Editorial

Is the Gene Expression Pattern of Lung Cancer Detected by Screening With Spiral Computed Tomography Different from That of Symptom-Detected Lung Cancer?

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INTRODUCTION

There is growing support for the strategy of screening high-risk populations for early cancer detection because of the lack of progress in improving outcomes with advanced metastatic disease (1, 2). In light of recent promising reports with spiral computed tomography (CT)-based lung cancer screening, this approach is conceptually attractive for lung cancer (3–5). However, a critical question in evaluating the benefit of any screening detection technology is whether the natural history of asymptomatic disease detected by the technology is the same as that of disease that comes to medical attention in the conventional way, because of symptoms or signs (6). If lung cancer screening identified a less aggressive form of tumor that the patient would have died naturally with, rather than of, the screening results would look promising, but the apparent health benefit would be illusory.

This issue of potential "overdiagnosis" (*i.e.,* of benign or less aggressive disease) has been at the heart of a longstanding controversy over lung cancer screening by conventional chest X-ray. Apparent improvement in some clinical parameters obtained in National Cancer Institute-sponsored trials did not appear to translate into an overall improvement in lung cancer-related mortality (6). However, conclusions from the chest X-ray study are now being reconsidered because of concerns about possible methodological flaws in its Mayo component (6). As noted by Fontana (7), the study power of the Mayo chest X-ray screening trial was eroded by frequent chest X-rays in the control arm and low compliance in the experimental imaging arm. Additionally casting doubt on the negative interpretation of the study, a recent retrospective evaluation of tumor doubling times based on chest X-ray evaluations of the Mayo screen-detected cases concluded that the growth rates were generally consistent with those of clinically aggressive cancers (8). Also, as reviewed by Humphrey *et al.,* there is no conclusive evidence of "benign" lung

cancers analogous to the benign prostate cancers documented in autopsy series (6). Recent publications that explore the clinical consequences of small-volume cancers have indicated that they do, indeed, share the characteristic aggressive behavior of larger primary lung cancers (9, 10). An international panel of expert pathologists assembled by Cornell to evaluate the histological features of all primary lung cancers resected on their screening protocol has concluded that the histopathology is consistent with the invasive characteristics of conventionally detected lung cancers.[3] In contrast, some contend that lung cancer screening does involve some level of overdiagnosis. They cite, for example, the high rate of lung cancer detection with CT screening in nonsmoking Japanese women (6, 9, 11). In sum, the possibility of lung cancer overdiagnosis by screening modalities remains a point of contention.

Against this backdrop, the research group from Milan recently reported favorable experience with spiral CT-based lung cancer screening in a high-risk cohort of 1035 individuals over 50 years of age who had smoked >20 pack/years of cigarette (13). In that preliminary report of 2-year follow-up, 22 cases of lung cancer were diagnosed in their screening cohort. Of these cases, 77% (17 of 22) of the lung cancers detected were pathological stage I (100% at year 2), with a mean tumor size of 18 mm. No lung cancers were observed outside of annual CT screening in the 2.5 years of follow-up, suggesting that the CT-detection had been sensitive enough to pick up incipient cancers.

A lingering question, however, was whether the initial CT imaging had detected lung cancers as clinically aggressive as the symptomatic ones found in conventional work-ups. The clinical pathology had suggested that such is the case, but, in the present study, the clinicians from Milan have now gone a step further (14). Collaborating with a molecular diagnostics group in Oxford, England, they used cDNA arrays to compare gene expression profiles of 18 consecutive CT-detected primary lung cancer cases acquired in the course of a pilot case-control lung cancer screening trial and 19 matched symptom-detected primary lung cancers (13). The arrays, obtained from the Sanger Institute, consisted of 6000 human genes represented by 9932 cDNAs. The CT-detected cases were matched on the basis of age, gender, smoking history, tumor cell type, and tumor size with those that came to medical attention because of symptoms. Also included in the expression studies were profiles from four specimens of normal lung. In their analysis, the investigators conclude that the CT-detected tumors differed relatively little in

[3] Internet address: http://www.ielcap.org/professionals/m_conf_7_sum.htm.

gene expression profile from the symptom-detected ones, with corroborative data from a panel of five immunohistochemical markers.

In evaluating this report, critical issues are the level and type of evidence required to establish the extent of shared biology between screen-detected and symptom-detected lung cancers. The question is challenging since cDNA expression analysis, although conceptually appealing, is methodologically complex (15, 16). Although additional experiments and fuller detail of the statistical analysis would have been desirable, it does seem clear that the two types of tumor specimens were more like each other in expression profiles than either was like normal lung. It is not obvious that normal lung is the most appropriate standard of comparison (the mix of cell types in the normal tissue is likely to be too different from that in a tumor), but the raw expression data are being made available, and there will undoubtedly be additional analyses of them by the authors and others. We look forward to more extensive and extensively explained analyses in future publications.

Despite these caveats, the study is valuable for at least two reasons. First, the analysis of the microarray data by the authors, plus partially corroborative evidence from quantitative real-time PCR and immunohistochemistry, suggests that the aggressive biological potential of the CT-detected cancers is similar to that of symptom-detected ones. Second, the study's innovative use of expression profiling in the context of a case-control study is a potentially useful approach to translational research questions. Driven by advances in CT hardware and software, the average size of a CT-detected lung cancer has decreased by at least 50% over the last 10 years, and that trend is expected to continue (5). If this expression profiling approach to tumor biology is fully validated by additional experience, it may be useful to evaluate the molecular profiles of even smaller CT detected tumors. As the mean tumor size continues to shrink, the possibility of overdiagnosis below some critical size threshold will continue to exist, and additional development of the molecular profiling technology to provide surrogate measures of the biological potential of those tumors will continue to be important.

The present report (16) bolsters the argument based on recent clinical and pathological data that screen-detected lung cancers generally behave in an aggressive fashion (9, 10, 11). This is important information, the more so as the efficiency and cost of follow-up to detection are improving (12, 17, 18). Definitive evidence of mortality benefit remains the most critical criterion of lung cancer screening, but, as suggested recently by Smith (19), the prospects for ultimate success in lung cancer screening look more favorable than they once did. It will be prudent to pay serious attention to the critical requirements for moving to this kind of early lung cancer care in a safe, effective, and economical fashion.

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