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WOMEN'S HOSPITAL

Mary Horrigan Connors Center
For Women's Health and Gender Biology

HARVARD
MEDICAL SCHOOL
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Out of the Shadows
Women and Lung Cancer

Women's Health Policy and Advocacy Program

A FOUNDING MEMBER OF PARTNERS HEALTHCARE

Out of the Shadows

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Forward

Lung cancer kills more women than any other cancer – nearly 200 women each day. Most die within a year of diagnosis. Yet lung cancer remains the "hidden" women's cancer – little known and rarely discussed. It is the least funded cancer in terms of research dollars per death of all the major cancers, and one of the only cancers where patients are routinely blamed as responsible for their condition.

To bring lung cancer "Out of the Shadows," the Mary Horrigan Connors Center for Women's Health and Gender Biology has developed this first comprehensive overview of women and lung cancer. The Women's Health Policy and Advocacy Program gratefully acknowledges the Lung Cancer Alliance for its encouragement and assistance in this endeavor, and for its commitment to making this report a focal point for broader public health policy debate on women and lung cancer.

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Executive Summary

Lung cancer is the leading cause of cancer death in women and men in the United States, taking more lives each year than breast, prostate, colon and pancreatic cancers – *combined*. In 2010 alone, approximately 70,500 women will die from the disease. The financial toll of lung cancer is significant – about $9.6 billion is spent in the U.S. each year treating the disease, mostly during late stages when survival is highly unlikely. Despite lung cancer's strong association with tobacco use, one in five women who develop the disease has *never* smoked.

Lung cancer develops differently in women and men. There are sex differences in many facets of the disease, including risk factors, clinical characteristics, progression and length of survival. For example:

- Women who have never smoked appear to be at greater risk for developing lung cancer than men who have never smoked.
- Women tend to develop lung cancer at younger ages than men.
- Women are more likely than men to be diagnosed in early stages of lung cancer.
- Women are likely to live longer than men after treatment for the disease.

Research on sex differences in lung cancer is far from conclusive, but holds promise to change the landscape of this disease. Mounting research suggests that genetic, hormonal, behavioral and environmental factors are influencing the different patterns of lung cancer in women and men. A better understanding of the role these factors play can advance preventive, diagnostic and therapeutic practice and improve outcomes from this disease.

Lung cancer is at the dawn of a new frontier. Recent years have witnessed extraordinary advances in treatment, including minimally invasive surgery and targeted genetic therapies (sometimes called "smart drugs") that may replace traditional chemotherapy in treating certain forms of the disease. However, the lack of widespread screening – even for individuals at high risk from lung cancer – means that few patients are captured early enough in the disease's progression to realize the benefits of these advances. Computer-aided detection may enhance the accuracy and speed of radiologic screening, and biomarker tests that utilize blood, urine, sputum and breath to identify individuals at high risk are under investigation. Investments in these areas may help to reduce the social and financial toll of lung cancer in women and men. However, considerable political, scientific and financial barriers remain.

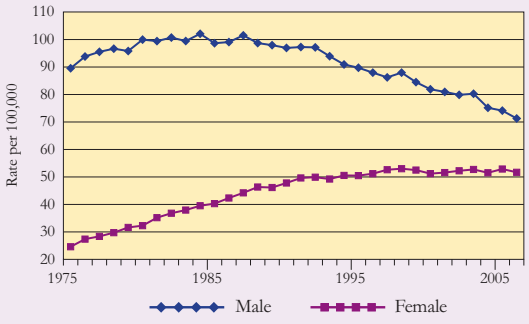
This report summarizes existing research on sex and gender differences in lung cancer, highlights gaps in current knowledge and recommends steps to reduce the burden of this disease in women and men. It is intended as a tool for public health advocates, researchers, clinicians, patients and policy leaders.

I. Introduction

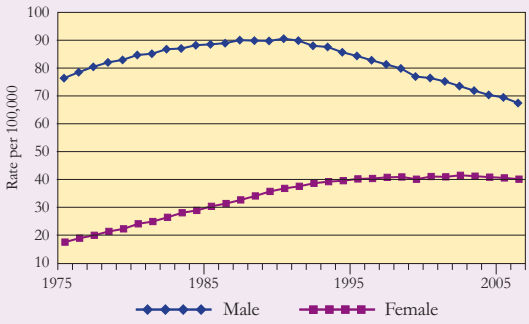
Lung cancer, once rare among women, surpassed breast cancer in 1987 to become the leading cause of cancer death among women in the United States.[1] Today, one in four cancer deaths in U.S. women is due to lung cancer.[2] A common misconception is that breast cancer takes the lives of more women than lung cancer, but this is not the case – more women are diagnosed annually with breast cancer, but lung cancer kills more women each year than any other malignant tumor.[2] In 2009, it is estimated that 70,490 women in the U. S. died from this disease.[3] Approximately $9.6 billion is spent in the U.S. each year on treatment of lung cancer.[4]

Lung cancer rates have historically been higher in men than women, but this gap is narrowing. While the *incidence* of lung cancer in men has declined, the incidence of women developing lung cancer has increased six-fold over the last 30 years.[5] Over the same period, the *death* rate from lung cancer has declined in men, while the death rate from lung cancer in women increased from the mid-1970s through 2003, only recently leveling off. [6]

U.S. Lung Cancer Incidence Rates
1975–2006



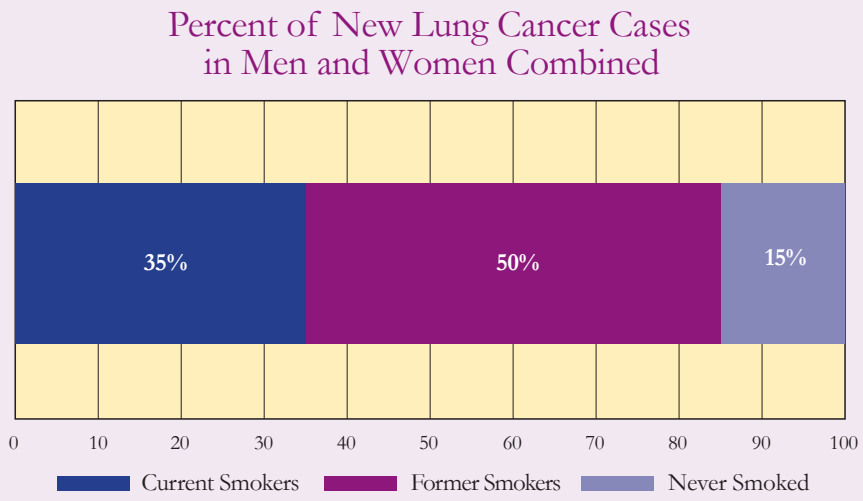
U.S. Lung Cancer Mortality Rates
1975–2006



Source: National Institutes of Health, National Cancer Institute, Surveillance Epidemiology and End Results

According to some experts, these trends partly reflect past tobacco smoking patterns of women and men.[7,8] Historically, smoking was less acceptable among women than among men. Women began to smoke in large numbers decades later than men as social norms changed. Because lung cancer is diagnosed an average of 20 to 30 years after exposure to tobacco carcinogens,[9] some experts believe we are observing the effect of women's later cigarette use on lung cancer incidence, particularly among women who were teens and young adults when they started smoking.[10] Smoking prevalence among women is lower than among men; 18 percent of women currently smoke versus 23 percent of men.[11] However, smoking among men has declined much more dramatically than among women over the past 40 years – the number of male smokers has decreased by about 50 percent since the 1960s, while the number of female smokers only decreased by 25 percent during the same time period.[12,13]

Changes in smoking behavior alone cannot fully explain the rise in the number of new lung cancer cases among women. Specialists report that the disease is increasing among young women who have never smoked (such as Dana Reeve, the widow of "Superman" actor Christopher Reeve).[5,14,15] One in five women and one in twelve men diagnosed with lung cancer today have never smoked; women with lung cancer who have never smoked outnumber their male counterparts three to one.[8,20] As a separate disease category, lung cancer deaths in never-smokers ranks as the sixth to eighth deadliest cancer in the U. S. and the seventh deadliest cancer worldwide.[16] Overall, over 60 percent of new lung cancer patients are either never smokers or former smokers, and the majority of those who have never smoked are women.[17,18,19]



Sources: Tong A. et al [17] Waren E, et al[18]; Jemal, A, et al[19]

Policy Implications. Mounting research suggests that the pattern and course of lung cancer differs between women and men, and that genetic, hormonal, behavioral and environmental factors are involved. A better understanding of the role these factors play will advance preventive, diagnostic and therapeutic practice and improve outcomes from this disease.[20]

The following sections highlight the most important sex and gender differences in lung cancer risk, screening, treatment and survival, along with implications for future research and public policy.

"Lung cancer takes more lives each year than breast, cervical and prostate cancers combined."

II. Lung Cancer Risk Factors

Clinical Characteristics of Lung Cancer

Lung cancer forms in the tissues of the lungs, but may spread to other organs of the body. It results from an uncontrolled growth of abnormal cells in one or both lungs. Unlike normal lung cells, cancer cells do not develop into healthy tissues; they instead become tumors that may gradually damage the lung and ultimately compromise its ability to supply oxygen to the rest of the body.[21, 22]

Most lung cancers fall into one of two primary groups: small cell lung cancer (SCLC), or non-small cell lung cancer (NSCLC). SCLC is the more rapidly progressing form of the disease, is largely inoperable, and constitutes 10 to 20 percent of lung cancer cases. The remaining 80 to 90 percent of cases are considered NSCLC, which includes a number of subtypes, particularly *squamous cell lung cancer* and *adenocarcinoma*.[23] Each of these subtypes has distinct cancer cells that grow and spread in different ways. Adenocarcinoma, though once rare, is now the most common type of lung cancer in men and women of all ages, particularly among young people who have never smoked.[24] Scientists do not yet understand why the incidence of adenocarcinoma has risen so dramatically.

Sex vs. Gender Differences in Risk

An individual's risk of developing lung cancer may be shaped by a combination of sex- and gender-related factors.[25] *Sex-related factors* refer to biological differences such as variation in genetic susceptibility and hormone levels between men and women, whereas gender-related factors refer to patterns of behaviors that are influenced by social and cultural notions of femininity and masculinity. *Gendered health behaviors* may include the age of men and women when they start smoking, the way they smoke (how many cigarette puffs are taken and how deeply smoke is inhaled) and the type of cigarette smoked, or even occupation and proximity to toxic cooking fumes.[26]

Smoking and Tobacco Exposure

Smoking is the single most important cause of lung cancer in the U.S., and is linked to an estimated 90 percent of lung cancer deaths in men and nearly 80 percent in women.[36] Many other exposures have been associated with lung cancer, but even their combined effect is small compared to that of cigarette smoking. Additional causal factors are primarily related to occupational and environmental exposures to agents such as asbestos, radon, arsenic, chromium, and nickel.[37,38] Some segments of the U.S. population, such as military veterans, may have specific carcinogenic exposures that increase their lung cancer risk, either combined with cigarette smoking or independently.[3]

Although the link between smoking and lung cancer is indisputable, whether women and men differ biologically in their susceptibility to smoking-related lung cancer remains fiercely contested. Some studies find that once the amount of smoking is taken into account, there is little evidence that female smokers are more likely to get lung cancer than their male counterparts.[40,41] Other studies show that female smokers have a greater risk of developing the disease at every level of smoking exposure, suggesting that women may be more susceptible to the carcinogenic effects of tobacco smoke.[42,43]

Approximately 20,000-25,000 people who have never smoked are diagnosed with lung cancer in the U.S. each year; more than 60 percent are women.[2] Many women with lung cancer, particularly the subtype adenocarcinoma, have never smoked or stopped smoking long ago. As noted earlier, over 60 percent of people diagnosed with lung cancer are non-smokers, a population that includes people who have *never smoked* as well as *former smokers.*[20] Among never-smokers who develop lung cancer, women are more likely to develop the disease than men.[2] In one major study, lung cancer incidence rates in women aged 40 to 79 who had never smoked ranged from 14 to 21 cases per 100,000 person-years, whereas incidence rates in men ranged from 5 to 14 cases per 100,000 person-years.[14]

While it is still unclear why never-smoking women have a relatively greater risk, their susceptibility may be associated with exposure to second-hand smoke,[44,45] a history of previous lung diseases,[46,47] and the influences of certain hormonal and genetic markers.[48] A recent study examining the prevalence of a defective tumor-suppressing gene may also explain the development of lung cancer in never-smokers. Researchers found that approximately 30 percent of non-smokers who developed lung cancer had the same rare variation in a tumor-suppressing gene that limited the gene's tumor-suppressing ability.[49] This research is a promising breakthrough in understanding lung cancer in never-smokers. The prevalence of lung cancer among never-smokers highlights the multiple and complex factors involved in the development of this disease.

Cigarette Marketing Towards Women During the 1990s, much outcry arose against the RJ Reynolds tobacco company, the maker of Camel cigarettes, for its use of a cartoon ("Joe Camel") in marketing cigarettes to children.[27,28] In a 1997 landmark victory for opponents of aggressive tobacco marketing, RJ Reynolds was ordered to stop the use of cartoon characters in association with its tobacco products.[29] Until recently, tobacco companies had continued to market to children in more insidious ways[28] and had remained virtually unchallenged in their marketing towards young girls and young adult women.[30,58] In order to influence young girls and women into smoking, tobacco companies sold cigarettes with fashionable names using sophisticated colors, often packaged with free products aimed at girls and women.[31]

Beyond the packaging itself, tobacco companies for decades had forcefully marketed "low-tar," "light" and "mild" cigarettes towards girls and women, always in connection with the claim that cigarettes help control weight gain.[32] Furthermore, tobacco companies rely heavily on social marketing to women, linking the consumption of cigarettes to confidence, sexuality, beauty and stress reduction.[78,32] Such marketing may have unintended mental health consequences; the association between smoking and depression is stronger in women than in men.[32]

The *Family Smoking Prevention and Tobacco Control Act*, signed into law on June 22, 2009, will give the Food and Drug Administration more authority to control cigarette marketing. The new law will prohibit the use of fruit-flavorings and clove in cigarettes as well as the marketing of tobacco products with "light," "mild" and "low-tar" labels.

Menthol Cigarettes Tobacco companies have also employed flavor additives, most notably menthol, to attract women and African Americans to their products. Menthol cigarettes are often marketed in association with messages of refreshing taste, youthfulness and fun, health and medicinal benefits and feminine aura.[33] Many popular women's cigarettes, including Virginia Slims, include menthol additives.

The popularity of menthol cigarettes in the African American community is alarming; over 70% of African American smokers prefer menthol cigarettes to non-menthol cigarettes.[34] Cigarette manufacturers heavily advertise menthol cigarettes in African American communities. They use African American models, and have marketed menthols with free gifts meant to appeal to African American women (i.e. hair oils and makeup).[34] The popularity of this type of cigarette among African Americans and women is especially worrisome because individuals who smoke menthols are more likely to inhale deeper, increasing exposure to nicotine and tobacco smoke.[35]

Biological and Genetic Influences

In addition to family and smoking history, there is accumulating evidence that hormonal influences and *genetic markers* may influence the onset of lung cancer, either acting independently or interacting with the effects of smoking. These include:

Hormonal Influences Studies have found a possible connection between hormones such as *estrogen* and lung cancer development, particularly adenocarcinoma.[50,51] In both men and women, estrogen primarily helps regulate certain functions of the reproductive system, but also is involved in other non-reproductive functions such as cell division and growth. Researchers believe estrogen can directly or indirectly promote lung cancer by triggering *estrogen receptors* that are present on non-small lung cancer cells, causing these cells to grow and spread in the lungs.[52,53]

Hormone Replacement Therapy Given the association between hormone replacement therapy (HRT) and breast cancer, understanding HRT's impact on lung cancer is important but also complex. The landmark Women's Health Initiative study concluded that in post-menopausal women, combined estrogen and progesterone HRT did not increase the risk of developing lung cancer. However, women who took combined HRT had an increased risk of dying from lung cancer, specifically after developing NSCLS.[54] Several less rigorous studies have also looked at a possible link between combined HRT and the risk of developing lung cancer, but the results have been mixed. These findings call for careful consideration before using HRT for women who have been diagnosed with lung cancer or who are already at high risk of developing lung cancer, including smokers.

Molecular and Genetic Markers Several *molecular and genetic markers* are thought to predispose some people to lung cancer. For instance, the process by which the *gastrin-releasing peptide receptor* (GRPR) becomes activated has been identified as a potential risk factor. Gastrin-releasing peptide is a protein that normally plays a role in cell growth, but has been associated with the development of a variety of cancers, including lung tumors. One study showed that GRPR is activated more frequently, at an earlier age and with lower exposure to tobacco smoke in women compared to men.[55] Furthermore, since the gene for GRPR is located on the X-chromosome, the authors have suggested women may be more vulnerable to the effects of smoking because they have two X-chromosomes and potentially two functional copies of the gene for GRPR.

Women also appear to have more frequent changes than men in another protein called *epidermal growth factor receptor* (EGFR).[56,57] EGFR can be found on the surface of some cells and, like GRPR, may cause them to divide and grow. However, abnormally high levels of the protein have also been found on lung cancer cells, indicating they may help to spread lung cancer in the body.[58]

Other research studies have reported that changes in the DNA of cells in the lungs can influence the development of cancer. DNA is the chemical in cells that contains genetic information and instructions on how cells function.[23] Changes in certain genes such as p53 and Rb, which work to stop tumors from forming in the body, may put people at an increased risk for developing lung cancer.[59,60,61] Another important risk factor is the absence or deletion of a gene called *GTSM1*, which normally makes toxic agents, including tobacco carcinogens, less harmful to the body. People with non-functioning GTSM1 – particularly female smokers – seem to have a greater susceptibility to the disease.[62]

Exposure to tobacco smoke contributes to many genetic changes and mutations in the lung. Interestingly, women appear to have significantly more DNA damage and mutations, even if they smoke less than men.[63,64,65] Such genetic changes may influence the development of tumors by affecting the body's capacity to break down and remove tobacco carcinogens in the lungs.[66,67] Additionally, experts have reported that women may be less able to repair DNA damage than men, which could make them more likely to have lung cancer.[68]

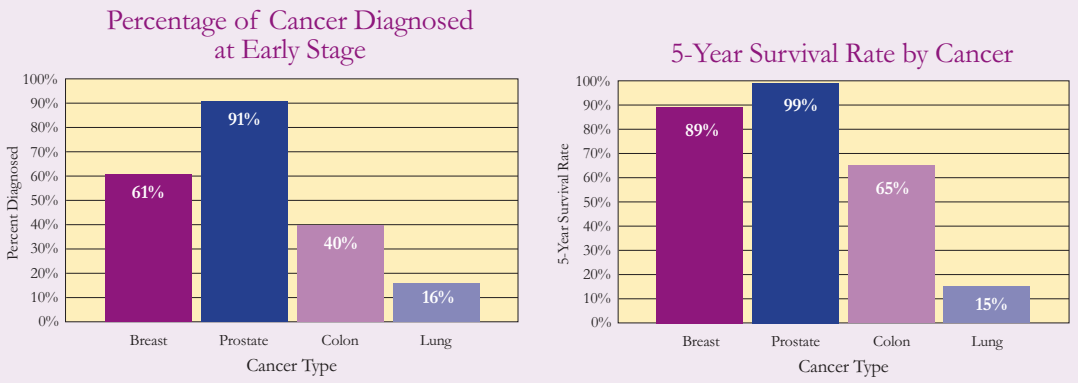
Policy Implications. Although mounting evidence indicates that an individual's risk of developing lung cancer is shaped by a combination of sex- and gender-related factors, the precise role and interaction of hormonal and genetic influences, environmental exposures and smoking history is still under investigation. Given the significant rise in lung cancer in women over the past 30 years, further research on the complex interactions of these agents is vitally needed.

"There is accumulating evidence that hormonal factors and genetic markers influence lung cancer."

III. Lung Cancer Screening

The goal of screening is to detect cancer before symptoms become evident. The ideal screening test would find cancer early, even at pre-cancerous stages, and would be able to predict which cancers are likely to cause death. Cancer screening has not yet achieved this gold standard, however, and controversy remains even over widely-utilized tests such as mammography and prostate-specific antigen (PSA).

Unlike breast and prostate cancer, which utilize mammography and PSA respectively, there is no widely accepted screening protocol for lung cancer. It is therefore uncommon, outside of clinical trials, to detect lung cancer in its earliest, most treatable stage.[69,70,71] Only 16 percent of lung cancer patients are diagnosed before their disease has metastasized (spread to other parts of the body), compared to over 60 percent of breast cancer patients and over 90 percent of prostate cancer cases.[72] A number of these are incidental (unintentional) diagnoses resulting from a chest X-ray or computerized tomography (CT) scan ordered for reasons other than lung cancer screening. The lack of early detection, even for patients at high risk of developing the disease, is likely a key contributor to lung cancer's very low 5-year survival rate.



Sources: National Institutes of Health, National Cancer Institute, Surveillance Epidemiology and End Results

In addition to its potential for detecting tumors at early, treatable stages, lung cancer screening may have benefits in terms of risk reduction – one study found a voluntary quit smoking rate of 23 percent after CT screening, compared with the national average of 5 percent without screening.[73]

"There is no widely accepted screening test for lung cancer."

Tools for Detecting Lung Cancer

Currently, radiologic imaging tests such as x-ray and CT are the only available screening tools for lung cancer. X-rays produce flat, two-dimensional images while CT scanners take x-rays from multiple angles to construct three-dimensional images. CT scans can be analyzed and measured with greater accuracy than x-rays, and are consequently the best currently available tool for detecting early-stage tumors. Computer-aided detection (CAD) methods may enhance the accuracy and efficiency of CT screening and are under investigation. A recent European study incorporating a new CAD program recently reported unprecedented levels of 95 percent *sensitivity* (accurately detecting disease) and 99 percent *specificity* (accurately ruling out disease) in screening participants at high risk for lung cancer.[74]

Several new diagnostic tools are in early stages of investigation, including biomarkers tests that examine urine, blood, sputum or tissue samples for abnormal levels of certain substances.[75] For example, a new urine test may predict which smokers are most likely to develop lung cancer by checking the level of a chemical called *NNAL* in urine samples.[76,77] NNAL is produced when the body processes a carcinogen found in tobacco smoke. A blood test, *EarlyCDT-Lung*, has recently become available in the United Kingdom and to selected physicians in the U.S. to help with early detection.[78] This type of test looks for the presence of antibodies that circulate in the blood in reaction to proteins released from cancerous tumors, even in the localized stage.[79,80,81] These tools may have several advantages over radiologic screening, including enabling identification of individuals at high risk for developing lung cancer and allowing for careful monitoring and early treatment of pre-cancerous nodules. Biomarker tests also show promise for avoiding over-diagnosis by distinguishing which nodules are likely to become deadly cancers, eliminating costly and potentially harmful, unnecessary treatment.

While biomarker screening may some day pave the way for widespread and inexpensive personalized risk assessment, it is unclear whether or when they may become available to the public. Patients are advised to discuss their individual risk for lung cancer, as well as the benefits and risks of radiologic screening, with their physician.

The Debate over Lung Cancer Screening

As seen with recently revised recommendations for mammography, cancer screening guidelines can generate considerable medical, scientific and public debate.[82] Questions regarding the benefits, risks and costs of lung cancer screening, even for individuals at high risk of developing the disease, have not been definitively resolved. Some debate stems from differences in measurement of outcomes, such as whether screening increases *survival time* (the period between diagnosis and death) or whether it successfully reduces *mortality* (death rates) from the disease. Critics argue that screening may increase survival time, because a tumor is detected earlier, without reducing death rates from the disease. Some experts suggest that repeated exposure to CT scans over a period of years may result in unacceptably high levels of radiation exposure, although current radiologic studies utilize doses comparable to or just higher than a typical mammogram.[83,84] There is also concern that some nodules detected through screening may not become clinically significant, causing patients unnecessary risk, anxiety, cost and intervention.

Despite these concerns, research shows that CT scanning is effective in detecting lung cancer at clinical stage I, when the disease is most treatable and the likelihood of 5-year survival is greatest.[85] The National Institutes of Health estimates that about 70 percent of women whose cancers are detected at stage I are still alive 5 years later. Similarly, a recent first-ever study employing actuarial analysis to evaluate the effect of early detection on mortality concluded that early-stage diagnosis could significantly lower lung cancer mortality, perhaps saving as many as 70,000 lives in the U.S. each year.[86]

Policy Implications. Such complex factors as the length of time needed to measure mortality, varying research methodologies and the rapid pace of medical innovation have led to conflicting findings regarding lung cancer screening and left many critical questions unresolved. The good news is that emerging technologies are beginning to identify tumors at increasingly microscopic levels, while at the same time management of early stage disease is rapidly advancing. This has created unprecedented optimism for improving outcomes for lung cancer. Because the disease is so lethal and affects large numbers of patients, a sense of urgency is needed to resolve the multiple dimensions of this issue.

Sex Differences in Lung Cancer Screening

Little research has been conducted on differences between women and men in the methods and benefits of lung cancer screening.[87] However, since women and men develop different forms of lung cancer, with distinct cell types, some experts suggest that radiological imaging screening may not perform in the same way for each sex. When screening is offered, women tend to have better compliance than men, possibly because women undergo more frequent cancer screening throughout their lives (i.e. mammograms and pap smears for breast and cervical cancer). As technology for lung cancer screening evolves, recommendations may eventually differ for women and men based on different patterns of disease and treatment efficacy.

IV. Lung Cancer Treatment and Survival

The first course of treatment for patients with early stage, localized NSCLC is typically surgery to remove cancerous tumors or cells. Those who cannot tolerate surgery or are in more advanced stage of the disease are candidates for chemotherapy and/or radiation therapy, as well as *clinical trials* (research studies that help to evaluate new treatments). For certain subtypes of lung cancer, new treatment options are emerging in the form of targeted therapies taken orally, which may reduce side effects and replace more invasive remedies.

Sex Differences in Treatment Modalities

Although surgical recommendations are determined by the type and stage of lung cancer, the choice of treatment modality seems to differ between women and men. In a national surveillance database covering a 25-year period, researchers found that a higher proportion of women underwent surgery to treat lung cancer, whereas radiation therapy was more frequently administered to men.[88] The authors noted this difference might be due to male patients being older and presenting with more co-morbidities than women. However, more research is needed to fully understand why women and men undergo different treatment courses and what effect this has on survival rates for both sexes.

Women's Survival Advantage

Women with lung cancer tend to survive the disease longer than men.[89] Lung cancer is known for its poor prognosis – just 16 percent of patients survive 5 years after diagnosis. However, women generally live longer than men at every stage of the disease, regardless of the stage at diagnosis, type of lung cancer, or treatment choice.[90,91]

Studies show that following surgical resection, women with NSCLC experience superior 5-year survival compared with men.[92,93,94] However, the reasons for this disparity are unclear. Some studies have identified common subtypes of lung cancer or differences in stage of the disease as possible explanations. In addition, women tend to present at earlier stages of the disease, increasing the chances that surgical resection will result in complete removal of the tumor, and thereby increasing survival.[95] However, studies that adjust for these factors report that being female remains an independent factor to longer survival following surgery.[93] For both women and men, complete lobectomy (removal of an entire lobe of the lung) results in higher survival than smaller resections. In addition to female gender and lobectomy, younger age and smaller tumor size are positive predictors of survival.[94]

Similarly, women with NSCLC who are treated with *neoadjuvant chemotherapy* (chemotherapy prior to surgical removal of the tumor) experience better survival rates than men.[86] This survival advantage remains for women with advanced lung cancer of any tissue type who undergo chemotherapy treatment.[96] Radiation therapy also seems to be more effective in some subsets of women with NSCLC. A study examining radiation therapy and NSCLC survival rates found that women with stage 1 NSCLC who were not candidates for surgery had better overall survival after undergoing radiation therapy.[97]

Women diagnosed with SCLC also appear to fare better than men, but the reasons for this survival advantage are not yet well understood.[98,99] Additional investigation is needed to understand the interplay of factors contributing to women's survival advantage in all types and stages of lung cancer, and to improve survival rates for women and men.

Advances in Lung Cancer Treatment

Advances in targeted therapies for lung cancer over the past decade are changing the course of the disease. The frontier of lung cancer surgery continues to advance with developments in robot-assisted procedures, as well as advances in Video Assisted Thoracoscopic Surgery (VATS). VATS has gained popularity in recent years as a minimally invasive method of removing or biopsying lung tissue through a small incision in the chest. Research shows that a VATS lobectomy results in less pain, fewer perioperative complications and shorter duration of hospital stay as compared to previous, more invasive methods.[100]

Molecular-level treatments – sometimes called "smart drugs" – also show promise for improving the quality of life and survival of lung cancer patients at multiple stages of the disease, either in combination with surgery and/or chemotherapy or alone. New drugs are in clinical trials for both early-stage and advanced lung cancer.[101, 102]

Policy Implications. The lengthy and rigorous process to evaluate the risks and benefits of new therapies leaves uncertain when these agents may be approved and become available to patients not enrolled in clinical trials. Moreover, the lack of funding for lung cancer research, discussed below, impedes the rate at which new therapies are discovered, tested and deployed. That considerable strides that have occurred even with limited resources suggest there is potential to revolutionize lung cancer treatment. Combined with improvements in diagnostic screening, there is reason to be optimistic about improving outcomes for patients with lung cancer for the first time since the "War on Cancer" was declared in 1971.

"Advances in targeted therapies for lung cancer are changing the course of the disease."

Sex Differences in Targeted Therapies

Targeted agents allow doctors to consider the specific characteristics of a patient's tumor, including the *gene mutations* or *proteins* found in his or her cancer cells, to determine the best possible course of treatment. Current approaches focus on inhibiting certain cancer-causing mutations and blocking *growth factor receptors* that are normally involved in cell division and survival, but may also help lung cancer cells grow and spread.

One of the most promising molecular targets in lung cancer is *epidural growth factor receptor gene* (EGFR). Mutations in EGFR are more common in women who have never smoked and in those with adenocarcinoma of the lung.[103] Recent studies show that treatment with a drug that specifically targets the EGFR mutation, *erlotinib* (marketed as Tarceva), can prolong survival in patients with NSCLC.[104] Erlotinib inactivates the signal in the mutated EGFR that makes lung cancer grow.[105] Women who receive erlotinib have longer survival without progression of lung cancer and longer survival overall than men.[106] Patients who have never smoked, have adenocarcinoma, or are of Asian ethnicity also show better response rates to this drug than other patients.[107]

Another target, called *vascular endothelial growth factor receptor* (VEGFR), contributes to the growth of new blood vessels that feed tumors. A recent study showed that the addition of *bevacizumab* (marketed as Avastin), a VEGFR inhibitor, to the standard chemotherapy regimen in patients with recurrent or advanced NSCLC resulted in a two month survival advantage over those who received chemotherapy alone.[108] However, this survival advantage was not seen in women.[109]

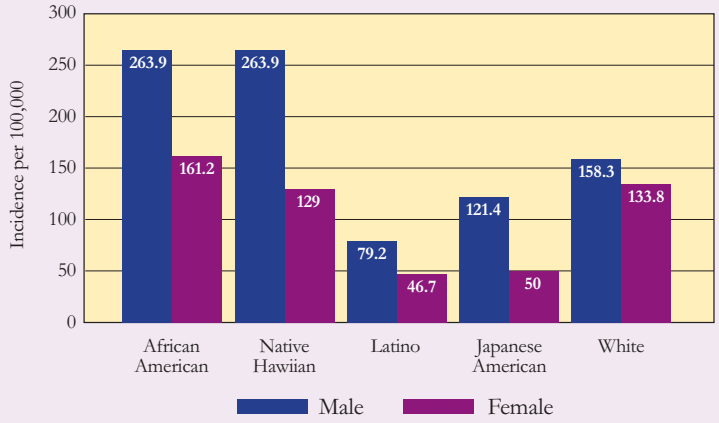
Vandetanib, a new drug targeting both EGFR and VEGFR in NSCLC is currently in clinical trials and shows promise as a future treatment.[110, 111]

With the success of targeted treatment for EGFR-positive lung cancers, researchers continue to search for other molecular targets of therapy. A recently identified target, the fusion gene *EML4-ALK*, has been shown to be more common in NSCLC in non-smokers.[112, 113, 114] Patients with the EML4-ALK mutation are younger and more likely to be male when compared to those with EGFR-positive tumors.[115] In one study, patients with the EML4-ALK mutation showed resistance to drugs that target EGFR, demonstrating the need for different treatment options depending on mutations present.[116]

V. Racial and Ethnic Differences

Just as there are differences between men and women in lung cancer risk, progression and survival, there is significant variation among racial and ethnic groups in their experiences with lung cancer. In the U.S., African Americans and Native Hawaiians have higher incidence rates of lung cancer compared to whites, while Japanese Americans and Hispanics have lower incidence rates.[117] Patterns of smoking behavior vary between each group, but there is not a direct correlation between rates of smoking and rates of lung cancer, indicating that biological factors are influencing development of the disease.[117]

Lung Cancer Incidence in Men and Women by Race



Source: Haiman CA, Stram DO, Wilkens LR, Pike MC, et al. Ethnic and racial differences in the smoking-related risk of lung cancer. *N Engl J Med.* 2006 Jan 26;354(4):333-42.

As a population, Hispanics have the lowest incidence of lung cancer of all major ethnic groups. Because they traditionally smoke cigarettes at lower rates than whites, lung cancer rates for Hispanics are about 50 percent lower than rates for whites.[118] Unlike other racial and ethnic groups, where the incidence of lung cancer among women has increased, the incidence of lung cancer among Hispanic women in the U.S. has declined; from 1994 – 2003, the rate decreased by about 1.5 percent per year.[118] This may be due in part to an influx of Hispanic immigrants, who are more likely to be non-smokers.[118] Despite an overall decline in incidence in both sexes, lung cancer remains the leading cause of cancer death among Hispanic men and the second leading cause of cancer death among Hispanic women.[118] Cigarette smoking accounts for 70 percent of lung cancer cases in Hispanic women.[119]

African Americans have the highest overall rates of lung cancer compared with other racial and ethnic groups, but the burden is not evenly distributed between the sexes. African American men have higher rates of lung cancer incidence and mortality than any other population[120] and are about 40 percent more likely to develop lung cancer than white men.[121] However, the incidence of lung cancer among African American women is virtually the same as for white women (54.6 vs. 54.9 per 100,000).[122] This is an alarming statistic considering that smoking rates among African American women are lower than smoking rates among white women – in 2007, about 16 percent of African American women smoked, while the rate among white women was about 20 percent.[123] In addition, African Americans smoke fewer cigarettes per day (an average of 12) than whites (daily average of 18). Similar disparities exist for non-smokers; African American women who have never smoked have higher death rates from lung cancer than white women who never smoked.[117] Incidence rates among African American women are rising about 0.8 percent each year, while among African American men incidence rates have declined since 1984.

In addition to having higher incidence rates than whites, African Americans as a population have a lower 5-year survival rate (12 percent versus 16 percent).[117] The poorer survival may be attributable to disparities in access to health care as well as different patterns of treatment for the disease. African Americans are less likely to have insurance coverage than whites.[124] Several studies have found that African Americans are less likely to receive care in the same amount of time as whites and may not receive the most effective treatment for their subtype of cancer.[125] One study found that African Americans patients underwent surgical resection less frequently than white patients (69 percent versus 83 percent).[126] Other reasons underlying the disparities in treatment patterns include differences in pulmonary function;[127] provider biases;[128] inadequate physician-patient communication;[129] distrust of the health care system and physicians;[130] and a greater likelihood of refusing surgery.[131] Such factors may impact survival and death rates, but do not explain the higher incidence of the disease in the African American population.

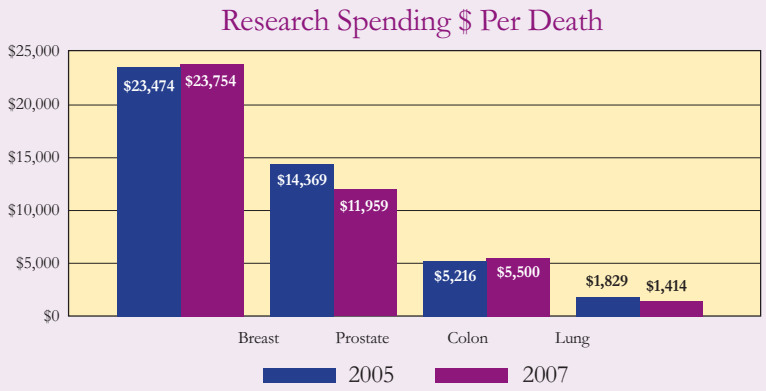
Policy Implications. Complex interactions among race, sex, smoking patterns and environmental exposures are implicated in lung cancer risk, incidence and mortality in varying populations. Different rates of lung cancer between men and women are evident across all major racial and ethnic groups in the U.S. At the same time, significant disparities exist between racial and ethnic populations. African American and Native Hawaiian smokers appear to be at significantly greater risk of developing the disease than whites, Hispanics and Asian Americans. Both biological and behavioral factors are likely contributors to these disparities. A multifaceted approach combining research on genetic mutations as well as targeted public health interventions will be needed to reduce risk and mortality among all racial and ethnic populations.

"Although smoking rates among African American women are lower than among Caucasian women, the incidence of lung cancer is the same."

VI. Lung Cancer Research

Disparities in Cancer Funding

Although lung cancer is the leading cause of cancer death for women and men, federal research funding lags behind other major cancers and many common diseases. For fiscal year 2009, the three major federal agencies that support medical research – the National Institutes of Health, Centers for Disease Control and Prevention and Department of Defense – allocated just $1,249 in research funding per lung cancer death. In contrast, they devoted $27,480 per death for breast cancer research and $14,336 per death for prostate cancer.[132] Federal research funding per cancer death is, based on some estimates, approximately 21 times greater for breast cancer and 13 times greater for prostate cancer than for lung cancer research.[133] Between 2003 and 2007, the National Institute of Health's funding of lung cancer research through the National Cancer Institute actually decreased while funding for breast cancer research increased.[133]



Sources: NIH Research Portfolio Online Reporting Tool; CDC Appropriations; DOD Cancer Research Funding; Surveillance, Epidemiology and End Results Program; CDC National Vital Statistics Report, Final Data for 2006.

Similar differences exist in funding for lung cancer prevention. In the Centers for Disease Control and Prevention's FY 2008 budget, $201,261,000 was allocated toward breast cancer while approximately $104,000,000 was allocated toward smoking cessation (not lung cancer specifically).[134] While preventing tobacco use is a critical goal in reducing lung cancer, an estimated 17,000 to 26,000 patients diagnosed each year have never smoked or already stopped smoking.

The effects of current funding gaps are undeniable when comparing five-year survival trends for cancer over the past 30 years. Between 1975 and 2003, the five-year survival rate for all cancers combined improved from 50 percent to 66 percent; in that period, breast cancer survival rose by 14 percent to 89 percent, prostate cancer survival rose by 30 percent to 99 percent, and ovarian cancer survival increased by 8 percent to 45 percent.[135] In that same time frame, the five-year survival rate for lung cancer increased just 3 percent to 15 percent overall.[136] Possibly because there are so few survivors, lung cancer advocacy has not gained traction as a movement demanding attention and research dollars as successfully as other cancer lobbies have.

Researchers and advocates agree that the stigma attached to lung cancer contributes to underfunding of research on the disease.[137] Because smoking is associated with the majority of lung cancers, people suffering from the disease are thought to be responsible for their own illness, and consequently not deserving of the same unconditional sympathy or research investments as patients affected by other deadly illnesses. This attitude may extend to clinicians who care for lung cancer patients as well. One study found that physicians were less likely to send lung cancer patients with advanced disease to an oncologist than they were to refer breast cancer patients, and that breast cancer patients were more likely to be referred for further therapy whereas lung cancer patients were referred only for symptom control.[138] As outlined in this report, however, more complex factors are involved in the development of lung cancer than cigarette smoking alone, including biological, metabolic and hormonal influences, environmental exposures and social norms. The lack of funding for lung cancer research over the past 30 years has significantly hindered the ability of researchers to understand why and how this disease progresses in different populations. Funding for early detection is a particularly crucial need, as the benefits of effective new treatments for early stage disease cannot be fully realized until lung cancer is found in patients before the disease has progressed.

Areas for Further Study

Recent years have seen major advances in diagnostic and treatment options for lung cancer. However, there is a critical need for new research across the spectrum of the disease. Areas of high priority for funding include:

- The rising trend of lung cancer in younger women who have never smoked;
- Genetic, hormonal, environmental and social influences on lung cancer risk in multiple populations;
- Sex differences in sensitivity to carcinogenic agents such as tobacco smoke and environmental toxins;
- Development of simple and inexpensive screening tests to detect early lung cancer;
- Targeted biotherapies for all stages of the disease;
- Interdisciplinary collaboration and advocacy.

Policy Implications. Expanding research funding for lung cancer is vitally needed to ensure optimal care for patients, improve their chances of survival and reduce the high financial and social burden of this disease.

VII. Lung Cancer and Health Policy

Understanding sex differences in lung cancer is a growing and vital area of research. Today, one in every 16 women will develop lung cancer in her lifetime.[139] Evidence suggests there are key differences between women and men with lung cancer which have implications for prevention and treatment of the disease. There is urgent need to conduct basic and clinical research that can translate knowledge of sex and gender influences into preventive, diagnostic, and therapeutic practice to confront this disease.[20] At the same time, renewed efforts toward smoking cessation and prevention must be embraced.

Federal Legislation

Advocates are working to reverse disparities in lung cancer research. In 2008, a milestone was achieved when Congress approved the first-ever dedicated federal funding for lung cancer. The *Peer Reviewed Lung Cancer Research Program*, administered and funded by the Department of Defense, was appropriated $20 million for FY 2009 and $15 million for FY 2010 to fund early detection and disease management. The program's priority is the development of integrated components to identify, treat and manage early curable lung cancer in military men and women at high risk for the disease.

Additional legislation now pending in Congress would build on this early success. The *Lung Cancer Mortality Reduction Act of 2009* (S.332, HR.2112) would authorize a comprehensive, multi-agency research effort to cut lung cancer's mortality in half by 2016. The first year of the five-year bill would provide at least $75 million to the Secretaries of Health and Human Services, Defense and Veterans Affairs to develop a comprehensive and coordinated research program.

The *21st Century Cancer ALERT Act* (Access to Life Saving, Early Detection, Research and Treatment) (S.717), introduced by Senator Kay Bailey Hutchinson (R-TX) and the late Senator Ted Kennedy (D-MA), addresses the entire continuum of cancer care, including prevention and early detection for those most at risk through support for innovative initiatives and new technologies such as biomarkers and imaging. A coalition of "lethal cancer" organizations – those cancers with 5-year survival rates of less than 50 percent, including lung cancer – are working to establish a special additional research program within this bill when it is introduced in the House of Representatives.

"The stigma attached to lung cancer contributes to underfunding of research for the disease."

These bills are pending at the confluence of two important trends: (1) an increase in the incidence of lung cancer in women, particularly younger women who have never smoked; and (2) advances in targeted, personalized treatment that could benefit patients who are found in the early stages of disease. Unfortunately, the conclusion reached by the Lung Cancer Progress Review Committee of the National Cancer Institute in 2001 that lung cancer has been funded far below its public health impact will persist as long as federal funding remains uncertain.

Policy Recommendations

The barriers to advances in lung cancer are as much political as scientific. Lung cancer carries a stigma almost unheard of with any other deadly disease, hindering the unconditional support and investment of resources afforded to patients with other serious conditions. The relatively small number of survivors, coupled with patients' experiences of blame and shame, impede the ability of advocates to develop momentum around the disease. The public also underestimates lung cancer's impact – 67 percent of respondents in one study stated that breast cancer is the leading cause of death in women, while only 30 percent correctly indicated that lung cancer causes the most cancer deaths.[140] These factors have contributed to significant funding disparities in cancer research. Given additional investment, the scientific community could expand efforts to understand the disease so that women and men both may realize lower incidence and improved prognoses. Without dedicated resources, lung cancer will continue to be under-funded relative to other cancers, hampering discoveries that could expand prevention and treatment for this disease.

The increased incidence of lung cancer in women, particularly younger non-smokers, is cause for alarm and should be a priority within the public health community. Removing the stigma of lung cancer as a "self-imposed" disease is a threshold step in reversing years of blame and neglect for the disease and achieving needed gains – including reduced incidence and mortality and enhanced screening and treatment options. The following eleven strategies are urged to improve outcomes for the disease:

1. Increase public awareness of risk factors, incidence, mortality rates and screening and treatment options for women and men.

2. Reverse the stigma of lung cancer among the public, caregivers and clinicians through education, dialogue and awareness.

3. Invest in research on sex differences in lung cancer and facilitate translation into clinical practice.

4. Enable federal funding of lung cancer research across the spectrum of the disease, emphasizing early detection and research on why and how the disease progresses in different populations. Improve inter-agency coordination to maximize results.

5. Refine screening technologies, including radiological and biomarker tests, to detect the deadliest cancers while still in the earliest stages. Investments in computer-aided detection and biomarkers tests that utilize blood, urine, sputum and breath are essential.

6. Advance early detection protocols through pilot programs, patient and provider education, and reimbursement policies.

7. Encourage individuals at high risk of lung cancer – including former smokers, first degree relatives of lung cancer patients, and those with protracted exposures to lung carcinogens such as Agent Orange, radon or asbestos – to speak with their doctors about the risks and benefits of screening.

8. Support research and development of early-stage, targeted therapies to improve survival rates and facilitate the development of personalized treatment.

9. Promote genetic testing of tumors as a routine diagnostic tool so that more patients can benefit from new therapies that target specific genetic mutations.

10. Eliminate racial and ethnic disparities in lung cancer through research on targeted treatment of individual tumors, improved health care access and culturally competent public health interventions.

11. Expand advocacy efforts through outreach, collaboration and coordination among policy leaders, clinicians, researchers, patients and lung cancer advocates.

Lung cancer advocacy is experiencing new momentum after years of neglect. Around the U.S., organizations devoted to increasing awareness, expanding research and providing support for patients and families are growing in capacity and effectiveness. It will be critical for advocates to collaborate with the public health, clinical and policy communities in efforts to make progress against this disease.

VIII. Lung Cancer Across the Globe

Future Trends in Lung Cancer Worldwide

The extraordinary rise in lung cancer in American women in the 20th century will be repeated in developing countries without considerable efforts to curb the widespread use of tobacco. In many countries, socio-cultural constraints that previously discouraged smoking in women are weakening. In China, for example, approximately 20 million women have started smoking over the past decade, while aggressive marketing campaigns targeting women in Japan have doubled smoking among women. These trends are troubling, and are likely to result in a significant burden of lung cancer in these nations in the future. In addition, if U.S. trends foretell global patterns, we may also see a rise in lung cancer among women in developing nations that is not attributable to smoking, but is grounded in a combination of toxic exposures in an increasingly industrialized culture as well as genetic and hormonal influences.

The unchecked rise in lung cancer incidence in women in the U.S. should serve as a warning and call to action for policy leaders at every level of governance. Despite enormous strides in scientific understanding of sex- and gender-based influences that have led to promising new screening and treatment modalities, lung cancer remains in the shadow of other high-profile diseases. The growth in knowledge has not yet led to a decrease in the death rate from this disease; among women, the incidence of lung cancer continues to increase. Improved knowledge of sex differences in this most deadly cancer can guide health care delivery and health policy, paving the way for improved outcomes for women and men alike.

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Out of the Shadows

About the Mary Horrigan Connors Center

The Mary Horrigan Connors Center for Women's Health and Gender Biology is an innovative interdisciplinary clinical, research, education and policy program in women's health whose mission is to improve the health of women and transform their medical care.

For more information, please see https://www.brighamandwomens.org/connorscenter

About the Women's Health Policy and Advocacy Program

The Women's Health Policy and Advocacy Program is a non-partisan initiative striving to inform the policy process, building on clinical experience and sex- and gender-based knowledge, to improve health and health care for women.

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