Correspondence

With the core result of the National Lung Screening Trial (NLST) already announced, Peter Bach (1) wrote that “Bodies that publish cancer screening recommendations will soon be contemplating this landmark finding and will be comparing it with several other CT screening studies.” He criticized the results of the International Early Lung Cancer Program (I-ELCAP), stating that proper consideration of its published findings “will require reconciling what in some cases appear to be contradictory, statistically unlikely, or outlier results.” Dr Bach based his assertions on literature reviews that were selective and missing critically relevant particulars. Moreover, his claim that I-ELCAP results are mutually inconsistent is wrong.

The 85% proportion of stage I diagnoses reported by I-ELCAP (2) was characterized by Dr Bach as an “outlier when compared with other studies.” By focusing on a particular set of eight studies, he computed, instead, a 56% proportion of stage I diagnoses. However, Dr Bach excluded studies that he himself had included in his prior reviews (3–5) with higher rates, some even higher than those reported by I-ELCAP. From a systematic review of 11 studies, Yau et al. (6) reported a rate at baseline of 79% (150/191).

The 85% rate of stage I diagnoses in I-ELCAP is derived from actual rounds of annual screening (rather than merely being in the screening arm of a trial) using a well-defined protocol and clinical presurgical staging—all important considerations bearing directly on the proportion of stage I patients. Dr Bach did not take these particulars into account. Yau et al. (6), on the other hand, recognized that, in the 11 studies, compliance with the repeat rounds was lacking, precluding analysis.

When properly comparing I-ELCAP with all the other studies, its proportion of stage I diagnoses is not an outlier.

As for survival rates, Dr Bach claimed that I-ELCAP “reported a five-year lung cancer-specific survival rate of 85% for all patients who were diagnosed with lung cancer through screening . . . However, other analyses . . . of this endpoint have produced a different, substantially lower estimate.” Again, he was mistaken. I-ELCAP did not report a 5-year survival rate; it reported a 10-year rate (2), nor did I-ELCAP address the survival rate in cases diagnosed “through” but under screening, which included both screen- and interim-diagnosed cases. As for the 5-year survival rates in other studies, Dr Bach again
excluded ones that he had included in his previous reviews (4,5), specifically ones with higher rates than those of I-ELCAP. Nor did he include the 86% 10-year survival rate reported by Sone et al. (7). Remarkably, Dr Bach’s current outlier claims (1) contradicted his previous declaration that his own results and those of others are in accord with those of I-ELCAP (5,8). Dr Bach’s statements are inaccurate in other ways as well. For example, he referenced five articles that purportedly gave 5-year survival rates, whereas none of them actually did so.

When the results of I-ELCAP are properly compared with all the other studies, its survival rate, just as its proportion of stage I diagnoses, is not an outlier.

As for Dr Bach’s claim that I-ELCAP’s results “in some cases appear to be contradictory,” he specifically stated that I-ELCAP in 2006 (2) reported “75 lung cancer deaths . . . however . . . two small subgroups of this study were reported to have more lung cancer deaths by an earlier follow-up date.” In 2011, we reported on the traditional measure of cumulative mortality of lung cancer in a New York State (NYS) cohort (9), a subcohort of I-ELCAP. There were 64 deaths from lung cancer by December 31, 2005. Of these 64, 43 were from cases diagnosed under screening (interim diagnoses included), whereas the remaining 21 were identified solely through the 2007 National Death Index (NDI) and had occurred after withdrawals from screening when not yet having any symptoms of lung cancer, much less diagnosis of it. Dr Bach combined the 43 deaths not only with those 21 but also with another 13 from his own 2007 report (7) on data from one of our screening sites outside of the NYS subcohort, also using the NDI.

Importantly, Dr Bach did not distinguish between deaths from cases diagnosed under screening and those from cases “in a screened cohort.” In a screened cohort, the members are not necessarily continually under screening; they may not fully adhere to the scheduled screening and, in any case, they tend not to be screened at all after the termination of the scheduled screening. In I-ELCAP, the focus is on the mortality consequence of being under screening instead of merely being a member “in a screened cohort.” Failure to appreciate the distinction fully explains Dr Bach’s erroneous claim that the I-ELCAP results were contradictory.

Although Dr Bach raised the need to compare the results of I-ELCAP and NLST, he did not take account of the fundamental difference between these two studies. I-ELCAP (2) reported the 10-year survival rate of 80% as an estimate of the cure rate under annual screening, specifically in a single round of well-defined annual screening. This cure rate leads to an estimate of the proportion of otherwise fatal outcomes that are prevented by screening-associated early treatment. The complement of this rate is the proportion of the cases that were fatal under the screening, which for I-ELCAP was 100% – 80% = 20%. The mortality rate of lung cancer is generally assumed to be approximately 90% in the absence of screening, and under the I-ELCAP regimen, it thus was reduced to approximately 20%. This I-ELCAP result should not be construed to be at variance with the 20% reduction in the 6-year cumulative mortality reduction reported from NLST. The NLST result would have been different with different choices of design parameters, notably, the number of rounds of screening and the duration of follow-up. Understanding the profound difference in the conceptualization of the magnitude of the mortality reduction between I-ELCAP and NLST, which may not be obvious, is critically important for any comparison of the respective results. Full explication of this is, however, beyond the scope of this letter.

Before the positive result of the NLST, Dr Bach (10) declared that the evidence from his own research did not show “a hint of a benefit.” He should have taken the NLST result to be a contradiction of his result and an affirmation of the essential results of I-ELCAP rather than as a cause to criticize the I-ELCAP.

I have here endeavored to give the clarifications Dr Bach was calling for and expect I-ELCAP to continue providing policy-relevant information—with high integrity, both scientifically and ethically.

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References

Notes
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Dr. Henschke declares that she renounced all financial benefit (including royalties) from patents and pending patent application in April 2009 both on the government patent site and to Weill Cornell Medical College.

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