Moving up in the world: screening for lung cancer

David L. Streiner, PhD, CPsych,[1,2] and Geoffrey R. Norman, PhD[2]

[1]Departments of Psychiatry, University of Toronto, Toronto, Ontario, Canada; [2]Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, Ontario, Canada

In one of our previous articles, we discussed a study of screening for prostate cancer.[1] Now we're going to move up a bit, at least anatomically, and discuss a study of screening for lung cancer.[2] We have previously defined ourselves as curmudgeons and skeptics; to those self-descriptions we now add a new term, "chutzpahniks." For those of you who may be unfamiliar with that Yiddish term, it means people who have chutzpah, which was defined by Leo Rosten[3] as: "that quality enshrined in a man who, having killed his mother and father, throws himself on the mercy of the court because he is an orphan." Our chutzpah stems from the fact that we are criticizing the results of a study that was published in the *New England Journal of Medicine* and highly praised in an editorial in that journal.[4] If we had less chutzpah, we wouldn't contemplate such a critique, but then again, if we had less chutzpah, we—a clinical psychologist and a nuclear physicist—wouldn't be writing articles in a cancer journal. So, on to the study.

Participants were people between the ages of 55 and 74 years who were currently or had previously been heavy smokers (at least 30 pack years), and were randomly assigned to be screened with either low-dose CT (26,722 participants) or chest radiography (26,732). They were screened at baseline and then 1 and 2 years later; those in whom lung cancer was diagnosed were not offered subsequent screening. What brought joy to the hearts of the researchers and the editorialist was the fact that there were 309 deaths from lung cancer per 100,000 person-years in the radiography group and only 247 deaths per 100,000 person-years in the CT group, representing a reduction of 20.0%. All-cause mortality was also reduced by 6.7% in the CT group. From a methodological point of view, it would be hard to fault this study. It involved over 53,000 patients enrolled in 33 sites, with adherence rates of 95% in the low-dose CT group and 93% in the radiography group over the three rounds.

Given these impressive figures, what leads to our curmudgeonly, skeptical, and chutzpahdikeh feelings? Actually, a number of things. The first is the sample size. As we've mentioned in a previous article,[5] sample size is much like the magnification in a microscope; the smaller the phenomenon you're looking at, the larger the sample size has to be. We have also said that you should be suspicious of relative statistics—the odds ratio and relative risk[6] (we just love it when we can quote ourselves). Both factors come into play here. Our feeling is that if you need over 50,000 patients, followed for 3 years, to demonstrate something, that something must be very small. That's masked by presenting the results as a relative reduction in mortality. To the authors' credit, they also give us the actual numbers, so we can see how large—or small—the effect actually is. Using their figures, the absolute reduction in deaths was (309 − 247) per 100,000 patient years, or 1 additional year of life for 62 people for every 100,000 screened. We leave it to you to determine if that's a lot or a little. *Ceteris paribus* (that's Latin for "All other things being equal," and used here merely to be a bit pretentious), we should switch immediately from radiography to low-dose CT scans. But, all things being equal, all things are never equal. At least two questions need to be raised.

The first is economic; how much more will it cost to replace all the X-rays with CT scans, and all those X-ray machines with CT scanners? There is a concept from economics called "opportunity costs;" that is, what opportunities are we foregoing by spending money on a given program? Money for health care is finite, as we are constantly reminded, so every extra dollar that is spent for CT scans rather than X-rays means that one

Commun Oncol 2012;9:110-111
doi:10.1016/j.cmonc.2012.02.011

less dollar is available to spend on other screening programs, prevention interventions, surgery, rehabilitation, or whatever.

The second question is risk. CT scans have a huge radiation dose relative to radiographs. In one review article, a dose for chest CT was 300-400 times greater than for CXR.[7] So-called "low-dose" CT is perhaps 20% of that; still a large amount of radiation. To put that in perspective, our favorite statistic in this regard, direct from BBC World, is that if you are fool enough to add a whole body CT scan to your annual physical, at a cost, we're told, of about $1,000, you will receive the same amount of radiation you would get standing a mile and a half from ground zero at Hiroshima when the bomb went off. More seriously, there is some evidence that diagnostic imaging may induce delayed cancer.[8]

But, there is still a larger issue; that of false positives. When we wrote about mass screening,[9] we pointed out many problems that it can cause, especially when the prevalence of the disorder is low, the course of the disease is variable (aggressive in some people and lethargic in others), and the treatment far from perfect. The major difficulty is that, with a low prevalence, there will be many false positive results. This then leads to follow-up evaluations, with their associated costs and possible risks.

This is a particular problem in this study. There were a total of 75,126 low-dose CT scans given over the three screening rounds. Of these, 18,146 (24.2%) were positive. So far, so good; not a bad detection rate. But, of this number, there were only 649 confirmed cases of lung cancer. This represents less than 1% of all scans done. More tellingly, it means that the false positive rate was a whopping 96.4%. For the other group, there were 73,470 radiographs performed, of which 5,043 (6.9%) were positive, and 279 were confirmed to have lung cancer—fewer than 0.4% of the tests, and a false positive rate of 95.5%. That's about the same false positive rate as mammography, by the way.

And the result of these extremely high false positive rates? An additional 14,130 imaging examinations, 494 percutaneous cytological exams or biopsies, 896 bronchoscopies, and 952 surgical procedures, including mediastinoscopy or mediastinotomy, thoracoscopy, and thoracotomy. We'll leave it to the health economists to figure out the cost of all these. We have no way of figuring out the psychological costs due to the anxiety generated by a false positive diagnosis of possible lung cancer.

There's one last point that we haven't mentioned, because it's not mentioned in the paper – what was the false negative rate? That is, even with all those scans and X-rays, were any cases missed? Unfortunately, all the paper says is "Detailed calculations of sensitivity, specificity, positive predictive value, and negative predictive value are not reported here" (p. 400).[2] Reporting on diagnostic tests without giving those figures is tantamount to ripping out the last chapter of a murder mystery before passing it on. We want to know who done it or, in this case, who got cancer that wasn't detected. The results may not be known for some years, but it's a vital piece of information before we can pass judgment on these two diagnostic approaches. In the meantime, we'll stick with the Scottish legal phrase of "Not proven."

References

1. Streiner DL, Norman GR. Size, follow-up, daata analysis—good; post hoc analysis, interpretations—not so much. *Commun Oncol*. 2011; 8(8):379-380.

2. National Lung Screening Trial Research Team. Reduced lung-cancer mortality with low-dose computed tomographic screening. *NEJM*. 2011:365(5);395-409.

3. Rosten L. The joys of Yiddish. New York: McGraw-Hill; 1968.

4. Sox HC. Better evidence about screening for lung cancer. *NEJM*. 2011:365(5);455-457.

5. Norman GR, Streiner DL. *P* less than 0.05: statistical inference. *Commun Oncol*. 2009:6(6);284-286.

6. Streiner DL, Norman GR. Measures of risk. *Commun Oncol*. 2010:7(1);39-41.

7. Wall BF, Hart D. Revised radiation doses for typical X-ray examinations. *Br J Radiol*. 1997;70(833):437-439.

8. Eisenberg MJ, Afilalo J, Lawler PR, Abrahamowicz M, Hughes R, Pilote L. Cancer risk related to low-dose ionizing radiation from cardiac imaging in patients after acute myocardial infarction. *CMAJ*. 2011;183(4):430-436.

9. Streiner DL, Norman GR. Mass screening: when does it make sense? *Commun Oncol*. 2010;7(2):93-95.