Biology of Lung Cancer With Implications for New Therapies

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Purpose/Objectives: To provide an overview of the biology of lung cancer with respect to genetic carcinogenesis and specific mutations and to discuss new therapies being developed to target lung cancer's biologic processes.

Data Sources: Published articles, abstracts, book chapters, lectures, and personal experiences with experimental agents.

Data Synthesis: Lung cancer is the number one cause of cancer deaths for men and women in the United States, with minimal changes in the five-year survival rate during the past decade. New understanding of the biologic process of lung cancer is providing potential new therapies that many hope will lead to increased survival for patients with lung cancer.

Conclusions: Exciting new therapies for lung cancer are being developed that target specific biologic processes of lung cancer.

Implications for Nursing: When nurses are familiar with the rationale behind biologic therapies, they can understand the drugs, assess toxicities, and help patients make educated decisions about therapeutic alternatives.

Lung cancer is the leading cause of cancer mortality for men and women in the United States and second only to cardiovascular disease as a cause of death for Americans. The American Cancer Society (ACS) estimates 171,900 new cases of lung cancer for 2003 (ACS, 2003). Smoking remains the greatest contributor to the development of lung cancer; in fact, 90% of all lung cancer cases are thought to be smoking related, with very few nonsmokers developing lung cancer (Greenlee, Hill-Harmon, Murray, & Thun, 2001). Lung cancer is considered to be one of the most preventable diseases because smoking abstinence and cessation drastically reduce its incidence. However, even if 100% of smokers were to cease immediately, new cases of lung cancer would continue to appear for many years because of the long lead time associated with the development of lung cancer (Greenlee et al.).

This article will review the biology of lung cancer and provide information on genetic carcinogensis, specific mutations found in lung cancer, and cells' signaling pathways. New therapies that target the specific biologic processes found in lung cancer will be explored. Further discussion will be provided about clinical trials and nursing implications.

Key Points . . .

- Lung cancer continues to be a leading cause of cancer-related death in the United States for men and women, with five-year survival rates of less than 15% for all types and stages of lung cancer.
- Genetic carcinogenesis in lung cancer produces specific mutations in particular oncogenes and tumor suppressor genes that affect particular biologic characteristics of lung cancer.
- Biologic characteristics particular to lung cancer can be specifically targeted by new therapies, which have the potential to improve the outlook for future patients with lung cancer.

Goal for CE Enrollees:

To further enhance nurses' knowledge of the biology of lung cancer and implications for new therapies.

Objectives for CE Enrollees:

On completion of this CE, the participant will be able to

1. Discuss the biology of lung cancer with respect to genetic carcinogenesis and specific mutations.
2. Describe three new therapies being developed to target lung cancer's biologic processes.
3. Discuss the nurse's role in the education of patients regarding clinical trials.

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Lung Cancer Overview

Clinicians divide bronchiogenic cancer into two subgroups, non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC), formally known as oat cell carcinoma. NSCLC is classified further based on histology into adenocarcinoma (bronchoalveolar cell carcinoma is a variant of adenocarcinoma), large cell carcinoma, and squamous cell carcinoma. Each type of lung cancer has unique biologic characteristics resulting in different responses to different therapies (Ginsberg, Vokes, & Rosenweig, 2001).

Lung cancer is associated with very poor outcomes, and treatments remain far from curative. Five-year survival rates for all stages of lung cancer remain a dismal 15%, with little improvement during the past decade (ACS, 2003). Mortality from lung cancer in the United States greatly exceeds that of AIDS. Poor survival rates probably are occurring because 85% of lung cancers present at an advanced stage (ACS). Like most cancer, lung cancer has the potential to be cured by surgery if it is detected when the disease is localized. Unfortunately, no current effective screening tools have been shown to detect disease at an early stage and prolong survival. Because most patients are asymptomatic until disease is advanced, they frequently present at a stage where treatment is not likely to be curative (Ginsberg et al., 2001).

Genetic Carcinogenesis

Lung cancer is thought to arise from bronchial epithelial cells. Once a malignant cell is produced, that single, mutated cell may develop into a tumor. This process is known as clonal expansion. No single mutation has been found to cause cancer; rather, multiple mutations in oncogenes and tumor suppressor genes are necessary in the development of malignancies. As tumors develop, cancer cells continue to mutate, gaining a growth advantage over normal cells. This produces continued mutant cancer cells that are even more malignant in their behavior, resulting in further proliferation, development of a blood supply (a process known as angiogenesis), metastasis, and drug resistance. This process, known as genetic carcinogenesis, is a continuum beginning with dysplasia and ending with an advanced malignancy (Sekido, Fong, & Minna, 2001).

Genes and Genetic Mutations

Studies of familial clusters of lung cancer have not found any substantial genetic influence, implying that very few lung cancers are inherited. However, all cancers are genetic diseases caused by abnormalities in the genetic mechanisms that control cell growth (Devereux, Taylor, & Barrett, 1996). Only 5%–10% of heavy smokers develop lung cancer, implying that some individuals' genetic susceptibility to developing cancer is greater than others' (Devereux et al.). The majority of genetic mutations are thought to be caused by environmental exposure to carcinogens, including viruses and chemical, dietary, and physical factors. Cigarette smoke alone contains more than 4,000 chemicals and 55 known carcinogens (Yuspa & Shields, 2001). Genetic susceptibility may involve individual variability in genes that encode proteins that are responsible for activation and detoxification of environmental carcinogens. An inherited variability may exist in other genes, such as tumor suppressor genes and oncogenes involved in DNA repair and cell growth, that may influence a person's susceptibility to developing lung cancer (Devereux et al.).

Genes contain particular sequences of DNA that encode directions for the synthesis of particular proteins that have specific functions. Each gene encodes directions for the synthesis of a different protein. Mutations are mistakes in DNA replication that are not corrected and result in failure of appropriate protein synthesis. Carcinogenic mutations usually occur in genes encoding proteins that control cell growth, cell death (apoptosis), or DNA repair. These genes are divided into two classes: oncogenes, which are important in the promotion of growth, and tumor suppressor genes, which are important in DNA repair or entry into apoptosis (Stetler-Stevenson & Kleiner, 2001).

Oncogenes

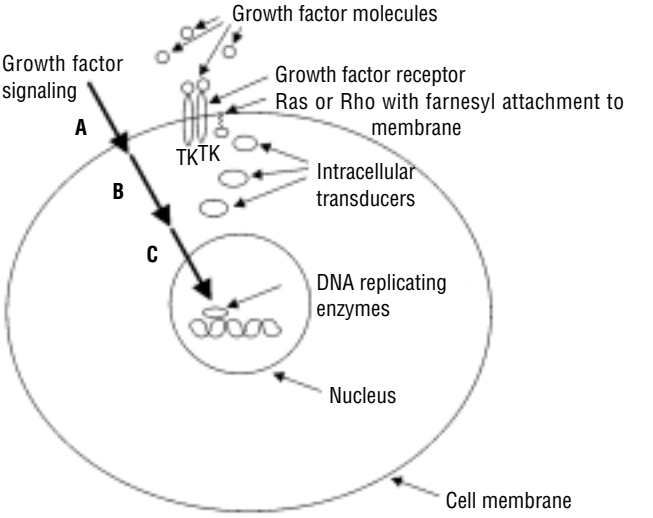
Oncogenes contain protein products that are involved in the regulation of cell growth. If a gene is mutated, every protein molecule encoded by that gene will be defective, resulting in a nonfunctioning or dysfunctional protein. Defective proteins involved in the regulation of cell growth can lead to inappropriate cell proliferation and dysplasia (Templeton & Weinberg, 2001). Oncogenes do not necessarily have to be mutated to cause problems; they also can be activated by several mechanisms to result in overexpression that can lead to malignancy through increased production of oncogenes' protein. Oncogenes also can be mutated in a way that their protein products become constitutively active, meaning they are essentially perpetually "turned on," resulting in an unremitting growth signal for the cell (Eskens, Stoter, & Verwelij, 2000).

Growth Signaling Pathway and Signal Transduction Inhibitors

Several drugs that target growth-signaling mechanisms implicated in carcinogenesis are being studied in preclinical and clinical trials. Signal transduction refers to the process of communicating growth signals from the extracellular environment to the inside of the cells. This process involves growth factor receptors on the cells' surfaces that bind with growth factors released from other cells. The growth factor binding effects change in the cells, leading to DNA replication in the nucleus followed by mitosis. Figure 1 illustrates the growth factor signaling pathway. When a growth factor binds to its receptor, it activates the receptor. The active receptor is a tyrosine kinase. The tyrosine kinase places a phosphate group on nearby small molecules called Ras or Rho. These phosphate groups activate Ras or Rho, which can activate other cytoplasmic molecules called transducers. The growth signal thereby is passed through the cytoplasm to the nucleus. These events culminate in DNA replication followed by mitosis. Different therapies are targeting different steps along this pathway, with the goal of interfering with the inappropriate growth signal that leads to uncontrolled cell growth (Sekine & Saijo, 2001).

Growth Factors and Growth Factor Receptors in Lung Cancer

Normally, growth factors and growth factor receptors control cell growth in a rational way, initiating cell growth only when it is needed. In many cancers, growth factors and growth



Growth factor signaling begins outside of the cell (**A**) where molecules of growth factors are present. The signal is transmitted to the inside of the cell when growth factor molecules (e.g., epidermal growth factor) bind to growth factor receptors (e.g., epidermal growth factor receptor). The growth factor receptors are tyrosine kinase enzymes that are activated when growth factor is bound to them. The tyrosine kinase activity is a signal that activates adjacent small molecules called Ras or Rho. These molecules, in turn, activate cytosolic signaling molecules (transducers) that transmit the growth factor signal to the nucleus (**B**). In the nucleus, the receipt of the growth factor signal (**C**) causes a series of events including duplication of the chromosomes by DNA replicating enzymes and culminating in mitosis, the splitting of the parent cell into two daughter cells.

Figure 1. The Growth Factor Signaling Pathway

factor receptors are thought to influence inappropriate malignant growth because they are overexpressed. This means that many more molecules of a particular growth factor or growth factor receptor are made by the cancer cells than is normal, resulting in a strong, constant growth signal. Research in lung cancer has identified several overexpressed or inappropriately expressed growth factors, including platelet-derived growth factor, insulin-like growth factors 1 and 2, *erbB2* oncogene, and, notably, epidermal growth factor. Overexpression of the epidermal growth factor receptor encoded by the *erbB1* gene is more common in NSCLC than SCLC and has been found to have a critical role in transmitting growth signals to the nucleus. Like other growth factor receptors, the epidermal growth factor receptor is a tyrosine kinase and is involved in the growth-signaling pathway. As noted previously, activation of this pathway leads to increased proliferation and decreased apoptosis. This role makes these receptor tyrosine kinases a promising target for therapy (Hodgson & Maher, 1999).

Tyrosine kinase growth factor receptors are one of the first steps in the internal signaling pathway that activate cell growth (Baringa, 1997). Tyrosine kinase inhibitors or antibodies to their receptors are being developed for therapeutic use as a means of inhibiting activation of the intracellular pathways by growth factor receptors as explained below (Bunn, Soriano, Johnson, & Heasley, 2000).

Epidermal Growth Factor Receptor

Drug development has been targeted to the epidermal growth factor receptor to interrupt the growth pathway. The antiepidermal growth factor receptor murine monoclonal antibody 225, which has been chimerized as C225 (cetuximab), is an example of a therapeutic antibody that has been developed to target the epidermal growth factor receptor. This antibody competes with epidermal growth factor for binding to epidermal growth factor receptor (Rowinsky, 2001). Preliminary results have demonstrated activity in renal cell carcinoma that usually responds poorly to all therapies. Numerous other antibodies and inhibitors against the epidermal growth factor receptor are in development and are showing promise as potential therapies for the future. Iressa® (ZD 1839, AstraZeneca Pharmaceuticals, LP, Wilmington, DE) and Tarceva™ (OSI-774, Genentech, Inc., South San Francisco, CA) are two small molecules that inhibit the tyrosine kinase enzymatic activity located on the cytoplasmic portion of the epidermal growth factor receptor and other growth factor receptors. These drugs are not completely specific for epidermal growth factor receptors and also may inhibit the tyrosine kinase activity of other growth factor receptors. They currently are being studied in clinical trials that include patients with lung cancer. As previously mentioned, 70% of NSCLCs overexpress epidermal growth factor receptor, so these strategies have particular importance for lung cancer (Green, Murray, & Hortobagyi, 2000; Sekine & Saijo, 2001).

ErbB2 Growth Factor Receptor

Overexpression of the growth factor receptor ErbB2 (also known as HER2-neu) is found in approximately 30% of all lung cancers and almost half of adenocarcinomas of the lung (Korrapati et al., 2001). The *erbB2* gene is duplicated (amplified) many times in some cancers; when multiple copies of the gene's protein product (ErbB2) are created, this process is called overamplification. ErbB2 overexpression is associated with a poorer prognosis in NSCLC as well as in breast cancer. ErbB2 overexpression is being studied for use as a prognostic indicator as well as a target for therapy. ErbB2 is a cell surface growth factor receptor related to the epidermal growth factor receptor that transmits growth factor signals from outside the cell into the cytoplasm, initiating the growth process. When amplification occurs, it results in overexpression of the receptor, and a much stronger growth signal exists (Bunn et al., 2000).

The humanized monoclonal anti-ErbB2 receptor antibody trastuzumab (Herceptin®, Genentech, Inc.) was developed to target ErbB2 receptors. Trastuzumab was found to be more effective in combination with chemotherapy than as a single agent. Clinical trials currently are under way to identify the efficacy of trastuzumab combined with chemotherapy for use in HER2-neu receptors overexpressing adenocarcinomas of the lung. Most of the trials are in the early phases, and results will not be available for some time (Green et al., 2000).

Ras Oncogenes

Three types of Ras proteins are known, H-ras, K-ras, and N-ras; however, their individual significance has yet to be determined (Bunn et al., 2000). Mutations of the *ras* genes are found in 20%–40% of NSCLC (Eskens et al., 2000) but rarely with other types of lung cancer. The presence of a K-ras point mutation has been found to correlate with decreased survival rates in patients with completely resected lung cancer. The result of mutant Ras expression is a constitutively activated protein product. This means that the protein is transmitting a

growth signal continually and no longer has an "off switch." Other genes, similar to the *ras* gene, produce protein products with similar function to Ras. One of these genes, called *rho,* also may be involved in promoting malignant behavior of cancer cells (Templeton & Weinberg, 2001).

Farnesyl Transferase Inhibitors

The Ras and Rho proteins are attached to the inner aspect of the plasma membrane through a farnesyl group. The enzyme that attaches the farnesyl groups is called farnesyl transferase. If the Ras or Rho proteins are unfarnesylated, they are not associated with the membrane and are not active. Several drugs have been developed that inhibit the enzyme that attaches the farnesyl group. These are called farnesyl transferase inhibitors (Eskens et al., 2000). Farnesyl transferase inhibitors are thought to prevent the farnesyl groups from being added to the Ras or Rho proteins, therefore stopping the signal transduction pathway that contributes to carcinogenesis. This theory about the mechanism of action appears to have changed from the original one that Ras was the most important farnesylated protein affected by farnesyl transferase inhibitors. Farnesyl transferase inhibitors also affect other farnesylated proteins, including RhoB and centromere-binding proteins. Farnesyl transferase inhibitors currently are being studied in clinical trials with various stages of lung cancer (Cox, 2001).

Tumor Suppressor Genes and the Apoptosis Pathway

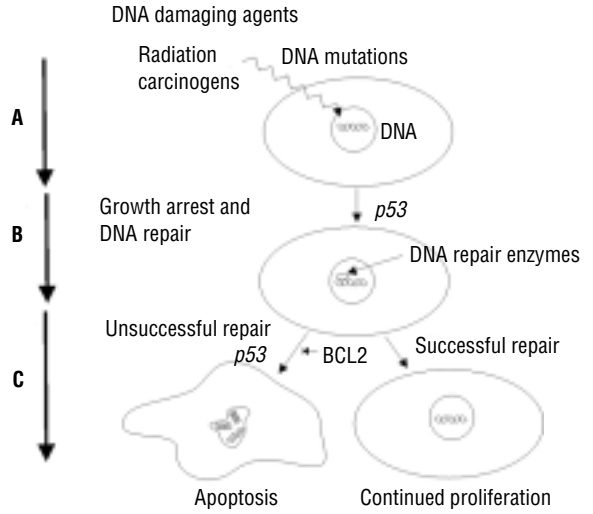
Tumor suppressor genes' protein products normally suppress malignant transformation and tumor formation. Some of these are important in the repair of damaged DNA, and others control entry into apoptosis. A loss of tumor suppressor genes has been found in many epithelial cancers, including lung cancer (Sekido et al., 2001).

Apoptosis

Apoptosis is the process of programmed cell death. It is a normal part of tissue dynamics. Many normally developing tissues eliminate senescent and mutated cells by consigning them to "commit suicide" through apoptosis. Cancer cells have the ability to escape apoptosis. Figure 2 illustrates the apoptosis process beginning with DNA damage and ending in either apoptosis or successful repair. The *p53* protein product plays a key role in apoptosis and is thought to direct cells down the pathway to apoptosis when the DNA damage cannot be repaired. According to Hodgson and Maher (1999), *BCL2* is an antiapoptotic gene that has been found to be overexpressed in 75%–95% of SCLCs, approximately 35% of squamous cell carcinoma and 10% of adenocarcinoma. Because *BCL2* is antiapoptotic, these cells also have a low rate of apoptosis. Because of the important role *p53* and *BCL2* genes play in regulating apoptosis, they are a current focus for the development of therapy. *p53* gene therapy has been ongoing for some time, and therapies involving *BCL2* are entering clinical trials.

p53 Tumor Supressor Gene

p53 is the most commonly lost tumor suppressor gene, and it is being studied in many solid tumors. The *p53* gene can be mutated at many different points with different types of lung



(**A**) DNA damaging agents, such as radiation or carcinogens, induce DNA mutations. (**B**) Through activity of *p53,* the cell enters a period of growth arrest, during which DNA repair enzymes repair the damaged DNA. (**C**) If the repair is successful, the cell can re-enter the proliferation pathway and continue to divide. If the repair is unsuccessful, *p53* will direct the cell to go into apoptosis. Apoptosis is a type of cellular suicide, during which the DNA fragments and condenses, the nuclear membrane develops irregularities, and the cell dies. Malignant cells frequently have nonfunctional *p53,* so the growth arrest and DNA repair period that are supposed to follow DNA damage do not occur and the cell replicates its DNA with mutations in place. In some cancers, the protein BCL2, which inhibits the entry into apoptosis, is inappropriately expressed. In these cells, BCL2 prevents cells with DNA damage from entering the apoptotic pathway. In addition, many people with a predisposition to cancer frequently have ineffective DNA repair enzymes, so mutations are incompletely repaired.

Figure 2. The Process of Apoptosis

cancer, with each mutation leading to its own biologic effect. *p53* mutations were found to be present in 80% of lung cancers (Bunn et al., 2000) and may be related to carcinogens in tobacco smoke that cause specific *p53* mutations whose products are inactive. Gene therapy to replace the mutated *p53* gene with an inactive one currently is being studied; however, researchers are encountering many barriers. Perhaps the biggest obstacle at this point is the systemic delivery of gene therapy and the cost of research. The IV route is not effective because the immune system detects the gene as foreign and eliminates it (Baringa, 1997). However, gene replacement therapy with the wild-type *p53* gene in animal studies has inhibited experimentally produced lung cancer. Early phase trials are under way in humans, with *p53* genes being injected directly into subcutaneous metastatic lesions or delivered to lung tumors bronchoscopically via an adenovirus vector (Bunn et al.).

Metastasis Pathways

Metastasis is a complex process by which cancer spreads to distant sites. Tumor cells must have the ability to invade the surrounding basement membranes and adjacent structures. The cells enter the blood or lymphatic vessels, a process known as intravasation. The cancer cells must have the ability to survive in the blood stream, escape the immune

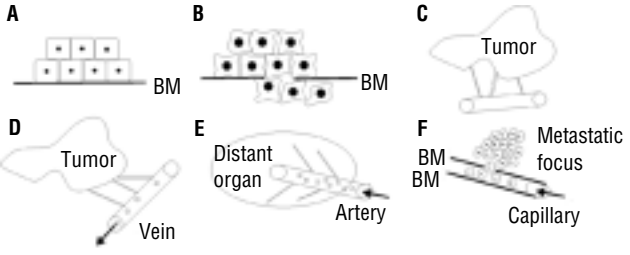
system's surveillance, and ultimately extravasate into a new site. Once this is accomplished, cancer cells require the ability to establish a new site and develop a blood supply, a process known as angiogenesis. Then, cancer cells must proliferate to become a metastatic focus. Tumors cannot thrive without a blood supply once they reach 1–2 mm^3 volume (Fong, Sekido, & Minna, 1999). Figure 3 illustrates the steps in metastasis. The process is very complicated, and not much is known about why some cancers metastasize whereas others do not. However, each step in the process can prevent or limit metastasis and provides potential targets for therapy. Because most patients die from their metastatic disease, this area is worthwhile to explore (Templeton & Weinberg, 2001).

Matrix Metalloproteinase Inhibitors

Matrix metalloproteinases are enzymes used by cells to destroy the basement membrane of surrounding tissue so that cells can invade adjacent tissue. They also may be used by invading blood vessels that are being formed in the process of angiogenesis. Lung cancer cells produce matrix metalloproteinase and can induce their neighboring cells to do so as well (Bunn et al., 2000). Matrix metalloproteinase inhibitors currently are being studied in clinical trials. Hess and Abbruzzese (2001) reported that preliminary results have been disappointing; however, these studies involved the use of matrix metalloproteinase inhibitors with advanced lung cancer and other advanced cancers. Perhaps the tumor burden may be too significant to affect change with any therapy. These compounds may be effective in earlier stages of cancer before the metastatic cascade begins.

Angiogenesis

Vascular endothelial growth factor and other angiogenic factors stimulate endothelial cell growth that is necessary for angiogenesis. Research has demonstrated that angiogenesis inhibitors prevent tumor growth in animals. Lung cancers are associated with an increase in vascular endothelial growth factor expression and increased angiogenesis. Multiple angiogenesis inhibitors, such as the drug thalidomide, and natural inhibitors of angiogenesis, such as endostatin and angiostatin, currently are being investigated (Bunn et al., 2000). Most of the compounds being studied are in the early stages of clinical trials (i.e., phase I and II), and it will be some time before effects on overall survival will be determined.



BM—basement membrane

(**A**) Normal epithelial cells are arranged regularly on a basement membrane. (**B**) Cancer cells are arranged irregularly and are able to cross the basement membrane by secreting enzymes, such as matrix metalloproteinases, which break down the basement membrane. (**C**) Tumors stimulate angiogenesis (i.e., the formation of new blood vessels) from existing vessels. (**D**) Tumor cells gain entry to blood vessels (i.e., intravasation) and exit the tumor site in the venous circulation. (**E**) Tumor cells enter a distant organ through the arterial supply. (**F**) Once in the distant organ, metastatic tumors cells can exit capillaries (i.e., extravasation) by breaking down the basement membrane, invade surrounding tissues, and form metastatic foci.

Figure 3. The Metastatic Process

Nursing Implications

Less than 5% of all patients with cancer participate in clinical trials, slowing the process of evaluation of new therapies. Oncology nurses need to educate themselves as well as their patients about the option of participation in clinical trials. Nurses must take a leadership role in helping patients identify potential therapies that may benefit them. The National Cancer Institute's Web site (www.cancer.gov) is an excellent resource for healthcare professionals and patients. Nurses and patients can access this site and find an international database of cancer clinical trials that are open to enrollment. The Physician Data Query (PDQ) area of this site allows users to search for clinical trials using a variety of search criteria, including specific types of cancer (e.g., lung cancer) or specific therapies under investigation. PDQ offers the latest information on cancer treatment, screening, prevention, genetics, supportive care, and clinical trials.

Many centers currently are participating in clinical trials involving new therapies, and nurses are involved in the coordination of these trials. Nurses will administer these biologic therapies in trials and as standard therapies in the future. Nurses must familiarize themselves with the rationale behind biologic therapies so that they can help patients make informed decisions. Moreover, they must understand the drugs and assess their toxicities. Nurses are the primary source of education for patients and must serve as patient advocates by providing as much information as possible about treatment options, including clinical trials.

Conclusion

Lung cancer has reached epidemic proportions in the United States and, despite smoking cessation efforts, will continue as a major cause of morbidity and mortality for some time to come. Resources should focus on preventing smoking and developing new treatments. Although prevention is the key to the control of lung cancer for the future, new cases will continue for some time because of the long latency for lung cancer development in smokers. Typical patients presenting with lung cancer have advanced disease and only a 15% chance for five-year survival. As the scientific community learns more about the process of genetic carcinogenesis and tumor progression, it is able to develop new therapies that will become the standard therapies of tomorrow. Research must continue to provide new understanding of the biology and pathogenesis of lung cancer. Many new therapies directed at biologic targets are under investigation with some promising results.

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For more information . . .

- Lung Cancer Online
  www.lungcanceronline.org
- Alliance for Lung Cancer Advocacy, Support, and Education
  www.alcase.org
- Lung Cancer Awareness Campaign: It's Time to Focus on Lung Cancer
  www.lungcancer.org

Links can be found using ONS Online at www.ons.org.

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