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Editorial

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Biomarkers Can Promote Risk Stratification in CT Scanning for Lung Cancer Detection

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Despite recent advances in surgical options, radiation and chemotherapy for the treatment of lung cancer, cure rates have not changed in 30 years, and lung cancer continues to kill more people than the next four leading causes of cancer death combined [1]. This occurs in part because lung cancer most often does not present itself until the advanced stages when it is essentially incurable. However, if lung cancer is detected early, surgery can cure a majority of patients [2]. If more patients are identified earlier in their disease course, lung death rates could drop significantly. To this end, low-dose spiral chest CT scans are effective in detecting lung cancer in its early stages, with a 20% reduction in mortality in heavy smokers who were screened [3-5]. As such, CT scanning is implemented as a prevention strategy, as the insurance company WellPoint, is now endorsing and recommending CT scanning for all heavy smokers [6]. Moreover, since a number of major cancer organizations have reviewed the available clinical data [7,8] and found that CT scanning does have an impact on lung cancer survival, there will be increased pressure to institute CT scans as a preventive measure by other insurers. The authors, a team of actuaries from the consulting firm Milliman and a Chicago lung cancer expert, say health insurers should start covering spiral CT lung cancer screening for people at high risk of lung cancer. As of 2010, the health insurance giant WellPoint is believed to be the only major insurer that does [9]. Despite the fact that national agencies have yet to develop cost-effective screening guidelines, which will eventually affect whether Medicare and private insurance companies cover CT scans, CT scan for lung cancer prevention is just around the corner as more pressure to cure lung cancer mounts.

The same studies have identified several problems with large-scale screening for lung cancer using CT scans [10-13]. First, while the major risk factor for lung cancer is cigarette smoking, only about 10% of smokers develop lung cancer [2]. Thus, screening people for lung cancer based solely on smoking would entail screening far too many patients for the number of positive diagnoses. Screening all smokers could lead to many false positives: pulmonary nodules are not uncommon in patients without cancer; indeed, approximately 94-98% of nodules detected by CT scanning that are biopsied are noncancerous [12]. Further, transthoracic biopsy has a complication rate (e.g. pneumothorax or collapsed lung) of about 3-5% [14,15], which translates into many patients without cancer having unnecessary morbidity. Moreover, as about 15% of lung cancer patients have never smoked [16], using smoking history as the sole criterion would exclude these patients from preventive measures. This data highlights the need for more risk stratification within the clinical practice of lung cancer screening.

CT scans impart a much higher dose of radiation compared to other forms of radiography, and thus repeated scans pose the potential risk for future cancers, such as brain tumors and leukemia, especially in pediatric patients [17] but possibly in adults as well. Consider that a single CT chest scan is comparable to approximately 400 chest x-rays in terms of radiation dose [18]. There are also estimates that as few as 0.4% to as many as 2% of cancers in the United States may be linked to radiation from CT scans [19,20]. CT scans comprise about 12% of total diagnostic radiologic procedures in the United States, yet they account for nearly 50% of total radiation exposure due to all x-ray exams [21]. Even if more frequent low-dose scans are performed, those would likely be coupled to higher-dose diagnostic scans if a lesion was discovered, thus, putting the patient at an even greater risk. Therefore, it may not be in the patients' best interest to undergo systematic radiologic scans in hopes of early detection, given that a significant proportion of the population tested will have a relatively lower risk of developing lung cancer.

Additionally, as reported by McMahon et al. in 2011, the cost of annual CT screening of smokers aged 50-74 costs between $110,000 and $169,000 per quality-adjusted life-year gained (QALY), based on their simulation model [22]. Recent trials where smokers were screened for lung cancer do show a decreased mortality rate [23], but screening parameters have yet to be defined. Questions arise as to when screening should begin and how often, and at what point the benefits of screening outweigh the risks and low cost-effectiveness. On the other hand, although colon and breast cancer screenings are targeted to a more widespread population than those for lung cancer, the cost-effectiveness ratios for colon and breast cancer screenings are much lower [24,25]. Some have suggested alternative imaging techniques for early lung cancer detection, such as MRI or PET, although even with improved image quality and sensitivity, MRI remains more costly than CT, and its use does not necessarily preclude the necessity of CT scans for higher resolution if nodules are discovered [26-28]. Given the widespread use of CT, its many benefits of early cancer detection, and the aforementioned concerns, better guidelines are needed to define the population at highest risk for lung cancer. This will limit the number of individuals who are screened, and thus reduce the cost burden, both in terms of dollars and patient health risk. One way to target a more specific population at risk for lung cancer is to pinpoint unique biomarkers, not unlike the methods to predict breast cancer recurrence (e.g. Oncotype Dx®), in estrogen receptor-positive breast cancers. Oncotype Dx® and other gene expression profiling tests were found to be more cost-effective than what had previously been considered standard clinical practice [29,30].

For over twenty years, researchers have been looking for a clinically useful panel of biomarkers for risk stratification that correlate with lung cancer risk. More than 100 studies of varying sample sizes and populations have examined known polymorphisms in general or those associated with specific genes, and their associations with

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lung cancer risk. Unfortunately current biomarkers, including polymorphisms at a single locus, for lung cancer have not been validated, and are not linked to a specific gene or function. While some polymorphisms linked to genes that control cell proliferation, metabolism, DNA repair and others, were found to be associated with lung cancer in specific studies, how these polymorphisms biologically contribute to lung cancer risk is unclear [31-35]. Not only are the odds ratios not always significant, some of these studies have not been substantiated [31]. Other polymorphisms that have been identified as potential lung cancer susceptibility genes are associated with disease risk only in distinct populations.

Typically, polymorphisms that occur in the protein coding region of a gene are thought to change the activity or function of the gene ever so slightly. However, many of the polymorphisms found to be associated with lung cancer are not located in or anywhere near by a cancer-related gene, making it difficult to know exactly how a polymorphism functions to enhance cancer development. In addition, Genome Wide Association Studies (GWAS) and other surveys have mapped lung cancer risk to certain chromosomal regions [35-38]. These studies are hampered because there are many genes within a given region, and there is great difficulty determining which genes actually underlie or are responsible for this measured risk [36-39]. The high sample sizes analyzed in GWAS would likely detect most of the common variants that have a remote impact on disease risk, yet the impact of those common variants has been modest, and has opened the possibility of lower frequency variants contributing more to disease risk [40]. As such, many polymorphisms have very weak correlations with risk, making their individual impact or significance low. Thus the vast majority of identified polymorphisms cannot be associated with a change in gene function or have a weak correlation with risk, which raises many questions about their contribution to cancer development and progression. Importantly, most if not all published polymorphic markers to date have failed to be confirmed by validation studies conducted by different investigators. If polymorphisms play a fundamental role in cancer development, their association should be found in different populations. As such, it is critical to validate any potential biomarker in different populations by different investigators before moving forward.

Candidate biomarkers are the polymorphic sites within the promoter of the Brahma (BRM) gene. These indel polymorphisms have been shown to correlate with cancer risk, and have been validated in repeat studies [41]. These polymorphic sites are unique in that they can be tied to the function of a gene, BRM. Homozygous variants of both polymorphisms have also been found to be statistically correlated with loss of BRM expression in primary lung tumors [41]. In turn, in vivo and in vitro data have shown that BRM is an anticancer gene. In mice, the loss of BRM in itself does not cause cancer, but when combined with a carcinogen, loss potentiates tumor development. Re-expression of BRM induces growth arrest in BRM-deficient cell lines [42]. Mechanistically, BRM is known to be required for Rb function and without BRM, Rb function is impaired [43]. Since these polymorphic sites correlate with BRM expression and probably regulate BRM in an unknown yet undefined mechanism, unlike many other polymorphic sites, BRM promoter polymorphic sites have an emerging underlying mechanism that potentially explains why they are associated with cancer risk.

The polymorphisms in the BRM promoter are just one promising example that identifies a potentially vulnerable subset of people. However, lung cancer is a multifactorial disease, and probably results from the complex interaction of many genes and environmental factors. In order to realistically employ CT scans for screening, additional biomarkers and polymorphisms must be identified and defined to maintain patient health and cost effectiveness.

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