BRIGHAM AND
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Mary Horrigan Connors Center
for Women's Health and Gender Biology

Lung Cancer: A Women's Health Imperative

The Connors Center for Women's Health and Gender Biology and the Division of Women's Health at Brigham and Women's Hospital, led by Paula A. Johnson, MD, MPH, are committed to improving the health of women and transforming their medical care through the discovery, dissemination, and integration of knowledge of women's health and sex- and gender-based differences and the application of this knowledge to the delivery of care. We are committed to building awareness of issues related to women's health and gender biology among clinicians, patients, and the general public, advocating for changes in public policy to improve the health of women, and advancing the field of women's health globally by developing leaders with the experience and skills to have a major impact on improving the health of women. For more information, please see www.brighamandwomens.org/connorscenter.

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Lung Cancer: A Women's Health Imperative

A Report of the Mary Horrigan Connors Center for Women's Health and Gender Biology at Brigham and Women's Hospital

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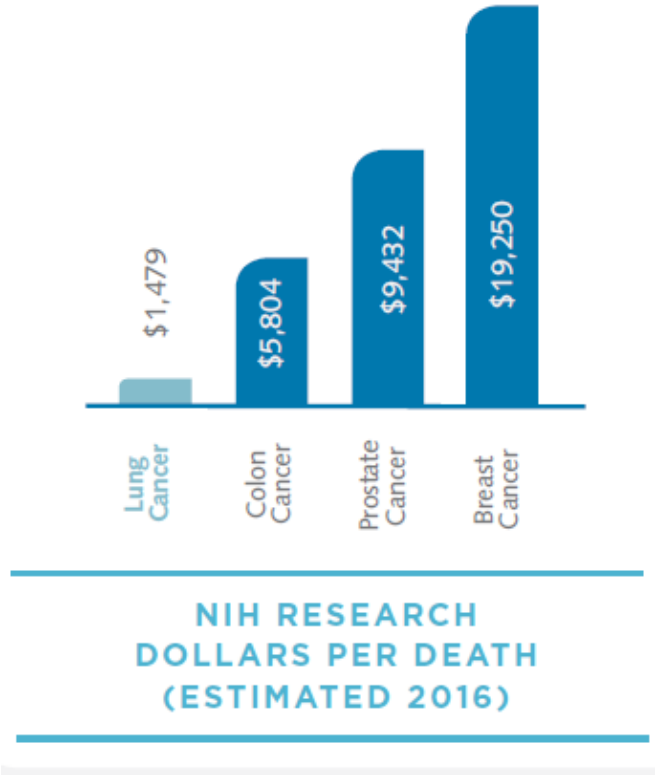
EXECUTIVE SUMMARY

Lung cancer is the number one cancer killer of women both in the U.S. and around world. The disease is the second most common cancer among women and kills more women in the U.S. each year than breast, ovarian, and uterine cancers combined. The American Cancer Society estimates that, in 2016, 106,470 women in the U.S. will be diagnosed with lung cancer and more than 72,000 women will die from the disease. Despite substantial improvements in the overall survival rates for many cancers, including prostate (99.3%), breast (90.8%), and colon (66.2%), lung cancer survival rates have only risen to 18.8% over the past three decades up from13.2%. Despite the impact of the disease, funding for lung cancer research lags far behind funding for other types of cancer (see Graph 1).

Graph 1



Source: Lung Cancer Alliance. 2016 Lung Cancer Facts. 2016.

Five years ago, our groundbreaking report, *Out of the Shadows: Women and Lung Cancer*, created awareness of the issue of lung cancer in women. Since then, new lung cancer guidelines, screening technologies, and targeted therapies put us on the verge of radical improvements in

lung cancer survival. Part of that medical innovation comes from sex and gender-specific research which demonstrates that there are notable differences in lung cancer between men and women:

- Women are at higher risk for lung cancer due to such factors as genetic susceptibility and hormonal impact.
- Sex hormones, particularly estrogen, influence lung cancer risk, development, and mortality.
- Controversy persists on whether women who smoke are more likely than men to develop lung cancer suggesting a need for additional research.
- Although smoking is an important risk factor for lung cancer, one in five women who develop lung cancer have never smoked, and non-smoking women are three times as likely as non- smoking men to get the disease.
- Women have higher five-year survival rates than men across all ages with comparable stages of lung cancer.

While scientists have begun to unlock knowledge on how sex- and gender-specific genetic, hormonal, behavioral, and environmental factors influence patterns of lung cancer in women compared to men, more research is needed. Despite evidence of the importance of sex and gender differences in lung cancer, women—particularly those from racial and ethnic minorities—are still less likely to be enrolled in lung cancer clinical trials than men. Even when studies do include women, researchers often fail to analyze data by sex- or gender-specific factors, such as hormone status, making it difficult to uncover differences in incidence, prevalence, survivability, and treatment responses between men and women.

In this report, we hope to bring greater awareness to the impact lung cancer has on women. We also hope to show that a national strategy to address the study of sex- and gender-specific aspects of the disease, including the necessary funding, will ultimately benefit both women and men. Finally, we offer the report as a resource for policymakers by including policy implications and recommendations designed to nurture the innovations that will surely arise from sex- and gender-specific medical research in lung cancer to address this often deadly disease.

Lung Cancer: A Women's Health Imperative

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INTRODUCTION

Five years ago, our groundbreaking report, *Out of the Shadows: Women and Lung Cancer*, created awareness of the issue of lung cancer in women. . Since then, new lung cancer guidelines, screening technologies, and targeted therapies demonstrate great promise in improving survival rates. Part of that innovation comes from sex and gender-specific research. Although we still have a long way to go, scientists have begun to unlock knowledge on how sex- and gender-specific genetic, hormonal, behavioral, and environmental factors influence patterns of lung cancer in women, as compared to men [1].

> Lung cancer is the leading cause of cancer death among women. More women die from lung cancer each year than from breast, ovarian, and uterine cancers combined.

Despite these advancements, lung cancer continues to kill more women in the U.S. each year than breast, ovarian, and uterine cancers combined [2], and non-smoking women are still three times as likely as non-smoking men to get lung cancer [3-5]. Clearly, now is not the time to back away from research on sex- and gender-specific factors that affect the risks, screening, treatment, and mortality of this disease.

In this report, we hope to bring greater awareness to the impact lung cancer has on women. We also hope to show that a national strategy to address the study of sex- and gender-specific aspects of the disease, including the necessary funding, will ultimately benefit both women and men. Finally, we offer the report as a resource for policymakers by including policy implications and recommendations designed to nurture the innovations that will surely arise from sex- and gender-specific medical research in lung cancer to address this often deadly disease.

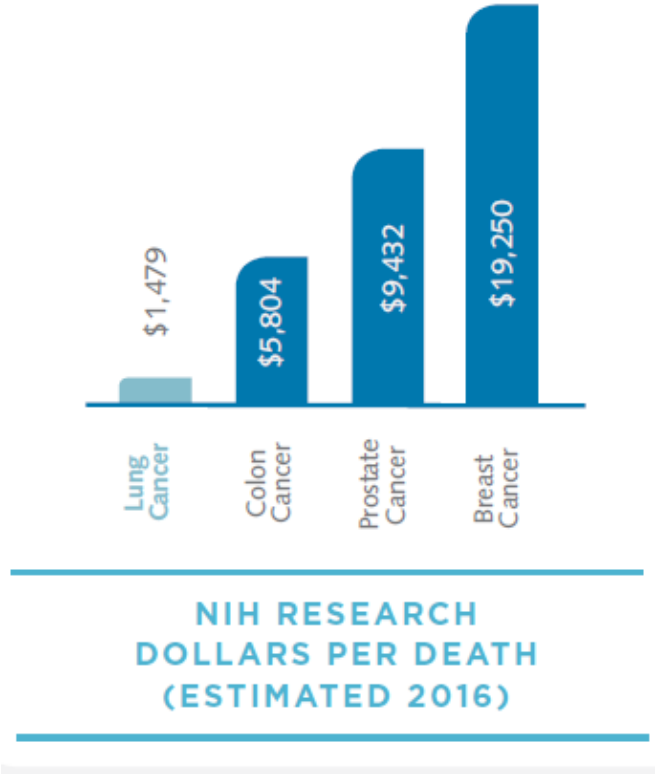
What is Lung Cancer?

Lung cancer develops from an uncontrolled growth of abnormal cells in the tissue of one or both lungs. The abnormal cells become tumors, which can interfere with the supply of oxygen to the body and which can also spread to other organs [6-8]. There are several types of lung cancer. The two primary types are small cell and non-small cell lung cancer. About 10%–20% of lung cancers are small cell lung cancer, which progresses more rapidly than non-small cell lung cancer and is often inoperable by the time of diagnosis [8]. In this report, we focus on the more common form of the disease, non-small cell lung cancer, which accounts for 80%–90% of all lung cancers, and includes a number of subtypes, particularly squamous cell lung cancer and adenocarcinoma [9]. Adenocarcinoma is more common in women than in men and is more likely to occur in younger populations than other types of lung cancer [10].

INCIDENCE, MORTALITY AND SURVIVAL

A growing body of research demonstrates that the rates of incidence, mortality, and survival for lung cancer differ by sex. Still more research is needed to more fully explain these differences and their persistence over time. However, funding for research on lung cancer overall lags far behind those of other cancers (Graph 1).

Graph 1



Source: Lung Cancer Alliance. 2016 Lung Cancer Facts. 2016.

Incidence and Mortality

Lung cancer is the second most common cancer in the U.S. (13.3% of new cancer cases [11]), killing three times as many Americans as any other form of cancer (See Table 1) [12, 13]. It is the number one cancer killer of women, not only in the U.S. but across the world [14].

Lung cancer is the second most common cancer among women and it is the number one cancer killer of women, not only in the U.S., but across the world.

Table 1

Common Cancer Types	Estimated New Cases (2016)	Estimated Deaths (2016)
1. **Breast (Female)**	246,660	40,450
2. **Lung and Bronchus**	224,390	158,080
3. **Prostate**	180,890	26,120
4. **Colon and Rectum**	134,490	49,190
5. **Bladder**	76,960	16,390
6. **Melanoma of the Skin**	76,380	10,130
7. **Non-Hodgkin Lymphoma**	72,580	20,150
8. **Thyroid**	64,300	1,980
9. **Kidney and Renal Pelvis**	62,700	14,240
10. **Leukemia**	60,140	24,400

Source: National Cancer Institute. Surveillance, Epidemiology, and End Results Program. SEER Stat Fact Sheets: Lung and Bronchus Cancer. http://seer.cancer.gov/statfacts/html/lungb.html

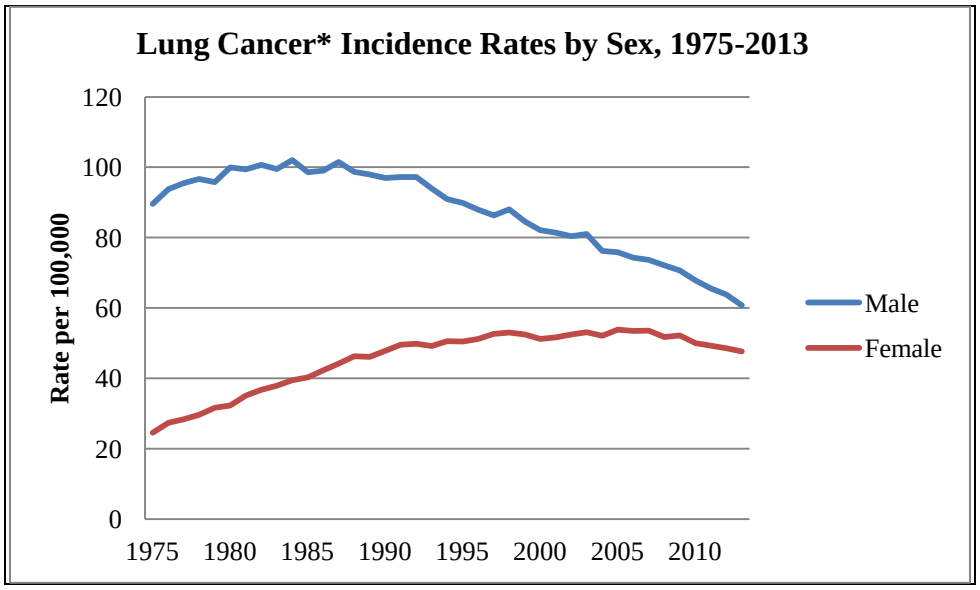
About one in seventeen women develop lung cancer [15]. The American Cancer Society estimates that, in 2016, 106,470 women in the U.S. will be diagnosed with lung cancer and more than 72,000 women will die from the disease [15]. When first diagnosed, 33,660 will be under 65 and 1,760 of those will be younger than 45 years of age [16].

While, historically, more men than women have developed lung cancer, the gap is narrowing [17]. As shown in Graph 2 the incidence of lung cancer in men has steadily declined, gradually approaching the incidence rates for women's lung cancer, which has held steady [18].

Sex vs. Gender

An individual's risk of developing lung cancer may be shaped by a combination of sex- and gender-related factors. Sex-related factors refer to biological variations such as genetic susceptibility and hormone levels, 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 (cigarette brands, how many puffs are taken, and how deeply smoke is inhaled), and even proximity to toxic cooking fumes [5].

Graph 2



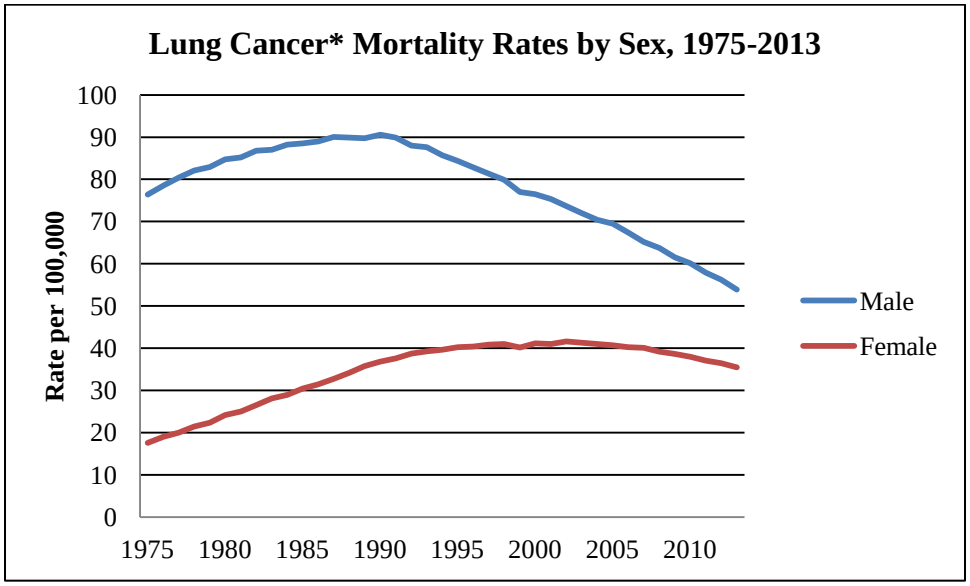
*Includes lung and bronchus cancer

Source: National Cancer Institute. Surveillance, Epidemiology, and End Results Program. Age-adjusted Incidence Rates data. http://seer.cancer.gov/faststats/selections.php?#Output

According to the Surgeon General and the Centers for Disease Control, between 1959 and 2010, smokers' risk for lung cancer increased dramatically, particularly for women: while men's risk doubled, the risk for women increased nearly ten-fold [19, 20].

Fortunately fewer people are smoking, which means a decline in lung cancer mortality rates. These rates vary over time by gender (Graph 3). Since 2008, mortality rates have decreased by 2.9% per year for men and by 1.9% per year for women [16].

Graph 3

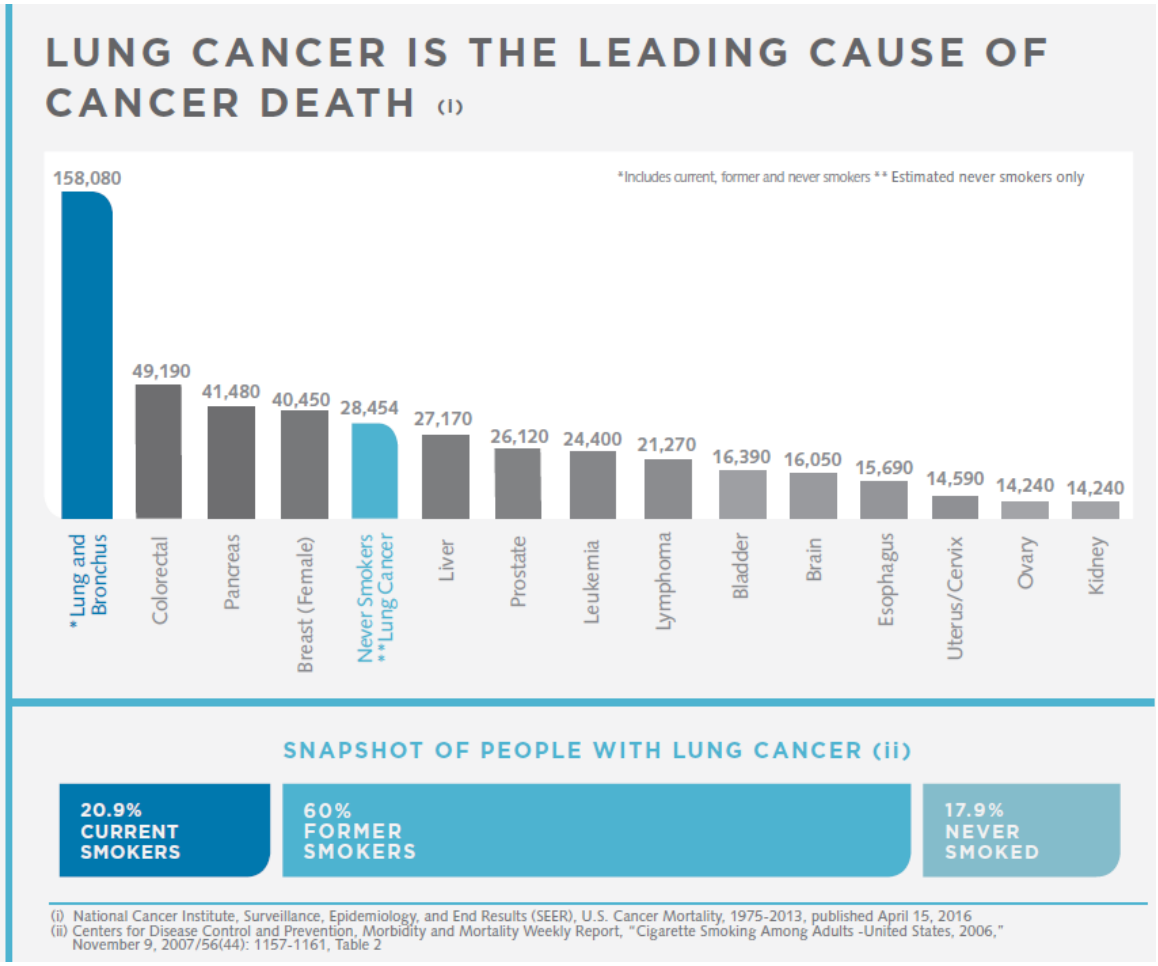


*Includes lung and bronchus cancer

Source: US Mortality Files, National Center for Health Statistics. CDC.

While cigarette smoking is an important risk factor for the disease, the incidence of lung cancer among people who have never smoked is also alarming. Two studies have found that lung cancer rates are increasing in people who have never smoked. One study conducted at a U.K. institution found the incidence of lung cancer in "never smokers" (those who have smoked fewer than 100 cigarettes in their lifetime) increased from 13% to 28% in a six-year period [21]. Another U.S. study examined lung cancer rates across three institutions and found a similar trend [22]. At one participating institution, the rate of never-smokers increased from 8.9% in 1990-1995 to 19.5% in 2011-2013 [22]. Graph 4 shows just how deadly lung cancer is in never smokers

Graph 4



Source: Lung Cancer Alliance. 2016 Lung Cancer Facts. 2016.

Additional research on the increase in lung cancer among never-smokers stratified by sex will be essential to understanding these disparities and the rates of increase in lung cancer among women who have never smoked. However we do know that, of all the women who develop lung cancer, 20% have never smoked compared to just 2%-6% of men [23]. Studies show that rates of non–smoking-associated lung cancer are higher in females than in males [24]. And women are three times as likely as non-smoking men to get the disease [3-5].

One in five women who get lung cancer never smoked compared to just 2%-6% of men with the disease. And nonsmoking women are three times more likely to get lung cancer as their male counterparts.

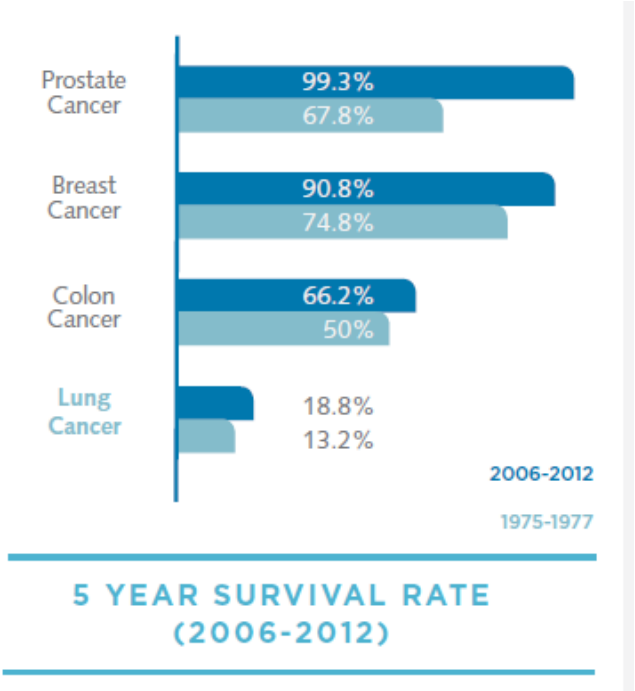
Despite the disparate impact of lung cancer on women, particularly women who have never smoked, there is little awareness and many misconceptions about this deadly disease. For

example, in a survey of 1,000 women conducted by the American Lung Association, only 1% of women cited lung cancer as the cancer they were most concerned about [25, 26]. Two-thirds of the surveyed women who were at high risk for lung cancer found breast cancer more concerning than lung cancer, and only a quarter had spoken to their doctors about lung cancer risks [26].

Survival

Despite substantial improvements in the overall survival rates for many cancers, including prostate (99.3%), breast (90.8%), and colon (66.2%), lung cancer survival rates have risen over the past three decades only from 13.2% to 18.8% (Graph 5).

Graph 5



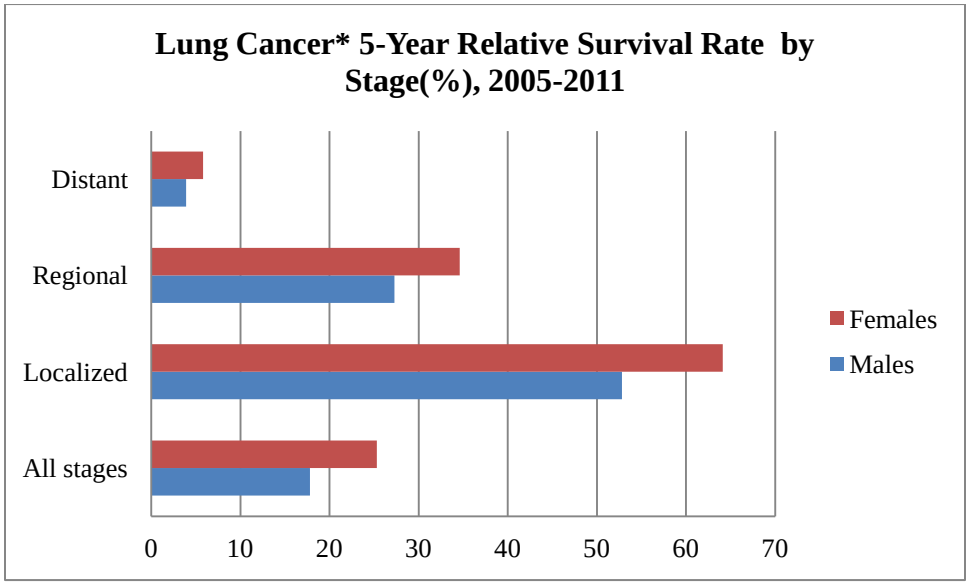
Source: Lung Cancer Alliance. 2016 Lung Cancer Facts. 2016.

The development of low-dose computed tomography (also called low-dose CT scan) for screening for lung cancer, and findings from clinical trials that this screening reduces mortality rates, puts us on the verge of radical improvements in lung cancer survival.

When it comes to survival rates, women actually have an advantage over men [27]. Women have higher five-year survival rates than men across all ages with comparable stages of lung cancer (Graph 6).

More research is needed to understand why women have better five-year lung cancer survival rates than men.

Graph 6



*Includes lung and bronchus cancer

Source: National Cancer Institute. Surveillance, Epidemiology, and End Results Program. Non-Small Cell Cancer of the Lung and Bronchus (Invasive). Table 15.14 http://seer.cancer.gov/archive/csr/1975_2012/browse_csr.php?sectionSEL=15&pageSEL=sect_15_table.14.html

Cancer Stages

Localized- the cancer tumor has not spread beyond the original organ (in this case, the lung).

Regional- the cancer tumor has spread beyond the original organ, but the boundary between the localized and regional tumors is well-defined

Distant- the cancer tumor has metastasized, which means that the tumor cells have broken away from the original tumor and have traveled to other parts of the body, growing in new locations. The boundary between regional and distant spread is not always clear.

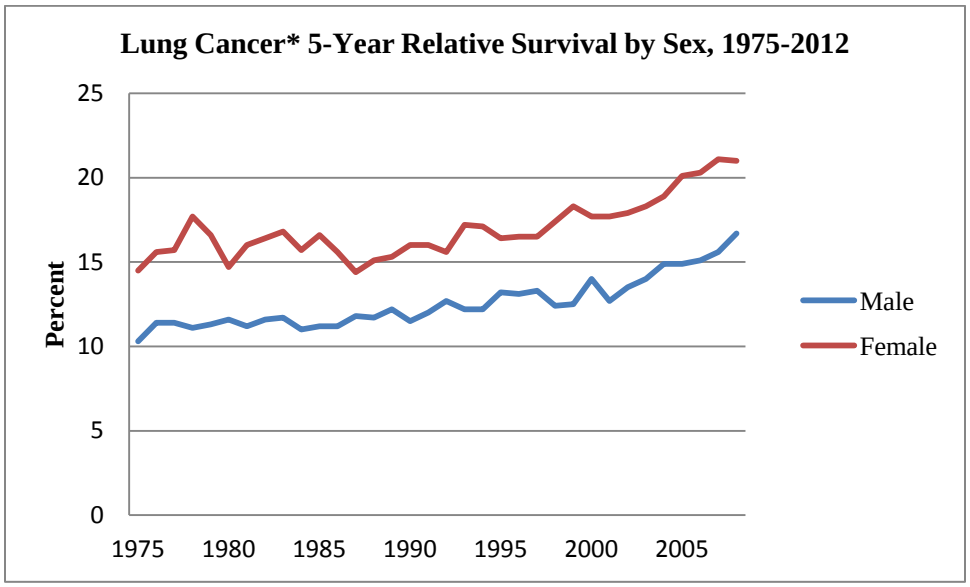
SOURCE: http://training.seer.cancer.gov/ss2k/staging/review.html

Even when controlling for behavioral differences, women still live longer following lung cancer treatment [28]. The reasons for these disparities remain unclear and more research is needed.

Data from the National Cancer Institute demonstrate a five-year survival rate of 21% for women with invasive lung or bronchus cancer compared to 16.7% for men (Graph 7) [29].

Survival rates vary by type of lung cancer; the 5-year survival rate for small cell lung cancer (7%) is lower than that for non-small cell (21%) [16]. For non-small cell lung cancer, women survived longer and responded better to chemotherapy [30].

Graph 7



*Includes lung and bronchus cancer

Source: National Cancer Institute. Surveillance, Epidemiology, and End Results Program. Age-adjusted 5-Year survival data. http://seer.cancer.gov/faststats/selections.php?#Output

The predominance of adenocarcinoma in women may also explain these disparities [27] as adenocarcinoma usually spreads more slowly than other types of lung cancer and is more likely than other types of lung cancer to be found before it spreads [31]. Women's overall longer life expectancies may be another reason for the difference in survival rates as is the possibility of estrogen as a protective factor [27].

Policy Implications

- While the incidence and mortality rates for women seem to be leveling off, researchers must explore why non-smoking women are more likely than non-smoking men to develop the subtype of lung cancer called adenocarcinoma and why these rates are increasing, particularly among young women.

- There is a gap in research on why women survive lung cancer at higher rates than men. New studies must be funded to close this research gap and improve survival rates for both women and men.

RISK

The risk of developing lung cancer is shaped by both biology and environmental factors, factors that can vary between women and men. Controversy persists on whether women who smoke are more likely than men to develop lung cancer: some studies have demonstrated a higher risk for women [32-34], while others have not found any major differences between the sexes [32, 35, 36]. The uncertainty itself suggests a need for additional research.

More research is needed to address the controversy that persists on whether women who smoke are more likely to develop lung cancer than men who smoke.

Biology

Women find themselves at higher risk for lung cancer due to such factors as genetic susceptibility and hormonal impact [4, 37, 38]. Research shows that sex correlates with the incidence of gene mutations associated with lung cancer. For example, women with adenocarcinoma, a subtype of non-small cell lung cancer (the most common type of lung cancer) are much more likely than men to express specific genetic mutations in proteins found on the surface of their cells [4, 39]. Several studies suggest the need to further explore hereditary risk factors by sex, particularly for non-smoking women [40-43]. These sex-specific findings may shed light on lung cancer treatments that target hormonal and genetic factors.

Sex hormones, particularly estrogen, influence lung cancer risk, development and mortality.

Research also demonstrates that hormones, particularly estrogen, also influence lung cancer risk (as well as development and mortality) [44]. Estrogen receptors, a group of proteins found in and on cells, are found in 45%-70% of non-small cell lung cancer tumors for both sexes, and may play a significant role in stimulating lung cancer cell growth [4].

Estrogen may also increase risk of lung cancer in never-smokers [44]. Women who have never smoked are much more likely than men who have never smoked to get lung cancer [3-5] with the incidence and mortality particularly striking among young women [45, 46]. The reason remains unclear, although some studies have cited estrogen as a factor [44].

The suspected role of estrogen in lung cancer has led to research on the impact of hormone replacement therapy on risk for the disease. One large clinical trial found that women with lung

cancer who took hormone replacement therapy faced higher mortality rates and developed tumors that spread and metastasized more quickly [47, 48].

Estrogen is also associated with faster metabolism of nicotine [49]. Women who use estrogen-only oral contraceptives metabolize nicotine faster than women who do not use hormones [49]. Conversely, women using progesterone-only contraceptives metabolize nicotine more slowly than women not on contraceptives [49]. How quickly women metabolize nicotine may impact their smoking behaviors, including how much they smoke and how much smoke they take in when smoking [49]. If women smoke more cigarettes or inhale more deeply because they metabolize nicotine more quickly than men, they may expose themselves to greater levels of the toxins present in tobacco smoke [49].

Smoking

Smoking tobacco is still the largest risk factor for lung cancer, contributing to 80% of lung cancer deaths in women and 90% in men [50, 51]. Although both sexes are smoking less than before, the decrease among women occurred decades after that of men [52-54]. This may partially explain the drop in lung cancer rates seen a decade earlier in men than in women [52-54]. Currently, about 19% of men and 15% of women smoke [55], and lesbian and bisexual women are twice as likely to smoke as straight women [56, 57]. Unfortunately, adolescent women are one of the fastest growing demographics of smokers, due in no small part to targeted marketing by companies [4]. And, although smoking rates have dropped overall, cigarettes' long-term effects in women have yet to be fully studied, due both to the lag time between smoking and development of lung cancer and to the scarcity of gender specific research [32].

Women's faster metabolism of nicotine may get in the way of smoking cessation efforts if nicotine replacement medications have inadequate dosages.

The ability to stop smoking also differs between women and men. Women are more likely to smoke to alleviate stress and depression [58]. Ovarian hormones that fluctuate during a woman's menstrual cycle and mood changes caused by oral contraceptives may also stymie attempts to stop smoking [59]. And the faster metabolism of nicotine mentioned above may also get in the way of smoking cessation efforts if nicotine replacement medications have inadequate dosages. Women may need higher doses of, say, nicotine gum to suppress their withdrawal symptoms [49].

E-Cigarettes

As smoking tobacco cigarettes has declined, more and more people have taken up e-cigarettes[60]. E-cigarette companies claim their products are safe and even beneficial, despite their use of nicotine [61]. More research is needed on the adverse health effects of nicotine in e-

cigarettes[61], as well as on the impact of e-cigarette vapors, given recent findings that the vapors may damage cells' DNA [62].

Women are significantly more likely than men to have tried e-cigarettes [63] in part due to marketing that targets women such as flavor options and the portrayal of products as "clean" and "safe." If companies can persuade women that e-cigarettes have minimal risk, non-smoking women of reproductive age may start using them [61]. But even small amounts of nicotine have been shown to be unsafe for both mother and child [64].

Secondhand Smoke and Environmental Exposures

Beyond the risk of smoking, exposure to second-hand smoke can cause lung cancer, heart disease, and other health risks. About two out of every five nonsmoking adults are exposed to secondhand smoke, with men having higher rates than women [65]. Globally, the risk of secondhand smoke exposure for women and children is particularly problematic [32].

The gender-specific difference in secondhand smoke exposure intersects with income. As income increases, secondhand smoke exposure decreases more so for women than for men [65]. This dynamic should be explored, especially given that women are more likely to have lower incomes than men [66].

Exposure to radon is the second-leading cause of lung cancer, responsible for 10% of lung cancer cases [61]. Asbestos, arsenic, nickel, cadmium, metal dusts, polycyclic aromatic hydrocarbons, and vinyl chloride can also cause lung cancer, but account for only a small number of cases among women within the U.S. [32]. Studies have shown that prolonged inhalation of cooking fumes from oils at high temperatures in poorly ventilated rooms contributes to the high rate of lung cancer in nonsmoking women in China and Taiwan [23, 32], underscoring the need for a gender-specific lens when examining the risks and treatment of lung cancer in women both in the U.S. and globally.

Policy Implications

- As with any disease, the risk of developing lung cancer depends to a great extent on biology. Estrogen and other sex hormones likely play an important role. The scientific community must conduct more research on biological and molecular differences between the sexes that can help identify risks specific to women, as well as to men.
- Smoking remains the primary risk factor for lung cancer. Scientists must conduct additional sex-specific research to determine how smoking differentially impacts women's risk for lung cancer.

- Public health campaigns have done an amazing job of highlighting smokers' risk of lung cancer. However, awareness of the risk for women who have never smoked is sorely lacking. Public health officials must develop local and national campaigns to make never-smokers aware of their risks and of the resources they need to prevent, detect, and treat the disease.
- Smoking cessation researchers should study sex differences to determine how women's metabolism of nicotine impacts efforts to quit. Given the impact that hormones may have on nicotine metabolism, researchers must include women of childbearing age, particularly those using contraceptives, in studies on the effectiveness of smoking cessation methods.
- Given that women are at particularly high risk for exposure to secondhand smoke that takes place outside of the home, governments must create public policies that specifically protect women at work and in public venues.
- Funding research on risk factors other than smoking history is a key aspect of addressing the rise of lung cancer among never smokers.

SCREENING

Early detection is the key to lung cancer survival. In the years since we released our last report, Out of the Shadows, lung cancer screening- which can detect lung cancer at its earliest, most curable stage- is now an "essential health benefit" reimbursed by private insurers under the Affordable Care Act (ACA) and covered by Medicare. Insurance plans must now cover lung cancer screenings for current or former heavy smokers and usually without out-of-pocket costs. This new benefit gives those at high risk much better access to screening.

Low-dose Computed Tomography (Low-Dose CT Scan)

Low-dose CT scans, when compared to traditional radiography screening in a large trial, decreased lung cancer mortality rates by 20% [67]. Given these findings and results from other smaller studies, the United States Preventive Services Task Force has recommended annual low-dose CT scans for moderate to heavy smokers between the ages of 55 and 80 (including those who have quit within the past 15 years) [68]. These recommendations, led to the ACA's designation of lung cancer screenings as a minimum essential benefit [68]. The Centers for Medicare & Medicaid Services followed suit adding coverage for lung cancer screening for Medicare recipients with the same risk profile (with adjusting the age range to cover ages 55 to 74 [69]). One actuarial study conducted in 2010 found that early stage diagnosis in 50-64-year-olds could save over 70,000 lives per year [70].

> Lung cancer screening was found to reduce mortality and be cost-effective. Strong oversight and clear guidelines for implementation of this provision will impact its ultimate success.

Covering lung cancer screening not only reduces mortality rates; it is also cost-effective for the bottom line [71, 72]. Studies have also found that the cost benefits of lung cancer screening are comparable to the cost benefits of colorectal and cervical cancer screening, and actually surpass the cost benefits of breast cancer screening, all of which are recommended by the United States Preventive Services Task Force [71, 73]. However, the success of lung cancer screening depends on successful implementation of this ACA provision. We know that challenges remain in the monitoring and implementation of the ACA preventive services provision given the lack of oversight and clear guidelines [74].

Despite these new measures to cover screening, screening guidelines are not sex- or gender-specific. Researchers examined National Lung Screening Trial Research data to determine if mortality risk reduction varied by sex, age, smoking status, and type of cancer [75]. The researchers found no significant differences in lung cancer mortality risk by age or smoking status. However, they did find that low-dose CT scans lowered mortality rates somewhat more for women than for men depending on lung cancer type, but the reasons for these differences are not particularly clear [75] demonstrating the need for more research.

The benefit of screening for lighter smokers, nonsmokers and never-smokers is less clear from the research. And although smoking accounts for nearly 90% of lung cancer deaths in men, and 70% in women, an increasing number of nonsmokers are developing lung cancer [22, 76]. For them, the benefits of low-dose CT scans have not yet proven to outweigh the risks associated with radiation exposure, over-diagnosis, and false positives [28].

Policy Implications

- Implementation of new screening guidelines under the ACA and Medicare must be evaluated to ensure that this important screening is accessible to everyone, particularly the traditionally underserved. Only by ensuring broad and comprehensive accesscan we be sure to capitalize on the potential for saving lives and money.
- The Centers for Medicare and Medicaid Services have mandated that a registry be available for reporting data on lung cancer screening so that quality and outcomes can be monitored. The Centers must routinely analyze and report these data by sex to ensure that women and subgroups of women are being effectively screened.
- While the guidelines have successfully improved access to insurance reimbursement for screening high-risk individuals for lung cancer, further research into sex-specific criteria is essential for determining when women are at high risk. Researchers must find evidence-based screening tools, the benefits of which outweigh the risks, for never-smoking women, who suffer higher rates of lung cancer than do never-smoking men.

TREATMENT

While the pace of innovation of treatments for lung cancer continues to accelerate (see below), in order to maximize their potential impacts, their outcomes must be analyzed by sex.

Minimally Invasive Thoracic Surgery

The preferred treatment for patients with early stage, localized non-small cell lung cancer 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, targeted therapies, or radiation; some patients may be treated with these modalities in combination with surgery. The development of minimally invasive surgical techniques has been an important advancement for treating patients with lung cancer. Video Assisted Thoracoscopic Surgery (VATS) is a minimally invasive method of removing or biopsying lung tissue through several small incisions in the chest [8, 77]. Research has demonstrated that when the tumor is amendable to a VATS lobectomy, this approach results in less pain and a shorter hospital stay compared to other more invasive methods such as a thoracotomy [78]. One study examined sex differences for short-term outcomes after lung cancer surgery and found that women had lower in-hospital and 30-day mortality rates compared to men [79]. Some risk factors for mortality were sex-specific, but further research is warranted to determine why women have this survival advantage.

Anti-Hormone Therapies

The type and degree of estrogen receptor expression differs significantly between normal lung tissue and lung tumors [80], suggesting that estrogen may play a role in the development of lung cancer. This has led to the investigation of anti-hormone therapy as a treatment for lung cancer. Breast cancer patients on anti-estrogen therapy, for example, have demonstrated a reduced risk of death from lung cancer, which provides additional evidence of the role estrogen plays in the progression of lung cancer [81]. As science elucidates the role of hormones in the development and progression of lung cancer, more prospective studies evaluating the role of anti-hormone therapy in lung cancer treatment and even lung cancer incidence are necessary to help benefit both men and women who suffer from this disease.

Targeted Therapies

One of the most significant advancements in lung cancer therapy in the last several decades (for both women and men) is that of precision medicine, where unique molecular and genetic mutations guide specific drug therapies. Targeted therapies 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 gene mutations and blocking malignant growth and the spread of cancer cells.

Clinical trials that track data by sex have shown that some lung cancer targeted treatments work better for women than for men.

The incidence of specific genetic mutations correlate with sex. Adenocarcinoma of a woman's lung (a type of lung cancer more common in women than man) is far more likely to express specific genetic mutations in proteins found on the surface of cells than do similar tumors in a man's lung. Importantly these mutations can predict the patient's response to specific targeted therapies [4, 82, 83]. In fact, clinical trials that track data by sex have shown that some lung cancer targeted treatments work better for women than for men. In the initial clinical trials of tyrosine kinase inhibitors (a targeted therapy), 82% of the patients who responded were women, making sex and smoking history the two most important factors in predicting therapeutic efficacy [4, 84]. This targeted therapy has become one of the most effective drugs to treat lung cancer, but its benefit would have been missed had the researchers not evaluated sex-specific data. This is an important example of why the FDA's drug evaluations should present efficacy data separately for men and women.

Policy Implications

- Unless lung cancer research and clinical trials include adequate numbers of female subjects and assess sex differences, important benefits and advancements in treatment will be missed. Sex-specific research with female animals at the basic science level is also essential for understanding the role of hormone receptors in lung and other types of cancer.
- Surgery must be aggressively pursued, and all patients must have access to both qualified surgeons and centers of high-quality care to reduce mortality rates for women as well as men. We must support research in surgical outcomes that investigate sex differences.
- Researchers must include women when testing targeted therapies, and track and evaluate sex-specific data. Post-market surveillance must also track differential outcomes by sex.

RACIAL AND ETHNIC DISPARITIES

Lung cancer is the second most common cancer among white, Black, Asian/Pacific Islander, and American Indian/Alaska Native women and the third most common among Hispanic women [14]. Differences in care that lung cancer patients receive are due to many factors including access, culture, communication, outright

Black women smoke less than white women but experience similar rates of lung cancer.

prejudice, and other systemic and structural impacts of race, sex, gender, and class [85]. Differences in care lead to differences in outcome.

Black women smoke less than white women but experience similar rates of lung cancer [17, 86, 87]. Black men, too, smoke less than white men, and yet have even higher incidence rates of lung cancer [88, 89]. Some studies suggest differences in smoking history, age, and socioeconomic factors contribute to racial and ethnic differences [90]. Other research suggests health access and other racial disparities as contributing factors [28]. Mortality rates differ as well when stratified by sex/gender and race/ethnicity. Black men have age-adjusted death rates that are 22.5% higher than white males; white women have age-adjusted death rates that are 8.4% higher than Black women [91]. Many complex factors, from genetics to behavior and environmental conditions, may contribute to these outcomes and are important areas of further study.

Secondhand smoke is an important environmental factor that puts Black women at a higher risk for lung cancer. Specifically, over half of non-Hispanic Black women report secondhand smoke exposure compared to about 30% of non-Hispanic white and Hispanic women [61]. Nonsmoking Black women are more likely to report living in a household with a smoker than are white and Hispanic women [65].

Though often overlooked, environmental influences that may harm genes are another important research area for addressing lung cancer disparities in minority women. For example, women are disproportionately affected by environmental pollutants, yet their mechanisms and impact on genetics are poorly understood [23].

Finally, the breakthroughs in lung cancer screening and targeted therapies will improve racial and ethnic disparities only if implemented effectively for these groups. Analysis and routine reporting on outcomes stratified by sex/gender and race/ethnicity will be key to ensuring that minority subgroups receive these life-giving breakthroughs.

A note of caution: Although the study of genetics offers ever more precise treatments, genomic information should not be overused for assessing disease risk. Overreliance on genetics would miss some of the root causes of health disparities, and could, quite possibly, aggravate those disparities. Other risk factors beyond sex/gender and race/ethnicity should also be researched, including access to care, biases in medical settings, socioeconomic variables, lifestyle choices, and environmental factors.

Policy Implications

- Research findings must be stratified by sex/gender and race/ethnicity to determine how lung cancer incidence, prevalence, and mortality among subgroups of women and men differ.
- Disparities related to both smoking and exposure to secondhand smoke should be explored. The increased risk of secondhand smoke exposure among minority groups is an important issue to consider when implementing comprehensive smoke-free laws.
- For targeted therapies and precision medicine to be successful at addressing health disparities in lung cancer treatment, racial and ethnic minority women, historically underrepresented in clinical trials, must be included at every step of the process, with adequate numbers to ensure adequate understanding of genetic markers.

POLICY RECOMMENDATIONS

This report highlights the differential impact lung cancer has on women, particularly on women who have never smoked, and outlines the sex- and gender-specific factors driving all aspects of the disease. Given the recent breakthroughs in lung cancer screening and targeted therapies, we're on the verge of an exciting time in lung cancer research. Significant improvements in survival and mortality rates are within our grasp. However, many aspects of medical research, policymaking, and public health initiatives fail to address sex- and gender-specific factors. To successfully combat this deadly disease with the tools now in our arsenal and those we've yet to develop, lung cancer research must understand its effects in women. The following policy recommendations outline a call to action essential to this cause.

1. Break down barriers to advancements in lung cancer by making the public aware of important differences in the way the disease develops in women and men.

- Lung cancer is one of the deadliest cancers for women, yet only 1% of women surveyed named it as the cancer they were most concerned about [25]. While public health campaigns have done an amazing job of highlighting the risk of lung cancers in smokers, awareness of the larger toll that lung cancer takes on women smokers and never-smokers is sorely lacking. Public health efforts should empower women with information about their particular risks and the benefits of early detection and sex-specific treatment options.
- Medical education on lung cancer must address sex and gender so that providers are aware of the risks to their female patients and can personalize prevention, screening, and treatment plans to meet their unique needs.

2. ***Create a national strategy to accelerate the implementation of preventive lung cancer screening services for women.***

   - Survival rates for lung cancer have historically been low due to a lack of effective screening methods for high-risk groups. Now that the ACA and Medicare cover lung cancer screening for high-risk adults, we need a national strategy to ensure that women know their rights under the law.
   - The new provision of preventive screening services will work only if high-risk individuals are aware of the benefit. Public health campaigns should include outreach education to make people aware of who is at risk and how to get screened. These campaigns should be developed with an awareness of differences in sex and gender to ensure that women are effectively targeted. The campaigns should also be coordinated with the state and federal marketplaces, where many newly insured will obtain coverage.
   - The federal agencies that track the screening data should stratify it by sex/gender and race/ethnicity to make sure that women and minority women, particularly underserved populations, are availing themselves of the services.
   - No early detection or screening protocols are currently available for nonsmoking women, and current screening guidelines are not sex-specific. Researchers must develop and improve screening methods that address the unique risk factors for women, both smokers and nonsmokers.

3. ***Fund sex- and gender-specific lung cancer research to bridge the gaps in lung cancer innovations.***

   - Lung cancer, though pervasive and deadly, is not funded at the level of other types of cancer, deterring advancements in the field. A federally-funded study, conducted by lung cancer experts, scientists, and relevant stakeholders, should address the lack of sex- and gender-specific research on lung cancer and make recommendations to bridge these gaps.
   - Research has demonstrated the important impact that sex and gender have on the genetic, hormonal, behavioral, and environmental factors involved in lung cancer. To continue innovating cutting-edge, lifesaving screening and treatments, research studies must include female animals (at the level of basic science) and women, and attention to sex and gender differences must become the norm in biomedical research.
   - Despite the National Institutes of Health (NIH) 1993 Revitalization Act's mandate that women and minorities be included in NIH-funded clinical research, a 2015 Government Accountability Office report found that NIH has not effectively monitored the inclusion of women or tracked sex and gender differences in its funded research of specific diseases, including lung cancer. This situation may change with the Advancing NIH Strategic Planning and Representation in Medical Research Act (favorably reported out by the Senate Committee on Health, Education, Labor, and Pensions in April 2016) which improves planning, collaboration, and demographic representation of women and other underserved groups in research conducted and funded by NIH, and the NIH's recently announced policy that requires researchers to expand inclusion of female cells and lab animals in NIH-funded medical research. However, failure to monitor and evaluate these new policies with transparency and accountability will mean that we

continue to risk innovation in the screening and treatment of lung cancer and other diseases. Failure to recognize and examine the different impacts that lung cancer has on the sexes will hurt us all, women and men alike.

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