumors may be benign (noncancerous) or malignant (cancerous).

Malignant tumors, or cancers, that develop in the mesothelium are called mesotheliomas. Over two-thirds of these cancers develop in the pleural mesothelium, and most of the other cases are found in the peritoneal mesothelium. Other places where mesothelioma may develop include the pericardium and the mesothelium surrounding the ovaries, fallopian tubes, or testes.

Benign tumors may interfere with normal functions, but they do not invade other tissues and generally do not threaten life. In contrast, cancers can destroy the

normal tissues in which they arise and invade surrounding structures. Also, cancer cells can break away from a primary tumor and metastasize, or spread, to other parts of the body through the lymphatic system or the bloodstream to form secondary (metastatic) tumors. When viewed under the microscope, the cancer cells that form secondary tumors are usually identical to cells of the primary (original) cancer. As such, these tumors have many of the characteristics of the original cancer, despite being located in another part of the body. These secondary tumors are thus referred to as "metastatic mesothelioma" to indicate that they are all part of a single disease and do not represent new cancers originating in these organs.

Incidence

Mesotheliomas are relatively rare cancers. The National Cancer Institute's SEER (Surveillance, Epidemiology, and End Results) Program estimates an annual incidence of about 1.1 cases per 100,000 population in men and 0.3 cases per 100,000 in women. Only about 1,000 to 1,500 new cases of mesothelioma are diagnosed in the United States each year, as compared to an estimated 152,000 new cases of lung cancer in 1988. Other Western industralized countries have similar incidence rates for mesothelioma.

Mesothelioma occurs most often in white men after the age of 50 but it can appear at any age; cases of mesothelioma have been reported in children as young as 2 years old. The incidence of pleural mesothelioma appears to be increasing among white men older than 55.

Cause and Prevention

The major risk factor for mesothelioma is occupational exposure to asbestos, a group of minerals structurally related to talc that occur naturally as masses of fibers, which can be separated into thin threads and woven. Asbestos is strong, durable, flexible, and fire-resistant, making it useful in a variety of industrial products such as asbestos cement and plastics, insulation, and fabrics. The fiber masses have a tendency to break easily into a dust of tiny particles that can float in the air, stick to clothes, and may be easily inhaled or swallowed. Inhaled particles are carried into the airways of the lung, where they lodge.

Little doubt exists that asbestos exposure can cause mesothelioma as well as lung cancer and asbestosis (a noncancerous, chronic lung ailment). Estimates based on some population studies show that as many as 70 to 80 percent of all patients with mesothelioma have had some documented occupational or environmental exposure to asbestos fibers.

Asbestos exposure had been suspected as a risk factor for mesothelioma since 1943. It was not until 1960, however, that a study of asbestos miners and neighborhood residents in South Africa firmly established the association. Forty-seven cases of mesothelioma were observed among this population within 5 years. Since then, additional population studies have supported the connection between asbestos exposure and mesothelioma, and laboratory studies have shown that asbestos causes cancer in animals.

Since the early 1940's, millions of American workers have been exposed to asbestos dust, including many of the 4.5 million men and women who worked in shipyards during the peak shipbuilding years of World War II. Asbestos was a primary component in the insulation of ships. An increased risk of developing mesothelioma has been found among shipyard workers as well as workers in asbestos mines, asbestos mills and factories, and among workers who manufacture and install asbestos insulation.

The time lag for developing mesothelioma following asbestos exposure is usually 30 to 40 years. Thus, the apparent increase in cases of mesothelioma among white males older than 55 bears out the probable connection to the rise in use of asbestos in factories, shipyards, and other industrial settings that began in the 1940's. Because levels of asbestos in the workplace were not reduced until the 1970's, further increases in the incidence of mesothelioma can be expected for the next few decades. Current workers face smaller risks of asbestos exposure because of Government regulations and improved work practices begun in the 1970's, which permit continued use of asbestos for critical applications but vastly diminish the frequency of airborne asbestos fibers.

Nonoccupational exposure to asbestos also increases the risk of developing mesothelioma. Household contacts of employees who work with asbestos have higher-than-average rates of mesothelioma, lung cancer, and asbestosis, probably as a result of exposure to asbestos dust brought into the home on the shoes, clothing, skin, and hair of workers.

A number of consumer products, ranging from toasters to pipe insulation, contain asbestos. Before 1978, certain types of hand-held hair dryers were made with asbestos to protect the heat casing. In such hair dryers, air forced across the heating coil could become contaminated with asbestos fibers. Questions about these appliances may be directed to the U.S. Consumer Product Safety Commission (CPSC), whose address is listed at the end of this booklet.

Because of its useful properties, asbestos is present in many manufactured products and has a history of widespread use. For example, between 1960 and 1969, over 40,000 tons of fireproofing material containing 10 to 20 percent asbestos were sprayed each year in buildings during construction. Individuals exposed to asbestos from such sources may be at increased risk of developing mesothelioma or other asbestos-related illnesses. Information about how to reduce exposure to asbestos is found in the NCI publication *Asbestos Exposure: What It Means, What To Do.*

Zeolite, a family of mineral fibers of volcanic origin found in Cappadocia, Turkey, and elsewhere, has also been associated with mesothelioma. This finding has led to further questions about the cancer-causing properties of other natural and man-made fibrous materials, but evidence to date is inconclusive. Other studies have shown that exposure to high levels of ionizing radiation may also increase the risk of mesothelioma.

Cigarette smoking, the major cause of lung cancer, has not been shown to be related to the development of mesothelioma. At this time, exposure to asbestos is the only *known* risk factor for mesothelioma.

Detection and Diagnosis

Symptoms

Careful monitoring of individuals who are known to have been exposed to asbestos is critical so that mesothelioma can be detected early enough to permit successful use of current methods of treatment. Pleural mesotheliomas may develop slowly over a period of years, with gradual painless accumulation of fluid in the chest cavity. Eventually, the buildup of fluid causes symptoms, such as shortness of breath and vague chest pain that may radiate to the shoulders or upper abdomen. As the disease progresses, breathing difficulty often increases. Other symptoms may include loss of appetite, fatigue, hoarseness, weakness, and weight loss. If the cancer has spread to underlying organs, such as the heart, lungs, or ribs, bone destruction and soft tissue masses may occur.

Pain and swelling in the abdomen are the most common symptoms of peritoneal mesothelioma. Other symptoms may include nausea, vomiting, bowel and urinary obstruction, swelling of the legs and feet, and fever.

Diagnosis

Because the clinical signs of mesothelioma and the microscopic appearance of the cancer cells are similar to a number of other cancers, diagnosing this disease is often difficult. Diagnosis begins with a review of symptoms and medical history, as well as a complete physical examination. Procedures used to diagnose mesothelioma include chest x-rays for pleural mesothelioma and computed tomographic (CT) scans for both pleural and peritoneal mesothelioma. CT scanning combines x-rays and computer processing to produce pictures of cross-sections of the body.

Confirmation of a diagnosis of mesothelioma depends on microscopic examination of a sample of tumor tissue (biopsy). Sometimes it is possible to obtain samples of pleural tissue with a thoracoscope, a thin, lighted tube inserted through a small incision in the chest. This procedure is usually performed using local anesthesia. The physician can look through the thoracoscope, view the inside of the chest, and collect tissue samples for microscopic examination. A similar procedure called peritoneoscopy can be used to examine the inside of the abdominal cavity and collect tissue samples from the peritoneum. At times it may be necessary to obtain tissue using a surgical procedure called thoracotomy for pleural mesothelioma or laparotomy for peritoneal mesothelioma.

Staging

Once mesothelioma has been diagnosed, it is important to determine the extent (stage) of the disease in order to plan treatment. Although several systems for staging mesothelioma have been proposed, none has proved generally useful. Mesothelioma most commonly spreads by invasion of nearby structures and usually does not metastasize to lymph nodes or other organs until late in the disease. For this reason, many scientists divide mesothelioma into two general stages: localized (limited) mesothelioma and advanced (diffuse) mesothelioma. Mesothelioma is classified as localized when only a single tumor is present or if the cancer is confined to the membrane surface in which it originated (sometimes called intracavitary mesothelioma). Advanced mesothelioma means that the cancer has spread by local invasion or has metastasized to other organs.

Treatment

Mesothelioma is an uncommon disease and accounts for only a small percentage of all cancer deaths. However, at present, standard treatment for all but localized disease is not curative. Because current therapy is rarely effective, all patients are encouraged to consider participation in clinical trials (treatment studies conducted with patients) that are designed to evaluate new approaches to therapy. Information about clinical trials is found on page 8 and in the NCI booklet *What Are Clinical Trials All About?* (see page 9).

Certain recent trends do offer some encouragement for the development of better ways to control this cancer. For example, a greater awareness of the risk of mesothelioma among people exposed to asbestos and improved diagnostic procedures have increased the likelihood of identifying patients with limited disease, which may be more amenable to successful treatment.

Treatment to relieve symptoms for patients with localized or advanced disease may include drainage of fluid with a tube (called thoracentesis—removal of fluid in the chest—and paracentesis—removal of fluid in the abdominal cavity) and use of drugs to prevent further fluid accumulation. Radiation therapy and surgery may also be helpful in relieving symptoms.

Surgery

Patients with localized pleural mesotheliomas may be treated with surgery to remove the cancer and, if possible, an area of surrounding normal tissue. Surgical procedures that may be used include pleurectomy (removal of a portion of the pleura) and pleuropneumonectomy, sometimes called extrapleural pneumonectomy (removal of the lung and its surrounding pleura along with the adjacent portions of the diaphragm and pericardium).

While surgery alone rarely leads to cure of pleural mesothelioma, some studies suggest that a combination of surgery, radiation therapy, and chemotherapy may be of value and should be tested further in patients with pleural mesothelioma. Surgery also may be helpful in relieving symptoms (primarily chest pain and difficulty in breathing) of pleural mesothelioma.

Surgical removal of peritoneal mesothelioma is difficult, because the cancer usually invades many tissue surfaces within the abdomen. However, a recent study indicates that intensive therapy with surgery plus chemotherapy and radiation therapy may be helpful for a small number of patients, whose disease is diagnosed at an early stage. Since these are such rare patients, few surgeons have experience with the complex problems that may arise in the surgical management of limited mesothelioma. For this reason, physicians may refer patients with limited mesothelioma to cancer centers that have an established treatment program for this disease.

Radiation Therapy

Advances in radiation therapy have made it possible to give high doses of radiation with less damage to nearby normal tissue than was previously possible. Even with improved techniques, however, the damage from radiation to nearby organs such as the heart, spinal cord, and esophagus in the chest and the kidneys, intestine, and liver in the abdomen may require lowering the dose of radiation below that needed to kill mesothelioma cells. Localized radiation therapy is sometimes used to help control pain for mesothelioma patients, but this relief is usually temporary.

Chemotherapy

The usefulness of chemotherapy in the treatment of mesothelioma has not yet been established. Studies with single drugs, combinations of drugs, and the addition of drugs to other methods of treatment have produced conflicting and often discouraging results. However, at this time, three drugs appear to have some activity against mesothelioma: doxorubicin (Adriamycin), methotrexate, and cisplatin. Combinations of these drugs have not been shown to be more active than the drugs used singly.

Researchers are searching for new drugs that may prove helpful in the treatment of mesothelioma. In addition, clinical trials are under way to evaluate the usefulness of delivering anticancer drugs directly into the chest or abdominal cavity (intracavitary chemotherapy). This technique makes it possible to expose the cancer to high levels of the drugs while normal tissues such as the liver, kidneys, or bone marrow come in contact with much lower levels (after the drug has been taken up by the bloodstream). In this way, the normal organs are spared from some of the harmful side effects that often occur with the high doses of drugs that are needed to damage cancer cells. Results to date indicate that this technique may be useful for patients with early disease or for patients with more advanced disease when combined with other treatments. Again, additional research is needed to evaluate this approach.

Clinical Trials and PDQ

To improve the treatment for mesothelioma, the NCI supports clinical trials at medical institutions throughout the United States. Patients who take part in this research make an important contribution to medical science and may have the first chance to benefit from improved treatment methods. Physicians are encouraged to inform their patients about the option of participating in such trials. To help patients and doctors learn about current trials, the NCI has developed PDQ (Physician Data Query), a computer system designed to give doctors quick and easy access to:

- the latest treatment information for most types of cancer;
- descriptions of current clinical trials that are accepting patients, including information about the objectives of the study, medical eligibility requirements, details of the treatment program, and the names and addresses of physicians and facilities conducting the study; and
- names of physicians and organizations involved in cancer care.

To access PDQ, doctors may use an office computer with a telephone hookup and a PDQ access code or the services of a medical library with online searching capability. Most Cancer Information Service offices (1-800-4-CANCER) provide PDQ searches and can tell doctors how to obtain regular access to the database. Patients may ask their doctor to use PDQ, or they may call 1-800-4-CANCER themselves to request a search. Information specialists at this toll-free telephone number use a variety of sources, including PDQ, to answer questions about cancer prevention, diagnosis, treatment, and research.

Selected References

The materials marked with an * are distributed free of charge by the NCI. Ordering information is provided at the end of this publication. The other items are not available from the NCI; they can be found in medical libraries, many college and university libraries, and some public libraries.

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**What Are Clinical Trials All About?* Office of Cancer Communications, National Cancer Institute. NIH Publication No. 86-2706.