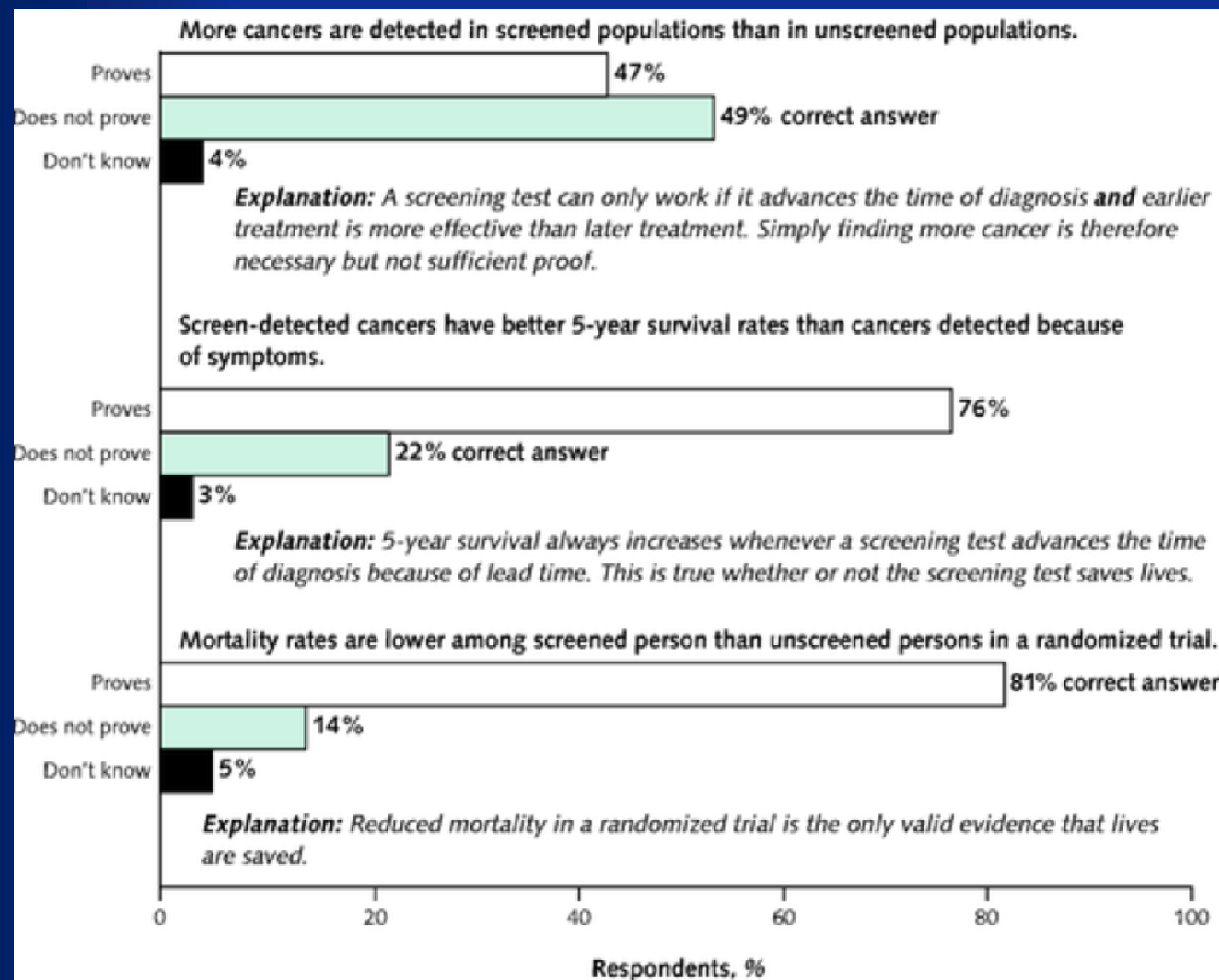# Lung Cancer Screening Update

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Outline

- **Screening; Some simple but necessary truths**

- **Do people benefit from screening?**

- **What are the harms (and are they outweighed by benefits)?**

- **Can it be done in a cost effective manner?**

Which of these establishes the efficacy of a screening test?

More cancers are detected in screened populations than in unscreened populations.

- Proves — 47%
- Does not prove — 49% correct answer
- Don't know — 4%

Explanation: A screening test can only work if it advances the time of diagnosis **and** earlier treatment is more effective than later treatment. Simply finding more cancer is therefore necessary but not sufficient proof.

Screen-detected cancers have better 5-year survival rates than cancers detected because of symptoms.

- Proves — 76%
- Does not prove — 22% correct answer
- Don't know — 3%

Explanation: 5-year survival always increases whenever a screening test advances the time of diagnosis because of lead time. This is true whether or not the screening test saves lives.

Mortality rates are lower among screened person than unscreened persons in a randomized trial.

- Proves — 81% correct answer
- Does not prove — 14%
- Don't know — 5%

Explanation: Reduced mortality in a randomized trial is the only valid evidence that lives are saved.

Respondents, %

Test detects more cancers than control group

Longer 5 yr survival in test vs. controls

Fewer tested patients die of the disease than controls

Outline

- **Screening background**
  - (Some simple obvious truths about screening)

- **Do people benefit from screening?**

- **What are the harms (and are they outweighed by benefits)?**

- **Can it be done in a cost effective manner?**

How did we get here?

- **Summary of CXR screening trials**
- **Three NCI screening trials in 1970s**
  - > 30,000 subjects
  - CXR detected more cases (Length Bias)
  - More early stage disease (Length and Lead time Bias)
  - Improved survival in the screened group (Length and Lead time bias)
  - *No difference* in mortality (Overdiagnosis?)
- *Q: How many compared CXR screening to no screening?*

NLST study design

- **Study design**
  - 50,000 healthy current or former (15 yrs), heavy (30 pk-yr) smokers, age 55-74
  - Yearly CXR *or* CT at 0, 1, and 2 years
  - 2002-2008, with follow up through 2011
- **90% power to detect 20% mortality benefit**
  - All cause mortality, Prevalence, incidence, interval cancers, PPV, NPV, Stage distribution
  - HRQOL, and Anxiety instrument
  - Medical resource utilization for positive screen and cost effectiveness

Cumulative Deaths from Lung Cancer.

B Death from Lung Cancer

500—

	Low-dose CT 26,722 people		Chest X-ray 26,732 people
Benefit: How did CT scans help compared to chest X-ray, an ineffective screening test?			
3 in 1,000 fewer **died from lung cancer**	18 in 1,000	versus	21 in 1,000
5 in 1,000 fewer **died from all causes**	70 in 1,000	versus	75 in 1,000
Harm: What problems did CT scans cause compared to chest X-ray?			
223 in 1,000 more had at least one **false alarm**	365 in 1,000	versus	142 in 1,000
18 in 1,000 more had a **false alarm leading to an invasive procedure,** such as bronchoscopy, biopsy, or surgery	25 in 1,000	versus	7 in 1,000
2 in 1,000 more had a **major complication** from Invasive procedures	3 in 1,000	versus	1 in 1,000

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Where we are now

USPSTF recommends *annual* screening for lung cancer with low-dose computed tomography (LDCT) in persons at high risk for lung cancer based on age (*55-80*) and smoking history (>30 pk-yrs, within 15 yrs)

LDCT Screening in asymptomatic high risk persons can reduce disease specific mortality by 20%

But 20% reduction in mortality isn't very high, is it?

How does this compare to other cancer screening strategies?

Intervention	Age	Screen frequency	RR of death	Baseline risk of death	NNS	$/QALY
PSA						
ERSPC[1]	55-69	q 2-7 years	0.80 (0.65-0.98)	0.4%	1,400	
PLCO [2]	55-74	Yearly X 6y	1.10 (0.80-1.50)	0.1%	N/A	
Mammography[3,4]						
	39-49[4]	Yearly X 2-9y	0.85 (0.75-0.96)	0.3%	1900	
	50-59	Yearly X 10	0.86 (0.75-0.99)	0.5%	1,300	
	60-69	Yearly X 10	0.68 (0.54-0.87)	0.8%	380	$58,000 [5]
Colon cancer						
Fecal occult blood [3]		~ 9 years	0.77	??	808	
Flex Sig/FOB [6]	50	q 5 years (with FOBT)	0.82	??	361	$92,900
Colonoscopy			(Probably better)	??	??	
Lung cancer						
CXR [7]	55 - 74	Yearly x 4	0.94 (0.81-1.10)	1.6%	NA	
Low-dose CT [8]	55-74	Yearly x 3	0.80 (0.73-0.93)	1.7%	320	$72,800* (vs. CXR)

1. Chou R, : Ann Int Med 2011; 155(11): 762-771
2. Andriole GL,NEJM 2009; 360(13): 1310-1319
3. Rembold CM. BMJ 1998; 317(7154): 307-312
4. Nelson HD Ann Int Med 2009; 151(10): 727-737
5. Stout JNCI 2006; 98(11): 774-782
6. Elmunzer BJ. PLoS Med 2013; 9(12): e1001352
7. Oken MM JAMA 2011; 306(17): 1865-1873
8. Aberle DR NEJM 2011; 365(5): 395-409

Summary

- **Evidence shows that the number needed to screen to save one life among high risk individuals is 320**

- **This compares favorably with other currently accepted methods of cancer screening both from an efficacy and cost standpoint**

- **Harms?**

Outline

- **Screening background**
  - **(Some simple obvious truths about screening)**

- **Do people benefit from screening?**

- **What are the harms (and are they outweighed by benefits)?**

- **Can it be done in a cost effective manner?**

What are the harms?

Can the harms be expected to be low in a general population?

Can they be further minimized?

"False positives"

- "Positive" is any non calcified nodule > 4 mm
  - 36% screened with LDCT had a positive finding (96% are not cancer)
  - Most are managed by follow up CT
  - A single additional CT at 6 months
    - 0,12 24 months or…
    - 0, 6, 12, and 24 months

An editorial comment

- **False positive implies a test that suggests a disease is present when it is not**

- **In the context of a LDCT, a 5 mm nodule is considered "positive"**

- **Is this really a _false positive_?**
  - **30+ years of cross sectional imaging makes this at worst, a manageable and very familiar problem (Shouldn't lead to invasive testing)**

Other screening harms?

- **Anxiety/QOL**
- **Invasive procedures**
- **Overdiagnosis/Overtreatment**
- **Additional testing and costs**

Anxiety/QOL

Impact of Lung Cancer Screening Results on Participant Health-Related Quality of Life and State Anxiety in the National Lung Screening Trial

Ilana F. Gareen, PhD[1,2]; Fenghai Duan, PhD[1,3]; Erin M. Greco, MS[1]; Bradley S. Snyder, MS[1]; Phillip M. Boiselle, MD[4,5]; Elyse R. Park, PhD, MPH[6,7,8]; Dennis Fryback, PhD[9]; and Constantine Gatsonis, PhD[1,3]

CONCLUSIONS: In a large multicenter lung screening trial, participants receiving a false-positive or SIF screen result *experienced no significant difference in HRQoL or state anxiety at 1 or at 6 months after screening* relative to those receiving a negative result.

KEYWORDS: quality of life, anxiety, lung cancer, screening, clinical trials.

Potential harms?

- **Anxiety/QOL**
- **Invasive procedures**
- **Overdiagnosis/Overtreatment**
- **Additional testing and costs**

Complications after the Most Invasive Screening-Related Diagnostic Evaluation Procedure, According to Lung-Cancer Status.

Table 4. Complications after the Most Invasive Screening-Related Diagnostic Evaluation Procedure, According to Lung-Cancer Status.*

Complication	Thoracotomy, Thoracoscopy, or Mediastinoscopy	Bronchoscopy	Needle Biopsy	No Invasive Procedure	Total
	number (percent)				
Low-dose CT group					
Positive screening results for which diagnostic information was complete	509 (100.0)	76 (100.0)	33 (100.0)	31 (100.0)	649 (100.0
No complication	344 (67.6)	69 (90.8)	26 (78.8)	26 (83.9)	465 (71.6)
At least one complication	165 (32.4)	7 (9.2)	7 (21.2)	5 (16.1)	184 (28.4)
Most severe complication classified as major	71 (13.9)	2 (2.6)	0	2 (6.5)	75 (11.6)
Most severe complication classified as intermediate	81 (15.9)	5 (6.6)	7 (21.2)	2 (6.5)	95 (14.6)
Most severe complication classified as minor	13 (2.6)	0	0	1 (3.2)	14 (2.2)
Death within 60 days after most invasive diagnostic procedure†	5 (1.0)	4 (5.3)	1 (3.0)	0	10 (1.5)
Radiography group					
Positive screening results for which diagnostic information was complete	189 (100.0)	46 (100.0)	29 (100.0)	15 (100.0)	279 (100.0
No complication	130 (68.8)	42 (91.3)	28 (96.6)	14 (93.3)	214 (76.7)
At least one complication	59 (31.2)	4 (8.7)	1 (3.4)	1 (6.7)	65 (23.3)
Most severe complication classified as major	22 (11.6)	1 (2.2)	0	1 (6.7)	24 (8.6)
Most severe complication classified as intermediate	32 (16.9)	2 (4.3)	1 (3.4)	0	35 (12.5)
Most severe complication classified as minor	5 (2.6)	1 (2.2)	0	0	6 (2.2)
Death within 60 days after most invasive diagnostic procedure†	4 (2.1)	5 (10.9)	1 (3.4)	1 (6.7)	11 (3.9)

Lung Cancer Confirmed

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Complications after the Most Invasive Screening-Related Diagnostic Evaluation Procedure, According to Lung-Cancer Status.

ole 4. Complications after the Most Invasive Screening

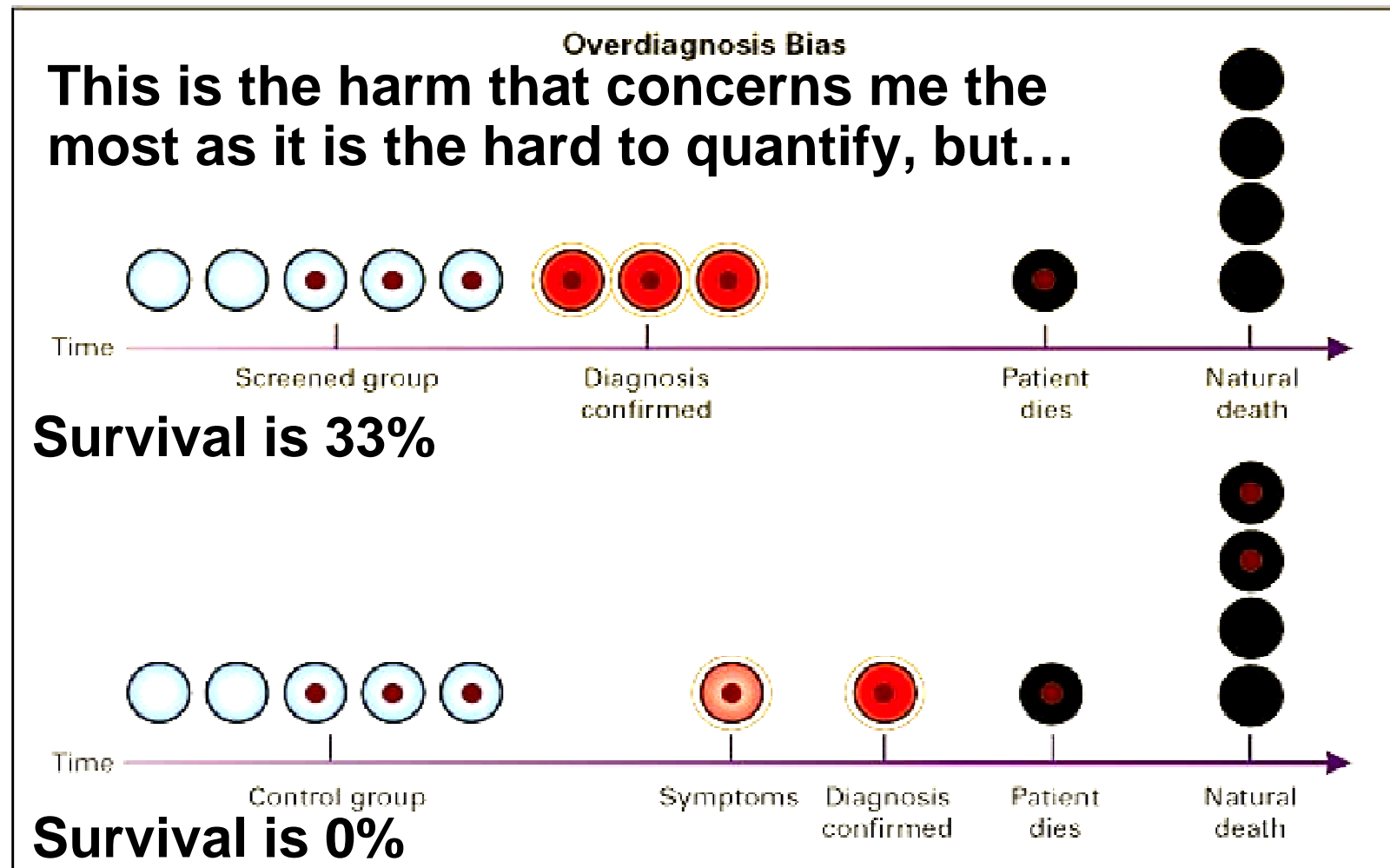| mplication	Thoracotomy, Thoracoscopy, or Mediastinoscopy	Lung Cancer Not Confirmed		No Invasive Procedure	Total
		Bronchoscopy	Needle Biopsy		
			number (percent)		
w-dose CT group					
sitive screening results for which diagnostic informati was complete	164 (100.0)	227 (100.0)	66 (100.0)	16,596 (100.0)	17,053 (100.0)
No complication	138 (84.1)	216 (95.2)	59 (89.4)	16,579 (99.9)	16,992 (99.6)
At least one complication	26 (15.9)	11 (4.8)	7 (10.6)	17 (0.1)	61 (0.4)
Most severe complication classified as major	9 (5.5)	2 (0.9)	0	1 (<0.1)	12 (0.1)
Most severe complication classified as intermedi	13 (7.9)	9 (4.0)	6 (9.1)	16 (0.1)	44 (0.3)
Most severe complication classified as minor	4 (2.4)	0	1 (1.5)	0	5 (<0.1)
Death within 60 days after most invasive diagnostic procedure†	2 (1.2)	4 (1.8)	0	5 (<0.1)	11 (0.1)
diography group					
sitive screening results for which diagnostic informati was complete	45 (100.0)	46 (100.0)	24 (100.0)	4,559 (100.0)	4,674 (100.0)
No complication	38 (84.4)	46 (100.0)	23 (95.8)	4,551 (99.8)	4,658 (99.7)
At least one complication	7 (15.6)	0	1 (4.2)	8 (0.2)	16 (0.3)
Most severe complication classified as major	1 (2.2)	0	0	3 (0.1)	4 (0.1)
Most severe complication classified as intermedi	6 (13.3)	0	1 (4.2)	2 (<0.1)	9 (0.2)
Most severe complication classified as minor	0	0	0	3 (0.1)	3 (0.1)
Death within 60 days after most invasive diagnostic procedure†	0	0	0	3 (0.1)	3 (0.1)

Invasive procedures

- **16 deaths within 3 months of screen**
  - **6 did not have cancer**
  - **0.06% of the false positive vs 11.2% of true positives CT screens were associated with a major complication**
- **Surgical Mortality _(1%)_**
  - **National average 3-5%**

Potential harms?

- **Anxiety/QOL**
- **Invasive procedures**
- **Overdiagnosis/Overtreatment**
- **Additional testing and costs**

Overdiagnosis Bias

Overdiagnosis Bias

This is the harm that concerns me the most as it is the hard to quantify, but…

Survival is 33%

Survival is 0%

Patz EF Jr et al. N Engl J Med 2000;343:1627-1633.

Potential harms?

- **Overdiagnosis/Overtreatment**
  - **Studies estimate that this occurs in 9%-18.5% of screen detected lung cancers**
  - **Estimates of overdiagnosis are time dependent (Relative to competing mortality)**
    - **Also dependent on comorbidity**

Potential harms?

- **Anxiety/QOL**
- **Invasive procedures**
- **Overdiagnosis/Overtreatment**
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Outline

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15-year costs of QALY saved by lung cancer screening.

	NY-ELCAP stage shift	NLST stage shift
Screening		
Lung cancer screening and treatment costs	$27,814,25?,242	$34,054,299,361
QALYs saved by screening and treatment	?85,???	722,795
Cost per QALY saved	$28,240	$47,115
Screening + light smoking cessation intervention		
Additional costs for cessation	$1,361,556,665	$1,361,556,665
Additional QALYs saved by cessation	273,566	273,566
Cost per QALY saved	$23,1??	$35,545
Screening + intensive smoking cessation intervention		
A. NRT generic plus behavioral		
Additional costs for cessation	$3,212,191,737	$3,212,191,737
Additional QALYs saved by cessation	930,754	930,754
Cost per QALY saved	$16,198	$22,537
B. Bupropion generic plus behavioral		
Additional costs for cessation	$?,???,??,???	$4,088,822,965
Additional QALYs saved by cessation	930,754	930,754
Cost per QALY saved	$16,656	$23,067
C. Chantix plus behavioral		
Additional costs for cessation	$5,342,861,783	$5,342,861,783
Additional QALYs saved by cessation	930,754	930,754
Cost per QALY saved	$23,826	$23,826

$47,115

$35,545

$22,537

*NLST estimate is $72k

Villanti AC, (2013) PLoS ONE 8(8). *e71379*

PLOS | ONE

Factors affecting cost effectiveness of LDCT screening

Increasing costs

- Higher cost of LDCT
- Screening lower risk individuals (*Steep*)
- Increased frequency of follow up CTs

Decreases Costs

- Higher lung ca risk
- Tobacco cessation
- Further catch up cases in CXR arm
- Efficacy of CXR screening (none)
- Fewer follow up CTs
- Increasing rate of tobacco cessation

Lung Cancer Risk?

KIRK, SPOCK, MCCOY, AND ENSIGN RICKY ARE BEAMING DOWN TO THE PLANET. GUESS WHO'S NOT COMING BACK.

http://www.brocku.ca/lung-cancer-risk-calculator

	A Characteristics to be entered	B Enter Values	C Centered or referent	D Coefficient	E Contribution to estimate	F ORs
6	Age in years	55	62	0.0778868	-0.5452076	1.08
7	Education (enter the highest level obtained) 1 = less than high school grad; 2 = high school grad; 3 = Post high school training; 4 = Some college; 5 = College grad; 6 = Postgraduate/professional.	4	4	-0.0812744	0	0.92
8	Body Mass Index (BMI, weight in kg/height in meters^2)	28	27	-0.0274194	-0.0274194	0.97
9	COPD, emphysema or chronic bronchitis (0=No; 1=Yes)	0	0	0.3553063	0	1.43
10	Personal history of cancer (0=No; 1=Yes)	0	0	0.4589971	0	1.58
11	Family history of lung cancer (0=No; 1=Yes)	0	0	0.587185	0	1.80
12	Race/ethnicity					
13	White (referent group) (0=No; 1=Yes)	1		0	0	
14	Black (non-Hispanic) (0=No; 1=Yes)	0		0.3944778	0	1.48
15	Hispanic (0=No; 1=Yes)	0		-0.7434744	0	0.48
16	Asian (0=No; 1=Yes)	0		-0.466585	0	0.63
17	American Indian/Alaskan Native (0=No; 1=Yes)	0		0	0	
18	Native Hawaiian/Pacific Islander (0=No; 1=Yes)	0		1.027152	0	2.79
19	Smoking status, 0 = Former-smoker 1 = Current-smoker	0		0.2597431	0	1.30
20	Average number of cigarettes smoked per day**	50	-0.202154161	-1.822606	0.368447387	nonlinear
21	Duration smoked (years)	30	27	0.0317321	0.0951963	1.03
22	Years ago quit smoking. Enter zero for current smokers	2	10	-0.0308572	0.2468576	0.97
23	Model constant			-4.532506	-4.532506	
24				xb =	-4.394631713	
25				EXP(xb) =	0.0123	
26	Probability of lung cancer =	0.012				
27						
28	* Reference: Tammemagi et al. *Selection Criteria for Lung-Cancer Screening*. **NEJM.** 2013;368(8):728-36.					

Summary

- **Evidence shows that *properly* screening *high risk* people saves lives**

- **Minimizing harms…**
  - **Follow published guidelines on management of nodules**
  - **Most nodules *DO NOT* require biopsy**
  - **Screen healthy, high risk people**

- **Maximizing benefits**
  - **Validate risk models**
  - **Develop biomarkers**