LOW DOSE CT LUNG CANCER SCREENING: IT’S TIME HAS COME

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OBJECTIVES

- Understand the controversies of screening for cancer control in a large population
- Understand primary and secondary prevention of lung cancer
- Understand the risk factors associated with lung cancer and the trends in lung cancer incidence and mortality
- Understand the NLST data and the implications for wide based LDCT lung cancer screening
- Understand the benefits and risks for LDCT lung cancer screening in the high risk population

LDCT – low dose CT  NLST – national lung screening trial
POPULATION SCREENING FOR CANCER CONTROL

- SCREENING – the presumptive identification of unrecognized (asymptomatic) disease by means of a test, examination or other procedure that can be applied rapidly.

- Screening as an approach to cancer control is controversial
POPULATION SCREENING FOR CANCER CONTROL

- WHY SCREEN?
  1) realization that methods for preventing and treating many cancers remain unsatisfactory
  2) compelling, intuitive appeal of the idea that early detection of cancer will be rewarding
OBJECTIVES OF A SCREENING PROGRAM:
1) Operational – application of a relatively simple, inexpensive test to a large number of persons to classify them as likely or unlikely to have the cancer that is the object of the screen
2) Outcomes – the objective of screening for a particular cancer is to reduce the morbidity and mortality from that cancer among the persons being screened
Diseases suitable for screening have 3 characteristics:
1) the disease should have serious consequences, cancer has the potential consequence of death
2) the disease must have a treatment that when applied to the screen detected stage of the disease is more effective than treatment applied after symptoms have led to a diagnosis. There is no point in screening for a disease that can be treated successfully after symptoms appear, nor is it reasonable to screen for an untreatable disease.
3) the detectable pre-clinical phase (DPCP) should have a high prevalence among the persons being screened. Otherwise too few cases will be detected to justify the expanse
POPULATION SCREENING FOR CANCER CONTROL

- **TPCP** – total preclinical phase – begins when cancer is first present - currently cannot be determined.
- **DPCP** – detectable preclinical phase – begins when the disease could be detected by the screening test to be used. A test that can detect a very early state of the cancer is associated with a longer DPCP than a DPCP associated with a test that can only detect more advanced states.

![Diagram showing stages of cancer development and screening phases](image-url)

TPCP – age 30-60  
DPCP – age 50-60
POPCULATION SCREENING FOR CANCER CONTROL

- Suitable test – for a screening program to be successful it must be directed at a suitable disease and must be based on a good test. A good test has both a high specificity and a high sensitivity.
  - SENSITIVITY – among people who have the DPCP of the disease, the proportion positive to the screening test.
  - SPECIFICITY – among people who do not have the DPCP of the disease, the proportion negative to the test.
POPULATION SCREENING FOR CANCER CONTROL

- DEFINITIONS:
  - **Prevalence** – proportion of people with a condition at a specified time – such as at an initial screening exam
  - **Sensitivity** – the effectiveness of a test in detecting cancer in those who have the disease
  - **Specificity** – the extent to which a test gives negative results in those that are free of that disease
  - **Positive predictive value** – among the persons positive to the screening test, the proportion found by diagnostic evaluation to have the disease in question

Sensitivity and specificity are measures of validity – ie. The extent to which a test does what it is suppose to
POPULATION SCREENING FOR CANCER CONTROL

- **TEST OUTCOME** | **EARLY DISEASE**
  - POSITIVE | A | B
  - NEGATIVE | C | D

- **SENSITIVITY** – $\frac{A}{A+C}$
- **SPECIFICITY** - $\frac{D}{B+D}$
- **POSITIVE PREDICTIVE VALUE (PPV)** – $\frac{A}{A+B}$

For a rare disease such as most cancers the major determinants of the PPV are the prevalence of the detectable pre-clinical disease phase, the specificity of the test and to a lesser extent its sensitivity.
POPULATION SCREENING FOR CANCER CONTROL

- WHY CONTROVERSIAL – DOESN’T SCREENING SAVE LIVES? YES BUT….
  1) hidden costs of screening and excess morbidity which screening can create. Screening may lead to a procedure which otherwise may never have been performed (many of which may have potential complications).
  2) screening may lead to more or earlier debilitating treatment whose cancers are incurable or would die of inadvertent disease before their cancers became symptomatic.
POPULATION SCREENING FOR CANCER CONTROL

WHY CONTROVERSIAL – DOESN’T SCREENING SAVE LIVES? YES BUT….

3) some screening benefits are illusionary. For example a screening program might bring about “improved survival” which may be only to the advancement of the time of diagnosis of cancer and not to the postponement of death (lead time bias)
POPULATION SCREENING FOR CANCER CONTROL

- LET US LOOK AT A CASE
  George is a 70 year old who sees an add for free prostate screening at a local mall. The add notes that 95% of men diagnosed with localized disease are cured. George’s PSA comes back elevated. George gets an appointment with a local Urologist 2 weeks later. During the wait he is scared out of his mind and thinks he is going to die. A biopsy of the prostate is eventually performed and he has 2/12 biopsy specimens showing cancer Gleason score 3/3. After consideration of multiple options George decides to undergo a robotically assisted radical prostatectomy.
LET US LOOK AT A CASE
Pathology showed a small focus of tumor (5mm) with a Gleason score of 3/3, low grade. He is ecstatic. But he is also now incontinent and impotent. 3 months after surgery his PSA is 0.9. George is convinced his cancer is not gone. He goes to see a Radiation Oncologist and eventually receives radiation of the prostate bed without definitive proof of residual cancer or recurrence. He develops a colo-vesicle fistula and ends up with a colostomy and ileoconduit!! All this for an indolent cancer that may have never impacted George’s life expectancy - overdiagnosis.
POPULATION SCREENING FOR CANCER CONTROL

- Population based screening for cancer control is a double edged sword with potential benefits as well as potential costs.
- This is why the potential benefits of a screening program must outweigh the potential costs.
LUNG CANCER SCREENING

**WHY**: number one cause of cancer related mortality in the US
224,000 new cases per year with 160,000 deaths per year
More people die of lung cancer than breast, colon and prostate combined
LUNG CANCER SCREENING

An unscreened population
RISK FACTORS

- A current or former history of tobacco use is the primary risk factor in 85% of patients diagnosed with lung cancer.
- Other risk factors include: radon exposure, asbestos, silica, cadmium, arsenic, beryllium, chromium, nickel, diesel fume and coal smoke exposure.
TRENDS IN TOBACCO USE

- **1965** – 42.4% smokers
- **2011** – 19% smokers
- Higher prevalence - military (1 in 3) vs (1 in 5) and lower socioeconomic groups
LUNG CANCER: INCIDENCE AND MORTALITY: US

Lung cancer incidence is declining, particularly in men
WHY: PRIMARY PREVENTION (SMOKING CESSATION)
LUNG CANCER: INCIDENCE AND MORTALITY: US

As the incidence of lung cancer has decreased so have the number of deaths. Despite this decrease 159,240 people will die from lung cancer this year in the US. The majority of people dying from lung cancer now are FORMER SMOKERS.
LUNG CANCER: INCIDENCE AND MORTALITY: US

- Most people dying from lung cancer now are **FORMER SMOKERS**
  - 50% OF LUNG CANCER DIAGNOSIS – FORMER SMOKERS
  - 35% OF LUNG CANCER DIAGNOSIS – CURRENT SMOKERS
  - 15% OF LUNG CANCER DIAGNOSIS – NEVER SMOKED

- Lung cancer 5 year overall survival has changed little in the past 40 years
  - 1975 – 12%
  - 2014 – 16-17%
LUNG CANCER: INCIDENCE AND MORTALITY: US

- Stagnant survival result of absent Secondary Prevention

Former smokers cannot benefit from primary prevention
Secondary prevention = lung screening
Lung screening – find disease at an earlier, more treatable stage
Lung screening goal – decrease mortality not incidence
Primary prevention goal (smoking cessation) – decrease incidence of lung cancer
LUNG CANCER SCREENING: What Does the Data Tell Us

- Henschke, CI, et al. Lancet 1999;345:99-105 – ELCAP (early lung cancer action project) study – were able to show that low dose chest CT greatly improved the likelihood of detection of small non-calcified pulmonary nodules compared with chest X-ray.
LUNG CANCER SCREENING: What Does the Data Tell Us

- NEJM October 2006 - results of the ELCAP study
  - 31,576 asymptomatic persons at high risk for lung cancer screened from 1994-2005
  - Lung cancer was found in 484 participants
  - 412 (85%) of cancers were stage 1 with an estimated 10 year survival of 88%
  - Among the stage 1 patients who underwent surgery within the first month after diagnosis 10 year survival was 92%
  - 8 patients refusing therapy died within 5 years

LUNG CANCER SCREENING: What Does the Data Tell Us

NSCLC:

Stage I, II and IIIA
- potential cure

Stage IIIB and IV
- palliative only

Survival in an unscreened population ranges from 73% for IA to < 10% for advanced stage disease

CONCLUSION: screening with the use of low-dose CT reduces mortality from lung cancer
National Lung Cancer Screening Trial: NLST

- Multicenter randomized controlled trial
  - Sponsor – NCI division of cancer treatment and diagnosis
  - 33 US screening centers
  - Cost - $300,000,000
National Lung Cancer Screening Trial: NLST: Methods

- **53,456** participants enrolled between August 2002 and April 2004 at high risk for lung cancer
- **26,722** were randomly assigned to low dose CT screening and **26,732** assigned to single view PA chest radiography
- Data on lung cancer cases and deaths were collected through December 31, 2009
- Age range – **55-74**
- Greater than a **30 pack year** smoking history
- Active **smoker or had quit** within the past **15 years**
- Patients had to be medically operable, asymptomatic and have no prior history of cancer within the past **5 years**
National Lung Cancer Screening Trial: NLST: Methods

- **Screening arms:**
  - Low dose chest CT (1.5 mSv or less)
  - PA chest radiograph (0.02 mSv)

- **Screening intervals:**
  - T0: baseline prevalence screen
  - T1: year 1 incidence screen
  - T2: year 2 incidence screen

- **Positive test:**
  - Non-calcified nodule greater than 4mm in diameter
  - Other findings suspicious for lung cancer (effusion etc)
  - Workup for positives determined by the PCP not NLST
National Lung Cancer Screening Trial: NLST: Results

- **Lung Cancer Specific Mortality:**
  - 20% reduction in lung cancer specific mortality
  - LDCT = 365 deaths, CXR = 443 deaths
  - median follow-up – 6.5 years
  - in November 2010 the study was halted early when the 20% reduction in cancer specific mortality was realized

- **Overall mortality:**
  - 6.6% reduction in overall mortality
  - LDCT – 1877 deaths, CXR – 2000 deaths
  - not statistically significant when lung cancer deaths were excluded
National Lung Cancer Screening Trial: NLST: Results

- Lung cancer prevalence: 1%
  1 in 100 at risk patients have lung cancer

- Lung cancer annual incidence: 0.5-0.8%
  the annual incidence decreases on follow-up scans such that 1 in 125 have lung cancer

- Small cell cancer: not detected at an earlier stage

- Number needed to screen to save (NNS) 1 life: 320
  -as a comparison the NNS for mammography to save 1 life ranges from 233 to 746 depending on age
National Lung Cancer Screening Trial: NLST: Rate of positive screenings

- LDCT (24.2%) greater than 3X more sensitive than CXR (6.9%)
  - T0 and T1 rate – 27%
  - T2 rate – 16.8%
- LDCT – at least one positive result (3 screens): 39.1%
- LDCT – significant incidental finding: 7.5%
- Any lung nodule that was stable for 2 years was considered benign based on Fleischner Society guidelines
- NLST group is a highly selected group representing approximately 3% of the adult population or approximately 7 million people
National Lung Cancer Screening Trial: NLST: False Positive Workup and Adverse Events

- **FALSE POSITIVES:**
  - Most will have non-invasive imaging follow-up
    * CXR: 14.4%
    * Chest CT: 49.8%
    * PET/CT: 8.3%
  - Invasive diagnostic procedures: 2.6%
  - Complication rate: 1.4%
  - Major complication rate: 0.06%

- **True positives:**
  - Invasive procedure major complication: 11.2%
  - Surgical resection mortality: 1%
National Lung Cancer Screening Trial NLST: False Positive Workup and Adverse Events

- **FALSE POSITIVE RATE:**
  - 24.2% rate – there is roughly a 1 in 4 chance you will end up with a false positive and will need further workup
  - Mammography has a 10-12% false positive rate

- **FALSE DISCOVERY RATE (THE CHANCE YOU DO NOT HAVE CANCER WITH A POSITIVE SCAN):**
  - 96% for LDCT
  - Mammography is about the same

- **FALSE POSITIVE BIOPSY RATE:**
  - LDCT: 0.4-2.4% if screened the patient will have an unnecessary invasive procedure
NATIONAL LUNG CANCER SCREENING TRIAL NSLT: STAGE AT DIAGNOSIS

- In an unscreened population 70% of cancers detected are stage 3 and 4 – incurable
- In the NLST 70.2% of the cancers detected were stage 1 or 2 – both potentially curable
- Remember the ELCAP study: 85% of patients screened had a stage 1 cancer and those who underwent surgery had a projected 10 year survival of 92%
- In an unscreened population the 5 year overall survival for stage 1A and 1B lung cancers are 73% and 58% respectively
- Thus 4 out of 5 patients screened are potentially curable
NATIONAL LUNG SCREENING TRIAL

- Over 3 rounds of screening 24.2% of scans were positive; 96.4% of these were false positive.
- Sensitivity – how well does the test detect the disease: 93.8%
- Specificity - how well does the test exclude those without the disease: 73.4%
- Positive predictive value for a pulmonary nodule over 4mm being a cancer: 3.8%
NCCN GUIDELINES

- NCCN (National Comprehensive Cancer Network) – came out with screening guidelines on 10/26/11.

- NCCN Considerations:
  - Prolonged debate
  - Cost to society
  - Patient anxiety associated with screening
  - Radiation exposure
  - False positives and their impact
  - Operational concerns

- NCCN gave low dose lung CT a category 1 recommendation which is the highest rating based on high levels of evidence and uniform consensus that the intervention is appropriate.
NCCN GUIDELINES: HIGH RISK GROUPS

- **GROUP 1**
  - 55-74 YEARS OLD
  - CURRENTLY A SMOKER OR HAVE QUIT WITHIN 15 YEARS
  - HAVE AT LEAST A 30 PACK YEAR SMOKING HISTORY

- **GROUP 2**
  - 50-74 YEARS OLD
  - HAVE AT LEAST A 20 PACK YEAR SMOKING HISTORY
  - HAVE ONE ADDITIONAL LUNG CANCER RISK FACTOR, NOT TO INCLUDE SECOND HAND SMOKE
NCCN GUIDELINES: HIGH RISK GROUP 2 RISK FACTORS

- Personal cancer history
- Family history of lung cancer in a first degree relative
- Chronic lung disease – emphysema, pulmonary fibrosis
- Carcinogen exposure – arsenic, asbestos, cadmium, chromium, diesel fumes, nickel, radon and silica
NCCN GUIDELINES: 2014

- The cut-off for suspicious non-calcified pulmonary nodules has been changed from 4 mm to 6 mm for further workup.
- This was done to decrease the number of follow-up LDCT scans of nodules that in all likelihood are benign: decrease the false positive rate.
Current NCCN guidelines no longer include close follow-up for 4 and 5 mm nodules.
LUNG CANCER SCREENING: RISKS AND BENEFITS

**RISKS**

- Futile detection of small aggressive tumors or indolent disease
- Anxiety of test findings
- Complications from diagnostic work-up
- False positive results
- False negative results
- Unnecessary testing
- Radiation exposure
- Cost
- Unproductive work-up

**BENEFITS**

- Decreased lung cancer mortality
- Improved quality of life
- Reduction in disease-related morbidity
- Reduction in treatment-related morbidity
- Improvement in healthy lifestyles
- Reduction in anxiety
- Cost effectiveness
LUNG CANCER SCREENING: RISKS

- **Unproductive diagnostic work-up**: NSLT – no specific mandate for the management of pulmonary nodules. NCCN guidelines now mandate specific follow-up based on nodule size and growth patterns.

- **Overdiagnosis**: screening related diagnosis and treatment of a cancer that would otherwise not have been important in the individual’s lifetime. Estimated to be 10-18%.

- **Quality of life (QOL)**: in the NSLT study adverse events were few. No studies have reported long term differences in anxiety or distress levels associated with LDCT screening participants.
LUNG CANCER SCREENING: RISKS

- **Radiation-related harms**: radiation dose per scan in the NLST was 1.5 mSv. Today an even lower dose is widely used (< 1.0 mSv). The American Association of Physicists in Medicine (AAPM) states: “predictions of hypothetical cancer incidence and deaths in patient populations exposed to such low doses are highly speculative and should be discouraged”. The threshold radiation dose cited by the APPM as being potentially associated with carcinogenesis is 50 mSv.

The risk of low-dose radiation exposure also has to be considered in the context of the screening setting. The screening population is a group of heavy smokers in their 6th decade of life most likely with other health factors limiting life expectancy. The latent period between radiation exposure and development of cancer is 15-30 years, probably well beyond the life expectancy of a heavy smoker.
## LUNG CANCER SCREENING: COST

### Cost Of Cervical, Colorectal, Breast, And Lung Cancer Screening Per Life-Year Saved

<table>
<thead>
<tr>
<th>Type of cancer</th>
<th>Screening technique</th>
<th>Cost per life-year saved (dollars, year of original study)</th>
<th>Date of original study</th>
<th>Cost per life-year saved (2012 dollars)</th>
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<tbody>
<tr>
<td>Cervical</td>
<td>Pap smear</td>
<td>33,000</td>
<td>2000</td>
<td>50,162–75,181</td>
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<td>Colorectal</td>
<td>Colonoscopy</td>
<td>11,900</td>
<td>1999</td>
<td>18,705–28,958</td>
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<td>Breast</td>
<td>Mammography</td>
<td>18,800</td>
<td>1997</td>
<td>31,309–51,274</td>
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<tr>
<td>Lung</td>
<td>LDCT (baseline scenario)</td>
<td>18,862</td>
<td>2012</td>
<td>18,862</td>
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<tr>
<td></td>
<td>LDCT (lowest-cost scenario)</td>
<td>11,708</td>
<td>2012</td>
<td>11,708</td>
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<tr>
<td></td>
<td>LDCT (highest-cost scenario)</td>
<td>26,016</td>
<td>2012</td>
<td>26,016</td>
</tr>
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</table>

The Milliman group published cost per life year saved estimates for lung screening and estimated that the cost per life year saved was just under $19,000.00

Pyenson et al. Health Affairs 31, no. 4 770-779: April 2012
JSCC: PATIENT FLOW

- Patient calls – 515-263-5370
  - Intake person
  - Evaluate eligibility
  - PCP order
JSCC: PATIENT FLOW

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  - May qualify – Call to be made by nurse to assess for a secondary risk factor
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      - Do qualify – record PCP and schedule appointment
JSCC: PATIENT FLOW

- Patient calls – 515-263-5370
- Intake person
- Evaluate eligibility

  - Do not qualify – refer back to PCP
  - May qualify – Call to be made by nurse to assess for a secondary risk factor
  - Do qualify – record PCP and schedule appointment

  - Obtain PCP order
  - 48 hour reminder

      Screen patient
      No IV
      No changing clothes

PCP order
JSCC: PATIENT FLOW

- Patient screened
  - Radiologist interpretation
  - Schedule 1 year F/U
    - If < 74
  - S negative
    - Lung Rads 1,2
Patient screened → Radiologist interpretation

- Schedule 1 year F/U if < 74
- 2/3 of screenings
- S negative
- Lung Rads 1,2
- 1/3 of screenings
- S positive or
- Lung Rads 3,4 or 5
- Follow NCCN guidelines – to be included in the report.
  Will be up to the PCP to order follow-up imaging.
LUNG RADS: STANDARD REPORTING

- LUNG NUMBER CATEGORY
  Category 1: negative 12 mo F/U

  Category 2: negative with benign pulmonary findings 12 mo F/U

  Category 3: positive, likely benign F/U per NCCN guidelines – 16-27% of cases

  Category 4: positive, suspicious for malignancy

  Category 5: known cancer

  S category: positive for extrapulmonary finding not for lung cancer but requires follow-up. Thyroid mass, renal or liver mass, aneurysm
62 year old woman with a history of well controlled hypertension. She returns for a routine, annual visit. She is completely asymptomatic and walks daily. She has a 35 pack year smoking history and quit 10 years ago. She has recently heard about LDCT lung screening and asks if this is appropriate for her?

How would you answer her?
CASE SCENERIO

- You discuss the benefits (earlier detection and possible cure) and the risks (false positives (24%), potential need for invasive procedures and anxiety associated with test results) with the patient (*shared decision making*) and she decides to undergo screening.

- She reports to the Radiology department at her appointed time and has a low dose CT scan all of which takes about 10 minutes.
A 7mm non-calcified pulmonary nodule is found. The Radiologists recommendation is a follow-up LDCT in 3 months based on NCCN criteria.
The patient calls and says she is worried about the findings and wonders if she should have surgery to remove it. What would you tell her?

Based on the NLST, 27% of individuals will have a finding in the lung on the initial screen which will require follow-up, most of which will be with repeat imaging.

96% of these findings will be benign.

If the nodule is found to be a lung cancer (screened stage 1A) she will have a 92% chance of being cured with surgery.

She agrees to a 3 month follow-up.
A 3 month LDCT is performed and the nodule has grown to 11mm. She was found to have a screened pathologic stage 1A lung cancer with a 92% projected 10 year survival. In the unscreened population 5 year survival is predicted to be 73%
LDCT LUNG SCREENING: THE BOTTOM LINE

- Screening should be performed using a shared decision making process between the primary care physician and the patient discussing the pros and cons of screening as well as potential diagnostic and therapeutic options.
- Patients must understand that this is an ongoing process.
- Facilities performing LDCT screening must adhere to strict performance criteria including ongoing analysis of dose, standardized lung Rads reporting and robust communication with the patient and PCP so appropriate follow-up and diagnostic decisions are made.
LDCT LUNG SCREENING

- Remember LDCT lung screening is a secondary prevention and appears to improve overall mortality from lung cancer

- **BUT**

- **EVEN MORE IMPORTANT IS PRIMARY PREVENTION - KEEPING PEOPLE FROM SMOKING TO START WITH!!!**
It's a Jungle out there!

Frankly, you look more dumb than cool, and you can't even light the darn thing!

Hagen Cartoons: http://www.hagencartoons.com
REFERENCES

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