Lung Cancer Risk Models Come of Age

John K. Field

Lung cancer is the most common cancer worldwide, with more than 1.3 million incident cases per year and the highest mortality rates (1, 2). More than half of all cases are diagnosed at an advanced stage, when surgical resection is unlikely to be feasible. In clinically advanced tumor stages, long-term survival is rarely achieved with conventional cytotoxic agents (3). Therefore, the overall 5-year survival rate is a low 15%, but survival rates differ substantially by stage at presentation (4).

The 15% 5-year survival rate includes ~70% for early stage Ia and 5% for locally advanced stage IIIb lung cancer, indicating that early diagnosis vastly improves outcome (5). The lung cancer community is awaiting the outcome of two large randomized controlled trials [i.e., the National Lung Screening Trial[11] and the Dutch-Belgian Lung Cancer Screening Trial (corresponding to the Dutch acronym NELSON; ref. 6)] of low-dose spiral computed tomography to ascertain whether this intervention will be the most appropriate way of advancing lung cancer control (7). The low-dose spiral computed tomography trials will not be in position to report until 2015. Even assuming positive results of the trials, one of the major issues for any national screening program will be cost-effectiveness. In this respect, the concept of identifying high-risk individuals for such national screening programs is very attractive because this will reduce overall costs and can be tailored to fit available funding (8). Furthermore, the choice of the risk group can be tailored to optimize the clinical balance of benefits and harms of screening.

There has been an increasing interest in developing methods of assessing individual risk for lung cancer, and the National Cancer Institute has identified risk modeling as an area of extraordinary opportunity (9).[22] Risk modeling has been successfully developed for coronary heart disease and was first published in 1976 (10). The 1980s heralded the initial breast cancer risk modeling, which calculated the probability that an individual would develop breast cancer over a defined period of time (11). Very few models have been developed to estimate lung cancer risk, in contrast with more prevalent modeling in the breast and certain other sites. The direction of new model development is to combine clinical and epidemiologic risk factors with new biological and genetic data to more accurately assess cancer risk (12).

Lung cancer risk modeling has come of age in this decade (6, 13–17). In particular, two recently published studies (16, 17) incorporated a range of epidemiologic data, apart from age and smoking history, and showed the potential for developing absolute lung cancer risk models with potential use in the clinic.

Two related article from the Spitz group in this issue of the journal (18, 19) have taken lung cancer risk modeling to the next level. Spitz et al. (18) included biomarkers in their risk model, thus adding independent "real-time" data into the risk modeling equation. It is important to appreciate that all the epidemiologic data entered into previous models have been based on questionnaires based on a subject's power of recollection. The data are rarely corroborated by clinical or health care files and rely entirely on the recruited individual's ability to correctly recall lifestyle and other important details, such as family histories. Spitz et al. (18) have incorporated two DNA repair assays that they have developed over many years. The host-cell reactivation and mutagen sensitivity assays have been shown to be independent risk factors for lung cancer (20, 21). Of note, the expanded model based on 725 White lung cancer cases and 615 controls performed better than did the baseline Spitz model, discriminating between cases and controls in 73% of the current smokers (baseline, 68%) and 70% of the former smokers (baseline, 67%). This improvement has to be considered modest, but clearly indicates the potential of adding clinical or molecular assays to risk models. This principle has been elegantly shown in breast cancer with the addition of mammographic density data to the Gail model (22).

The two assays used in the expanded Spitz model (18) have been widely used by this group; however, they are time-consuming and present some technical difficulties. They have been used successfully in a wide range of studies and have to be considered to be adequately "validated" at this point in time. The future development of lung cancer risk models depends on such molecular pathologic assays, and therefore the community will have to move toward the external validation and accreditation of these assays if they are going to be used in the clinical management of patients.[33]

To date, lung cancer risk models have been developed with data solely from White populations, and it is a matter of debate whether these models will be suitable for populations with differing ethnic or genetic backgrounds. It is clear that minority populations in the United States, especially Blacks and Hispanics, are generally underrepresented in clinical trials, a reality borne out in the Prostrate, Colorectal, Lung and Ovarian Cancer Screening Trial (23). Therefore, the study by Etzel et al. (19) in African Americans represents the first step in lung cancer risk models to address this issue. Future screening programs or lung cancer therapy or prevention

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[1] http://www.cancer.gov/nlst
[2] http://plan.cancer.gov/
[3] United States: http://www.fda.gov/oc/gcp/regulations.html; United Kingdom: http://www.mca.gov.uk/mhra/index.htm.

trials using risk model variables need to ascertain whether the current models fit all populations or if there is a need to develop specific ethnic models. The Japanese lung cancer risk models have shown some differences from the White lung cancer risk models of Western developed countries (24, 25). Etzel et al. analyzed 491 African Americans with lung cancer and matched controls and showed that current lung cancer prediction models are not appropriate for this ethnic group. These investigators showed that smoking cessation at a later age, pack-years, prior chronic obstructive pulmonary disease, exposures to asbestos and wood dust, and no history of hay fever were significant risk factors in the African American population. Some risk factors of this model overlapped risk factors included in the Spitz 2007 model (16) for White individuals (i.e., smoking-related measures, exposure to wood dust, emphysema, and no previous hay fever). Specific associations with lung cancer, however, were clearly different in African Americans [i.e., chronic obstructive pulmonary disease (a substantially higher association) and family history of lung cancer (not significantly associated)]. The comparative accuracy between the Spitz 2007 model for American Whites (67%) and the Etzel et al. model (79%) in predicting cancer in the African American case-control population shows the importance of developing ethnic-specific models. Clearly, there are "project-specific" contributory issues (e.g., the inclusion of smoking status and hospital-based controls from one region in the African American study) that could complicate the interpretation of this comparison. These issues, however, do not take away from the main conclusion of this article: Specific differences in risk factors (type or magnitude) between African Americans and Whites emphasize the importance of developing "ethnic-specific" risk models.

None of the lung cancer risk models published to date have been validated in independent populations; the main research groups concerned with these models are actively undertaking this work at present. Validation is required before the risk models can be taken into the general clinical setting; however, the Liverpool Lung Project risk model is currently being tested in a feasibility study in a high-risk general-practice environment (26).

The addition of functional analysis assays to a lung cancer risk model has been a major advance that has increased the

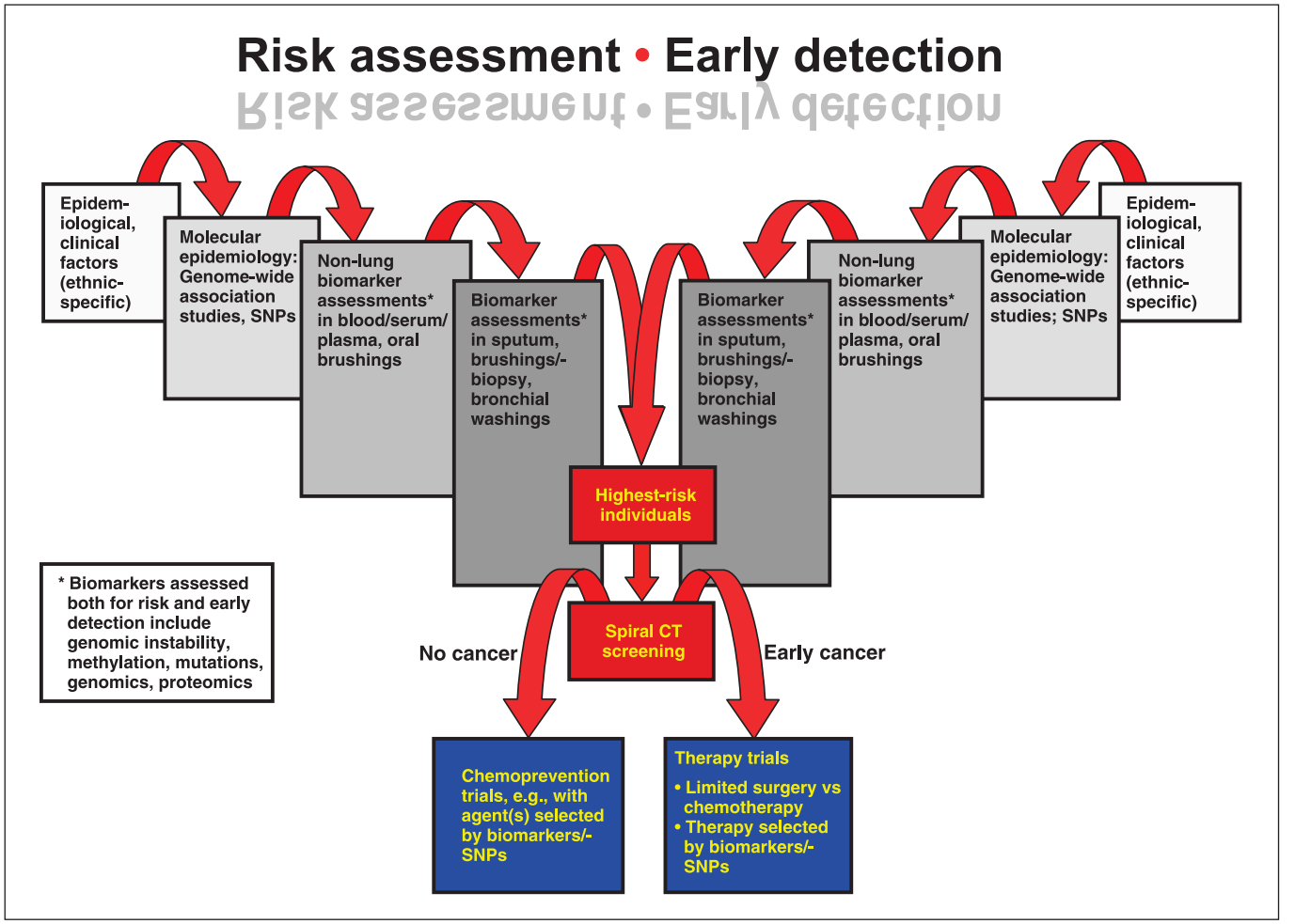

Fig. 1. Shared aspects of the cascades of lung cancer risk assessment (*left*) and early detection (*right*), mirror images. These cascades move from clinical and epidemiologic assessments to molecular epidemiologic assessments to biomarker assessments in non-lung samples and finally to biomarker assessments in lung samples. They merge in the middle with the identification of highest-risk individuals needing computed tomography (*CT*) screening that can select them for prevention (no computed tomography–detected cancer) or therapy (detected early cancer) research studies. SNP, single-nucleotide polymorphism.

power of the model; the next step will be to add genetic susceptibility data. The year 2008 will be remembered for the publication of three major genome-wide association studies in lung cancer with more than 25,000 cases and controls that were subjected to intensive analysis (27–29). All three studies identified variation in the same region of chromosome 15 (15q24/15q25.1) as the "top hit" for genomic association with lung cancer and containing a group of cholinergic receptor genes, which are strongly associated with lung cancer. The next stage will be to ascertain if there are subsets of susceptibility genes that contribute to the current risk models.

Ideally, the lung cancer community needs to develop risk models that embrace not only epidemiologic parameters but also molecular biomarkers that have been validated and comply with Good Clinical Laboratory Practice regulations. These models also should include a subset of susceptibility genes to identify high-risk individuals for future screening and chemoprevention study. These risk models will have to be developed and constructed within differing cultural and ethnic backgrounds. The concept of developing a "Lung Cancer Screening Cascade" was first mooted at the National Cancer Institute/American Cancer Society Early Lung Cancer Workshop in 2001 and was further developed at the 3rd International Early Lung Cancer Detection Workshop in Liverpool in 2003, subsequently published by Cassidy et al. in 2006 (30). Lung cancer risk models have come of age, as outlined in Fig. 1, which also reflects the mirror that early-detection research (*right*) holds up to risk modeling (*left*). In the first stage, higher-risk populations would be identified through clinical and epidemiologic risk factors such as those described in proposed models from the Liverpool Lung Project (17) and Spitz group (16, 19). Higher-risk individuals would subsequently be asked to provide a blood specimen to be tested for specific lung cancer susceptibility genes or single-nucleotide polymorphisms. Validated biomarkers detected in serum/plasma and bronchial lavage/induced sputum constitute the third and fourth stages, respectively. The cumulative risk of developing lung cancer at this point would trigger early-detection screening through spiral computed tomography imaging that selects individuals for potential prevention (high risk, no cancer) or therapy (early cancer) trials. It has been postulated that the combined results of imaging and molecular pathologic investigations will determine the individual's future lung cancer treatment regimen. A new generation of molecular targeted interventions is being evaluated to determine whether it may play a preventive role in high-risk individuals.

The lung cancer community now needs to take these concepts to the next level, which is the clinical trial environment.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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References

1. Hirsch F, Lippman S. Advances in the biology of lung cancer chemoprevention. J Clin Oncol 2005; 23:3186–97.
2. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin 2005;55: 74–108.
3. Schiller J, Harrington D, Belani C, et al; Eastern Cooperative Oncology Group. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. N Engl J Med 2002;346: 92–8.
4. van Rens MT, de la Riviere AB, Elbers HR, van den Bosch JM. Prognostic assessment of 2,361 patients who underwent pulmonary resection for non-small cell lung cancer, stage I, II, IIIA. Chest 2000;117:374–9.
5. Ganti AK, Mulshine JL Lung cancer screening: panacea or pipe dream? Ann Oncol 2005;16 Suppl 2: ii215–9.
6. van Iersel CA, de Koning HJ, Draisma G, et al. Risk-based selection from the general population in a screening trial: selection criteria, recruitment and power for the Dutch-Belgian randomised lung cancer multi-slice CT screening trial (NELSON). Int J Cancer 2007;120:868–74.
7. Mulshine JL, Sullivan DC. Clinical practice. Lung cancer screening. N Engl J Med 2005;352:2714–20.
8. Field J, Duffy S. Lung cancer screening: the way forward. Br J Cancer. In press.
9. Institute NC. The nation's investment in cancer research. A plan and budget proposal for the year 2006. Available from: http://plan.cancer.gov/; 2006.
10. Kannel WB, McGee D, Gordon T. A general cardiovascular risk profile: the Framingham Study. Am J Cardiol 1976;38:46–51.
11. Gail MH, Brinton LA, Byar DP, et al. Projecting individualized probabilities of developing breast cancer for white females who are being examined annually. J Natl Cancer Inst 1989;81:1879–86.
12. Freedman AN, Seminara D, Gail MH, et al. Cancer risk prediction models: a workshop on development, evaluation, and application. J Natl Cancer Inst 2005;97:715–23.
13. Bach PB, Kattan MW, Thornquist MD, et al. Variations in lung cancer risk among smokers. J Natl Cancer Inst 2003;95:470–8.
14. Colditz GA, Atwood KA, Emmons K, et al. Harvard report on cancer prevention volume 4: Harvard Cancer Risk Index. Risk Index Working Group, Harvard Center for Cancer Prevention. Cancer Causes Control 2000;11:477–88.
15. de Torres J, Bastarrika G, Wisnivesky J, et al. Assessing the relationship between lung cancer risk and emphysema detected on low-dose CT of the chest. Chest 2007;132:1932–8.
16. Spitz MR, Hong WK, Amos CI, et al. A risk model for prediction of lung cancer. J Natl Cancer Inst 2007;99:715–26.
17. Cassidy A, Myles J, van-Tongeren M, et al. The LLP risk model: an individual risk prediction model for lung cancer. Br J Cancer 2008;98:270–6.
18. Spitz M, Etzel C, Dong Q, Wei CQW, Hong W. An expanded risk prediction model of lung cancer. Cancer Prev Res. In press.
19. Etzel C, Kachroo S, Liu M, et al. Development and validation of a lung cancer risk prediction model for African Americans. Cancer Prev Res. In press.
20. Wei Q, Cheng L, Amos CI, et al. Repair of tobacco carcinogen-induced DNA adducts and lung cancer risk: a molecular epidemiologic study. J Natl Cancer Inst 2000;92:1764–72.
21. Wu X, Gu J, Spitz MR. Mutagen sensitivity: a genetic predisposition factor for cancer. Cancer Res 2007;67:3493–5.
22. Chen J, Pee D, Ayyagari R, et al. Projecting absolute invasive breast cancer risk in white women with a model that includes mammographic density. J Natl Cancer Inst 2006;98:1215–26.
23. Pinsky PF, Ford M, Gamito E, et al. Enrollment of racial and ethnic minorities in the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial. J Natl Med Assoc 2008;100:291–8.
24. Sobue T, Moriyama N, Kaneko M, et al. Screening for lung cancer with low-dose helical computed tomography: anti-lung cancer association project. J Clin Oncol 2002;20:911–20.
25. Nitadori J, Inoue M, Iwasaki M, et al. Association between lung cancer incidence and family history of lung cancer: data from a large-scale population-based cohort study, the JPHC study. Chest 2006; 130:968–75.
26. Ashton M, Mimnagh C, Forrest D, Field JK. A pilot study to explore lung cancer early detection and clinical intervention in a primary care setting in Knowsley, Merseyside. J Thorac Oncol 2008;3:S27.
27. Hung RJ, McKay JD, Gaborieau V, et al. A susceptibility locus for lung cancer maps to nicotinic acetylcholine receptor subunit genes on 15q25. Nature 2008;452:633–7.
28. Amos CI, Wu X, Broderick P, et al. Genome-wide association scan of tag SNPs identifies a susceptibility locus for lung cancer at 15q25.1. Nat Genet 2008;40:616–22.
29. Thorgeirsson TE, Geller F, Sulem P, et al. A variant associated with nicotine dependence, lung cancer and peripheral arterial disease. Nature 2008;452:638–42.
30. Cassidy A, Myles JP, Liloglou T, Duffy SW, Field JK. Defining high-risk individuals in a population-based molecular-epidemiological study of lung cancer. Int J Oncol 2006;28:1295–301.

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