# Computed tomography in screening for lung cancer

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## Findings by SBU Alert

**Technology and target group:** Approximately 2 800 new cases of cancer in the lungs and respiratory tract are diagnosed annually in Sweden. By the time it is diagnosed, the cancer has usually spread in the body, and the 5-year survival rate following diagnosis is approximately 10 percent. If cancer could be detected at an early stage, the hypothesis is that it would substantially improve the prognosis. Detecting lung cancer at an early, asymptomatic stage requires targeted screening. Earlier attempts to use chest radiography in early detection of lung cancer have not lowered the mortality rate from the disease. The development of spiral computed tomography (CT) and the use of lower radiation doses have, however, renewed the interest in screening. Smoking is the main cause of lung cancer. It has been estimated that it takes 20 to 30 years of smoking before lung cancer progresses to a symptomatic stage. A targeted screening program including all those who are or have been daily smokers, and are older than 45 years of age, would comprise 600 000 to 900 000 individuals annually in Sweden.

**Patient benefit:** Scientific studies have not confirmed that early detection of lung cancer leads to a reduction in mortality from the disease. As with assessments of screening for other types of cancer, eg, breast cancer, large, long-term, randomized trials would be required to answer this question. Six assessments, with major differences in design, have investigated the effectiveness of low-dose spiral CT in detecting early lung cancer. Lesions that led to followup examinations were detected in 5 percent to 69 percent. Between 0.4 percent and 2.7 percent of those screened were diagnosed as having lung cancer. The positive predictive value ranged between 2.8 percent and 11.6 percent. Two of the studies compared CT with chest radiography, and both studies showed that more tumors were detected with computed tomography. Most of the detected tumors were small (stage I).

**Economic aspects:** Detecting a single case of cancer at an early stage requires examination of a large number of people. This would suggest high costs for a screening program. Since the benefits of early detection have not been determined, model studies are the only way to estimate the cost effectiveness of the method.

**Ethical aspects:** Screening for lung cancer requires examination of a large number of healthy individuals in order to detect disease in, and offer treatment to, a few. Therefore, one must carefully weigh the advantages and disadvantages. Beyond subjecting patients to anxiety and time sacrificed in conjunction with the examination, the use of radiation involves some risk for induction of cancer. Also, a number of patients will be subjected to unnecessary invasive procedures due to false-positive test results.

**Scientific evidence:** Currently, there is good* scientific documentation of the capacity for low-dose CT to detect lung cancer at an early stage. There is no* scientific documentation to show how mortality would be affected by an organized program using low-dose CT for early detection of lung cancer. There is poor* documentation on the cost effectiveness of the method.

Before considering the appropriateness of routine screening for lung cancer, a positive effect on mortality must be demonstrated by large, controlled trials of screening programs.

*This assessment by SBU Alert uses a 4-point scale to grade the quality and evidence of the scientific documentation. The grades indicate: (1) good, (2) moderate, (3) poor, or (4) no scientific evidence on the subject. For further information please see “Grading of evidence”.

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## Technology

Tumors in the lungs and respiratory tract represent a common type of cancer in Sweden. The dominant cause is smoking. In 1999, nearly 2 800 new cases were diagnosed, 60 percent in men and 40 percent in women. The number of newly diagnosed cases is increasing. However, the number of newly detected cases in men has decreased by 1 percent per year during the past 20 years while cases in women have increased by just over 3 percent per year during the same period. In people below 54 years of age, equally as many cases of lung cancer are detected in both genders.

Most lung cancer patients die within 1 year after diagnosis, and the 5-year survival rate is approximately 10 percent, largely because lung cancer becomes symptomatic late in the course of the disease. In most cases, by the time that cancer has been diagnosed it has already spread in the body, and only 20 percent to 25 percent of the patients can be offered potentially curative surgery. No improvement in treatment results has been noted in recent years.

Theoretically, it would be desirable to detect lung cancer at an early stage. Of patients whose lung cancer was detected early (stage I = a tumor less than 3 centimeters in diameter and without metastasis), 70 percent are alive after 5 years. However, it is uncertain from scientific studies whether early diagnosed lung cancer increases the length of survival in patients compared to detection at a later stage (see under “Patient Benefit” below for discussion on sources of error in assessing the effects of early detection) [14]. Detecting cancer at an early, asymptomatic stage, requires some type of screening.

During the 1970s, several randomized trials of lung cancer screening were conducted with the aim to improve diagnoses and treatment. Asymptomatic smokers were examined by chest radiography (x-rays), often in combination with sputum cytology (study of cells found in mucus expelled by coughing). No reduction in mortality could be demonstrated in the group examined. The results led to discouraging the general use of lung cancer screening by chest radiography [10].

The development of low-dose spiral CT (computed tomography) focused renewed attention on the issue of screening. Computed tomography provides high-contrast images that distinguish different tissues from each other and can show small lesions. The radiation dose is substantially lower than with conventional computed tomography and only 3 to 5 times higher than with common chest radiography. The examination can be performed in 30 seconds or less.

If uncertain lesions are detected in the lungs, the examination is complemented by conventional computed tomography (involving a higher radiation dose) in the suspected region. If necessary, thin image slices through the suspected region are produced by high-resolution computed tomography (HRCT).

## Target group

Since smoking is the primary cause behind lung cancer, screening can be aimed at this group. It takes an estimated 20 to 30 years before lung cancer develops and becomes symptomatic. Hence, the incidence of lung cancer reflects smoking habits approximately 20 years back in time. Also, the rate of lung cancer is low up to 45 years of age, but then escalates rapidly with age.

Smoking habits in Sweden have varied over the years, but a rough estimate is that 20 percent to 30 percent of all Swedes aged 45 years and older either are or have been heavy smokers. A screening program aimed at this entire target group would cover between 600 000 and 900 000 individuals. It would be premature to speculate whether this entire target group would need to be screened, or whether selection should be established due to resource limitations.

## Relation to other technology

Chest radiography is a simple method used in lung cancer screening. The method is easy to use, generally accessible, and inexpensive. The radiation dose is low, approximately one tenth of the dose that most people receive annually from their normal surroundings. Chest radiography is used either alone or in combination with, eg, sputum cytology or computed tomography. However, the method has poor

sensitivity. In lung cancer screening programs that have compared chest radiography to low dose CT, researchers have found that CT detects approximately four times more tumors than chest radiography.

Sputum cytology has been used alone or in combination with chest radiography in screening studies. However, as a screening method, sputum cytology has poor sensitivity (capacity to identify disease), lower than that of chest radiography, particularly for detecting tumors other than squamous cell carcinoma. Furthermore, the method also has poor specificity (capacity to rule out disease). Two Japanese screening studies used sputum cytology to complement low dose CT and found some cases of lung cancer that had not been detected by CT.

Biological markers, eg, HnRNP A2/B1 in sputum [12] or analyses of exhaled air [15], open new areas for tumor diagnoses. Thus far, these methods have not been assessed for their usefulness in lung cancer screening.

Other methods that would be applicable, theoretically, in the future include positron emission tomography (PET) and magnetic resonance imaging (MRI). Currently, these methods face several practical and economic limitations in a screening context.

## Patient benefits

The primary question which must be answered before a screening program in lung cancer can be initiated is whether or not early detection can lower the mortality rate. When a tumor is detected by screening during the latent period (before it becomes symptomatic), this leads to extending the survival time after treatment, even if treatment itself is not effective. This is usually referred to as “lead-time bias”, and means that early detection of disease can appear to be more successful than it actually is. Another source of error is that all tumors are not equally aggressive and do not grow at the same rate. Screening examinations tend to detect tumors that are less malignant and grow more slowly, while rapidly growing tumors can become clinically symptomatic in the interim between screening exams. Hence, the results of screening can be overvalued (length-time bias). A third source of error is that the screening methods may be so sensitive that they detect tumors which would probably never become symptomatic, either because they spontaneously diminish or they have such a slow rate of growth that the patient would die from another disease before symptoms developed. Smokers have a high excess mortality rate, eg, due to pulmonary emphysema and cardiovascular diseases.

This type of source of error makes it difficult to assess the results of screening tests. One way to deal with this problem is to use randomized groups and control groups. This requires following intervention groups and control groups long enough to assess disease specific mortality. No such studies on CT screening for lung cancer have yet been published.

Some studies, however, have investigated the potential of low dose computed tomography for detecting lung cancer at an early stage.

Kaneko et al examined 1 369 individuals between 1993 and 1995 to study whether low dose spiral CT was superior to chest radiography in detecting peripheral lung cancer [8]. The study also included sputum cytology. The mean age of study subjects was 60 years (40–85 years), and 90 percent were men who were heavy smokers. Most were examined three or more times at 6-month intervals. Initially, lesions that required further investigation were found in 229 subjects (16.7 percent). This led to biopsy in 19 (1.4 percent), and biopsy showed lung cancer in 15 (1.1 percent). The percentage of tumors at stage I was 93 percent with low dose CT and 53 percent with chest radiography. A followup report presented 7 cases of lung cancer that had not been detected during the first round of screening [9]. Of 25 diagnosed cases of lung cancer, 22 were detected by low dose CT and 3 by sputum cytology, 15 were detected at the initial screening round. This yields a sensitivity of 60 percent and a specificity of 84 percent. The positive predictive value for a detected lesion was 6.5 percent.

Sone et al used low dose CT to screen lung cancer as a part of an ongoing general health screening program which otherwise included chest radiography (photofluorography) and sputum cytology [16,17]. The data covered 5 483 voluntary trial subjects. The median age was 63 years (40–74) and 54 percent were men. There was no selection with regard to smoking. The proportion of smokers in the group was 46 percent. The examination was conducted with a mobile spiral CT scanner once per year during 1996 to 1998. If the screening examination showed suspected lesions, the patient received chest radiography, complete conventional CT, and HRCT. In the first round of screening, lesions that required investigation

were found in 279 subjects (5.1 percent). This led to biopsy in 29 people, whereafter 22 (0.40 percent) were found to have cancer. As regards tumor classification, 88 percent were classified at stage IA. At the first annual followup, the frequency of suspected lesions was 3.9 percent and the frequency of cancer was 0.56 percent. At the second followup the corresponding figures were 3.5 percent and 0.23 percent respectively. Sensitivity in the first round was only 55 percent because a large share of the tumors that were found in the second round of screening could be seen retrospectively already in the first round. Sensitivity in the second round, was 83 percent. Total specificity was high (97 percent). The positive predicted value of prevalence screening was 7.9 percent, and in followed up patients it was 14.5 percent and 6.6 percent respectively. An interesting aspect of this study is the high rate of cancer in subjects who had never smoked (0.46 percent) versus smokers (0.52 percent).

From 1993 to 1998, Henschke et al conducted a study where annual exams using low dose CT were compared to chest radiography [5,6]. The aim was to investigate which method was superior in detecting lung tumors, the rate of tumors found that were malignant, and how often such malignant tumors could be cured. Advertising was used to recruit 1 000 asymptomatic heavy smokers above 60 years of age. The subjects consisted of 54 percent men with a mean age of 67 years. The initial low dose CT exam detected lesions that required further investigation in 233 individuals (23.3 percent). Using chest radiography, the lesions could be found in only 68 individuals (6.8 percent). Further examination led to biopsy in 28 individuals, whereof 27 (2.7 percent) were found to have lung cancer, and 85 percent of these were classified at stage I. The second round of screening included 841 people, and the third round included 343. The results for the individual rounds were not reported. In the 1184 repeat examinations using low dose CT, lesions were found in 63 subjects (5.3 percent), and further investigation showed lung cancer in 7. Given the fact that repeat screening identified 4 cases that were overlooked in the first round, sensitivity is 87 percent, specificity is 79 percent, and the positive predictive value is 11.6 percent.

Diederich et al studied 817 asymptomatic heavy smokers by annual low dose CT between 1995 and 1999 [3]. To date, only the results from the initial prevalence examination have been presented. Mean age was 53 years (40–78 years), and 72 percent were men. No comparison was made with chest radiography or other screening methods. Suspected tumors were found in 350 individuals (43 percent). Further examination led to biopsy in 15 individuals whereof 11 (1.3 percent) had lung cancer. The tumors were classified as stage I (58 percent) and stage III (25 percent). This yields a sensitivity of 100 percent, a specificity of 57.9 percent, and a positive predictive value of 3 percent.

Nawa et al used low dose computed tomography as part of a screening program from 1998 to 2000 [13]. No comparisons were made with other methods. The first round of screening included 7 956 people aged between 50 and 69 years, 77 percent were men and 62 percent were smokers. Lesions were found in 2 099 people (26.3 percent). This led, however, to further examination in only 541 (6.8 percent), which in turn led to biopsy/surgery in 51. Of these, 36 (0.45 percent) had lung cancer. It is remarkable that only 14 of these individuals were smokers. Stage I tumors accounted for 86 percent of the cancer cases. After one year, a repeat examination was conducted in 5 568 subjects, and further investigation was necessary in 148 (2.7 percent). Biopsy was conducted in 6 subjects, whereof 4 (0,07 percent) were found to have cancer. This yields a sensitivity of 100 percent, specificity of 93 percent, and a positive predictive value of 6.7 percent. The corresponding figures for round 2 are 100 percent, 97 percent, and 2.6 percent.

Swensen et al recruited 1 520 symptom free heavy smokers aged 50 years and older for low dose CT combined with sputum cytology during 1999, with planned annual reexamination for another 3 years. Mean age was 59 years (50–85), 52 percent were men. Results from the prevalence study and from the first two rounds of followup have been reported [18,21]. In the first round, suspected tumor lesions were found in 782 individuals (51 percent). At 1- and 2-year checkups, new lesions were found in 14 percent and 9 percent respectively. In total, after three rounds of screening suspected tumor lesions that needed to be controlled or operated were found in 69 percent of the participants. The continued investigation of lesions gave the diagnosis of lung cancer in 40 individuals, 26 during the prevalence round and 10 at the following screening rounds. Two cancers debuted between screening rounds, so called interval cancer, and another two were diagnosed by sputum cytology alone. 60 percent of the tumors were at stage IA. It was also reported that 8 of the people who received surgery had benign lesions. The results of the initial examination yield a sensitivity of 95.6 percent, a specificity of 49.2 percent, and a positive predictive value of 2.8 percent.

The studies published to date have very different designs, which makes it difficult to compare the results, and they all lack randomization and control group. None of the studies aim at studying the effects on mortality. Some studies have selected the older heavy smokers cohort while others have not selected

subjects based on smoking. Compliance with the study protocols has been relatively low mainly in the American study [6].

Two of the studies compared low dose CT with chest radiography to show peripheral tumor lesions in the lungs and report that low dose CT found 3 to 4 times as many tumors. However, this requires that many individuals who do not have lung cancer must be investigated further, which can lead to unnecessary anxiety. High rates of checkup exams also require high radiation doses since the checkups are not given with low dose technology. Screening tests lead to a high rate of false positive findings. The number of cases where biopsies have been performed on suspected malignancies, but where benign lesions were found, varies between 4 percent and 29 percent. The studies found that 60 percent to 90 percent of the identified lung cancer is at stage I where the opportunity for surgical intervention is most favourable and 5-year survival is greatest. Whether or not there are any effects on disease-specific survival remains to be seen.

The two most common types of lung cancer are squamous cell carcinoma and adenocarcinoma. The latter tends to be the most common. Adenocarcinoma usually grows more peripherally in the lungs, usually grows a little more slowly, and thereby has a somewhat better prognosis than squamous cell carcinoma. Screening with low dose CT can reveal only tumors that are peripherally situated in the lung tissue. The technique is not sensitive to diagnosis of intrabronchial tumors or those that grow next to the bronchi, ie, where most squamous cell carcinomas originate. Adenocarcinoma is the dominant type of tumor (>70 percent) reported in studies. In summary, there is a risk that screening detects mainly slow-growing, more benign adenocarcinomas, while intrabronchial tumors and more malignant squamous cell carcinomas go undiagnosed until they become symptomatic.

## Complications and side effects

The CT screening procedure does not involve any known complications. Radiation itself carries a small risk for induction of cancer. The radiation dose for conventional spiral CT varies somewhat depending on the method, but ranges from 3 to 10 milliSievert (mSv). Low dose CT substantially reduces the dose to 0.3–0.6 mSv, depending on the method used [2]. The dose should be compared with routine chest radiography which yields 0.1–0.2 mSv and the natural background radiation in the environment, which averages 3–5 mSv/year in Sweden. The International Commission of Radiation Protection (ICRP) has estimated the risk for induction of malignancy in the use of x-rays at 5 percent/Sv [7]. It is uncertain whether or not a linear relationship exists between dose and risk, but if one assumes that this is the case, the risk for cancer induction from low dose CT would be 2–3 cases per 100 000 individuals examined. This applies to the initial screening examination. If a suspected lesion is detected, further examination is required by conventional CT followed by checkups at 3- to 6-month intervals. Hence, the radiation dose can be high. The large number of false positive findings in screening creates a risk for induction of substantially more cancers.

It can be assumed that screening programs create anxiety in those screened. This particularly applies to individuals in whom lesions are detected and who require further examination. Published data show that initial screening with low dose CT detects lesions in 5 percent to 51 percent of those examined. After further examination, only a small percentage of these patients are found to have cancer. The positive predictive value is very low, between 2.8 percent and 11.6 percent. Certainly, additional thorough examination makes it possible to avoid unnecessary surgical intervention (20 percent to 30 percent in most of the cases). However, many individuals are subjected to repeat CT examinations before malignancy can be ruled out, causing considerable unnecessary anxiety. Another potential consequence is that individuals who undergo a screening examination where no disease is found, may acquire a false sense of security that they do not have cancer.

## Cost and cost effectiveness

Detection of a single case of lung cancer at an early stage requires the examination of a large number of healthy individuals. This indicates a high cost per case detected. A preliminary estimate of the costs for lung cancer screening in Sweden would suggest a high cost for a fully developed screening program [4]. As information is lacking concerning the effects of screening on mortality, estimates of cost effectiveness must be based on model studies. An American model analysis has used data from the Early Lung Cancer Action Program (ELCAP), where preliminary data on mortality showed positive effects from screening [5].

The model analysis based on this preliminary outcome data suggests that a reduction in mortality can be achieved at a reasonable cost by using low dose CT to screen for lung cancer [11]. However, it should be noted that the effects in this study are based on very tentative data.

Another American model analysis performed a more detailed calculation of the effects and costs of lung cancer screening. The effects were estimated, in part, based on a compilation of results from several different studies concerning the capacity for low dose CT to detect lung cancer at an early stage, and, in part, based on assumptions on how the early detection of the disease impacts on mortality. In estimating the costs, the authors considered a range of different aspects. The results of this model analysis show that screening in daily smokers would lead to a 13 percent reduction in mortality from lung cancer. Furthermore, the analysis showed that the costs per quality-adjusted life-year gained would be nearly 1 million SEK [20]. Therefore, the authors concluded that, currently, screening for lung cancer with low dose CT does not appear to have the potential to become a cost-effective method.

A cost-effectiveness analysis from Japan used a range of assumptions concerning the effects of using CT in lung cancer screening programs. These effects were then balanced against the estimated costs of the program. The most positive scenario assumed that 70 percent of all lung cancer could be detected by CT screening before the disease had metastasized. The cost per life-year saved was compared with ongoing screening interventions. The cost to save one year of life was found to be approximately three times higher for lung cancer than for cervical cancer and twice as high as for breast cancer [1].

## Structure and organization of health services

Computed tomography is available at most departments of radiology in Sweden. Most of the units are sufficiently modern to be used for low dose CT. However, in most places these units are utilized frequently during daytime hours. Utilization during evening/nights and weekends is not as high. If screening examinations can be organized during low-volume periods, the need for new CT units would not be as great. Presumably, the high volume of exams that screening would demand and the repeat exams that it would generate would require acquisition of a large number of new CT units in Sweden. Screening would also require substantial resources in terms of radiology staff, mainly physicians to interpret the large number of images. However, advancements in programs for computer-assisted diagnosis might be helpful [19].

## Ethical aspects

Health screening involves the examination of a large number of healthy individuals to detect asymptomatic disease in a small percentage of those examined. This involves ethical implications that must be carefully considered. Likewise, we do not know the effects that early detection and treatment of lung cancer will have on long-term survival. The risk for induction of lung cancer must also be considered as an ethical issue. The state of knowledge with regard to screening for lung cancer is such that screening should be performed only within the framework of scientific studies. Informed consent must be obtained from the participants.

## Diffusion in Sweden

Routine screening for lung cancer is not performed in Sweden. However, in Gävleborg County Council a screening program using low dose CT has been introduced with support from the Heart Lung Foundation within the framework of a pilot project.

## Current evaluation research

Reports released some years ago, which described that low dose CT could detect small lung tumors better and earlier, initiated further studies using a similar design [5,8,16]. These could confirm the initial, promising results. However, no randomized controlled trials have been completed [10].

The National Cancer Institute (NCI) in collaboration with the American College of Radiology Imaging Network (ACRIN) started a study in 2002 entitled the “National Lung Screening Trial (NLST) [22]. The

study includes 50 000 individuals at high risk for lung cancer who were randomized to low dose computed tomography or chest radiography. The study is being carried out in collaboration with 30 different centers in the United States. The aim is to determine whether or not a 20 percent or higher difference in lung cancer mortality can be found between the two arms of the study. The study covers 7 years, ie, 3 years of screening and 4 years of followup.

Large, randomized studies are also planned in Denmark, Holland, Norway, Germany, Great Britain, and possibly other European countries.

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