OBJECTIVES:

To provide an overview of the status of lung cancer screening.

DATA SOURCES:

Published articles, book chapters, websites, and research studies.

CONCLUSION:

Screening with chest x-ray and sputum cytology has not been shown to be effective in reducing lung cancer mortality. Although screening with helical CT is currently under investigation in randomized clinical trials, observational studies have not shown evidence that it can detect lung cancer that is curable.

IMPLICATIONS FOR NURSING PRACTICE:

As health care educators and caregivers, nurses should be informed of the status and current controversies associated with lung cancer screening.

KEYWORDS:

Lung cancer screening, helical CT, low-dose CT, spiral CT, cancer screening clinical trials

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LUNG CANCER SCREENING: PROMISE AND PITFALLS

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LUNG CANCER claimed more than 160,000 lives in 2007, out of the approximately 213,000 new cases of lung cancer estimated to be diagnosed in the United States.[1] Despite major advances in medical technology and therapies, the overall 5-year survival rate for all lung cancers is approximately 15%. However, the 5-year survival rate for lung cancer diagnosed in its earliest stages may be as high as 70%.[2-4] What remains to be determined by ongoing studies is whether early detection of smaller tumors will lead to a decrease in mortality rates, given that even small tumors may have high metastatic potential.[5] With over 90 million current and former smokers in the United States, the validation of an effective screening test, in conjunction with effective treatment, would have major public health implications.

In the past, randomized screening trials evaluated chest x-ray and sputum cytology as an early detection test, but did not find either to be effective in decreasing mortality rates. More recently, a newer imaging technology has emerged as a potential screening test for lung cancer. Low-dose computed tomography (CT), or helical CT, can detect tumors well under 1 cm in size. By contrast, x-ray detects tumors approximately 1 to 2 cm in size. Observational studies of helical CT have shown promising increases in survival rates.[4-6] But as we discuss below, a focus on survival rates alone may be deceptive, as decreasing mortality rates is the ultimate goal of screening techniques.

This article provides an overview of the elements of a screening trial, data from historical clinical trials, the status of ongoing studies, and a discussion of the controversies related to helical CT. Also, an overview of the National Cancer Institute (NCI)-sponsored National Lung Screening Trial, a large randomized controlled screening study for individuals at risk for developing lung cancer, is provided.

UNDERLYING CONCEPTS OF CANCER SCREENING

To understand and interpret findings from screening trials, one must be familiar with certain underlying concepts associated

with screening. First are the concepts of incidence and prevalence. For screening to lead to significant public health benefits, the target disease should have high incidence and prevalence rates in the screened population. Incidence refers to the number of cancer cases that develop during a defined period of time, and is expressed as cases per year per 100,000 individuals in the population.[7] Prevalence is the number of cancers that exist in a defined population at a given point in time, and is commonly expressed as cancers per 100,000 individuals in the population.[7]

Second, an effective screening test should detect disease at an early stage, while the individual is asymptomatic and while cure may be possible with treatment.[5] In other words, the test must lead to a decreased mortality rate. The test itself should be safe, inexpensive, and possess sufficient sensitivity (able to identify individuals with disease), and specificity (able to identify individuals without disease). To bring about a decrease in the mortality rate, an effective treatment must be available to those diagnosed following a positive screen. Effective screening tests, in conjunction with effective treatment, then, have the ability to effect a change in the natural history of the disease in a positive manner.

Third, the benefits of screening must outweigh the risks.[7,8] For instance, the incidence of false-positives and false-negatives must be evaluated against potential benefits. False-positives can result in unnecessary surgeries, treatments, anxiety, and public health costs. False-negatives, on the other hand, can lead to undetected disease that progresses beyond the benefits of available interventions.

Fourth, survival and mortality are two inter-related but often misunderstood concepts that are important in understanding the relative effectiveness of lung cancer screening techniques. Survival rates reflect the number of individuals alive at a given time relative to their diagnosis. Although frequently reported in observational screening studies, survival rates alone are not an adequate measure of screening benefit. The measure can be misleading because of several confounding biases: lead time bias, length bias, and over-diagnosis. It is important to note, however, that survival is appropriately used to compare the benefits of one form of treatment or intervention with another.[9]

Lead time refers to the period of time from cancer detection to the time symptoms would have occurred had the individual not been screened (Fig 1).[10] Essentially, the survival rate is artificially lengthened with the addition of the lead time. In effect, earlier detection prolongs survival independent of a delay in death. For example, if two individuals (one screened, one not screened) die of lung cancer at the same age, the screened individual's survival time is lengthened because his cancer was detected earlier (lead time), while he was still asymptomatic. The unscreened individual's cancer would have gone undiagnosed until symptoms occurred. The screened individual appears to have a longer survival time because of the addition of the lead time, but the mortality is the same. Such findings run counter to the often-held view that cancer is a consistently progressive disease. Research in screening has found that cancer encompasses a wide range of biologic behavior: some cancers progress rapidly to death, some more slowly, and some not at all.[11]

Length bias refers to the tendency of a screening test to detect indolent, rather than aggressive tumors (Fig 2).[10] Slow-growing cancers are more likely to have a prolonged pre-symptomatic period, allowing greater opportunity for detection. This extended period does not necessarily represent an actual improvement in survival, but rather reflects the underlying behavior of the cancer itself. In many instances the individual with an indolent disease would die from other causes first.

A related concept is over diagnosis, which is of particular interest in CT screening trials because advanced technology allows identification of many non-cancerous abnormalities, including

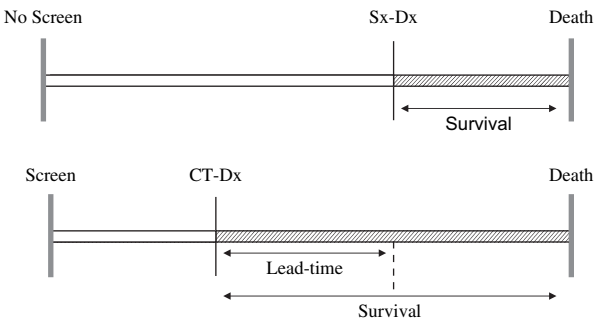

FIGURE 1. Lead-time bias. Lung cancer-specific survival is measured from the time of diagnosis of lung cancer to the time of death. Screening may appear to prolong survival even though death may not be delayed. Effective screening tests should detect disease before signs or symptoms occur and *must* lead to decreased mortality. (Data from US DHHS; http://www.cancer.gov/nlst/what-is-nlst#10b.[10]) Sx, symptoms; Dx, diagnosis.