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Commentary

Four Is Better Than 1—Strength in Numbers!

Ann M. Bode Ph.D. *, Zigang Dong M.D., Dr. P.H.

The Hormel Institute University of Minnesota, 801 16th Ave N.E., Austin, MN 55912, United States

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The Center for Disease Control reported that more men and women in the USA die from lung cancer than any other type of cancer (Siegel et al., 2016). In 2013, 111,907 men and 100,677 women in the US were diagnosed with lung cancer and 85,658 men and 70,518 women died from the disease (Siegel et al., 2016). The lung cancer 5-year survival rate is about 17.8%, which is lower than the other major cancers, including colon, breast and prostate (Howlader et al., 2013). Survival rate is about 54% when the cancer is localized to the lungs; but, unfortunately, only about 15% of lung cancers are diagnosed before metastasizing to other organs, which reduces survival to approximately 4% (Howlader et al., 2013). Furthermore, around 50% of lung cancer patients die within 1 year of diagnosis (Howlader et al., 2013). Early diagnosis would clearly improve prognosis, but detection is plagued by the lack of specific, reliable diagnostic methods.

Biomarkers are quantifiable measurements of homeostasis that discriminate between what is normal versus what is not. Lung cancer is generally categorized histologically as small cell lung cancer (SCLC; 15% of all lung cancers) or non-small cell lung cancer (NSCLC; 85% of all lung cancers), with 3 subtypes of NSCLC that include adenocarcinoma, squamous cell lung carcinoma, and large cell carcinoma. Cancer biomarkers should be able to predict lung cancer risk, but most importantly, should serve as diagnostic tools to detect cancer at the earliest possible stage. Early detection is key to treatment efficacy and overall survival. Ideally, effective biomarkers should guide treatment by changing e.g., expression in response to treatment thereby serving as a clinical endpoint.

The 2011 National Lung Screening Trial (NLST) assessed the risks and benefits of low-dose computerized tomography (LDCT) scans compared with chest radiographs to detect lung cancer in 53,000 current or former heavy smokers (National Lung Screening Trial Research et al., 2011). Although the results indicated a decreased mortality rate of 20%, a total of 96.4% of the positive screening results in the LDCR group and 94.5% in the radiography group were false positive results (National Lung Screening Trial Research et al., 2011). The large percentage of false positive results might be reduced by the development of noninvasive complementary biomarkers.

The identification of lung cancer biomarkers that can discriminate between normal, benign and malignant conditions could enable the development of more effective diagnostic tools for lung cancer. Circulating biomarkers in blood have been extensively examined for screening and diagnosis, and include proteins, microRNA, RNA, circulating cell-free DNA, methylated DNA, various metabolites, carbohydrates, autoantibodies, lipids, and circulating tumor cells. Common serum biomarkers utilized for lung cancer detection include cytokeratin 19 fragments (CYFRA 21-1), carcinoembryonic antigen (CEA), and progastrin-releasing peptide (ProGRP), but have not always exhibited consistent reproducibility, sensitivity or specificity.

Developing multiple biomarkers to be used simultaneously, rather than a single biomarker, might be a more rational approach because of the low sensitivity and specificity of a single biomarker. This is exactly the approach taken by Ma et al. (2016–in this issue) who identified and tested a panel of 4 serum proteins as biomarkers to predict lung cancer. Their objective was to first identify a robust subset of biomarkers to distinguish lung cancer patients from normal cancer-free subjects. They evaluated 20 circulating proteins and identified 3 proteins, C-reactive protein (CRP), prolactin and hepatocyte growth factor (HGF) that differed significantly between lung cancer patients and normal subjects. The 4th biomarker chosen was the circulating autoantibody against cancer-testis antigen NY-ESO-1, which had previously been shown to differentiate lung cancer patients from healthy subjects (Jia et al., 2014). Each of the 4 biomarkers (CRP (Chaturvedi et al., 2010), prolactin (Bigbee et al., 2012), HGF (Tanaka et al., 2011), and NY-ESO-1 (Tureci et al., 2006)) has been reported as a single biomarker for lung cancer but had never been combined as a panel until now.

Gender, age and smoking status did not correlate with the 4-biomarker results suggesting an independent association with lung cancer. In addition, the biomarkers seemed to be equally accurate for detecting either SCLC or NSCLC. CEA (carcinoembryonic antigen) was used as a positive control and was also higher in serum from lung cancer patients compared to healthy subjects. However, the 4-marker panel was superior in AUC (area under the curve), sensitivity and specificity compared to CEA. Notably, in a blinded test on patients with suspicious pulmonary nodules, the adjusted prediction model correctly discriminated patients

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* Corresponding author.
E-mail addresses: ambode@hi.umn.edu (A.M. Bode), zgdong@hi.umn.edu (Z. Dong).

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with 86.96% sensitivity and 98.25% specificity. Importantly, the 4-marker panel could detect lung cancer in CEA-negative patients, especially those with early-stage disease and adding CEA to the 4-marker panel also increased diagnostic accuracy.

The significance of these findings is that because of the high specificity, this panel of biomarkers might be suitable for detecting lung cancer, and especially early stage disease, increasing potential survival and directing the physician and patient in treatment decisions. This panel could also be useful to guide CT scanning to accurately identify and classify other pulmonary abnormalities. Thus, this panel of biomarkers could dramatically reduce patient anxiety and cost of additional testing, which would benefit everyone, including the general public.

Although numerous biomarkers have been identified, validated and tested in clinical trials, lung cancer is still the most prevalent cancer in the U.S. Technological advances are needed to improve the detection of low abundant lung cancer biomarkers that are specific to lung cancer subtypes. Combining the use of these 4 markers is clearly a step forward in the detection of lung cancer. On the other hand, the authors indicate that even though the panel of biomarkers is very promising, the results are still preliminary. Indeed, the continued successful development of this panel of 4 lung cancer biomarkers will entail their complete analysis in large (i.e., thousands) sets of clinical samples and patients, which might include other cancer types and other lung diseases, such as inflammation, chronic obstructive pulmonary disease, emphysema, pneumonia, or asthma, to verify that these markers are specifically detecting lung cancer. Importantly, this study was conducted only in Chinese lung cancer patients and would need to be expanded to other populations, including non-Hispanic black men and women, who are more likely to die from lung cancer than any other racial or ethnic group (Society, 2015). Compared to Asian/Pacific Islanders, who are least likely to die from cancer, the death rate in blacks is about double (Society, 2015).

Disclosure

Authors have nothing to disclose.

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