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Predicted for greatness: 1994 Molecule of the Year – The DNA Repair Enzyme

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Abstract

Lung cancer mortality is the highest of any cancer. Primary prevention has stalled, however, new lung cancer screening trials of low dose computerized tomography (LDCT) have shown that the mortality from lung cancer can be reduced by up to 20 percent among current and former smokers. There are potential harms that must be taken into account when evaluating any screening program. With LDCT, there is a 90 percent rate of false positives and the potential for high doses of radiation from subsequent workup of benign lesions. The development of biomarkers that might refine the ability of screening to identify individuals at high risk for developing and dying from lung cancer is a ripe area for investigation. Sevilya and colleagues have developed a highly promising set of biomarkers of DNA repair capacity that may satisfy that goal. The large estimate of risk, the thoughtful combination of functional assays of DNA repair capacity and the population-based design of the study make it reasonable to test these biomarkers in a larger study.

Lung cancer has received far less attention from the research community and the public than several other cancers with lower mortality, such as breast and colorectal cancer. The highest mortality from any cancer is that of lung, where the five-year survival rate is 16%. Primary prevention, or stopping smoking, would of course prevent many but not all lung cancer. After a successful public health campaign to prevent and stop smoking, the smoking rate has dropped from 42% of the population in 1965 but seems to sit stubbornly at 18% in the United States. At this point in time, at the 50-year mark for the Surgeon General's Report that smoking causes lung cancer, it is appropriate that Livneh and his group (1) have further developed a potentially valuable set of functional assays as biomarkers to predict lung cancer much earlier.

Secondary prevention, e.g., screening, had been focused on chest X-rays (CXR), which have been relatively inexpensive and as radiation exposure from the CXR have been reduced, the harms are much less than previous levels of exposure. New and potentially improved screening modalities have been developed, and of these, low dose computerized tomography (LDCT) has generated much excitement. Several systematic analyses of LDCT trials have identified the National Lung Screening Trial (NLST) randomized clinical trial as the study

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with the highest quality (2). The NLST enrolled 26,722 men and women for LDCT and compared them to 26,732 participants with CXR; these participants were followed for 6.5 years. Such trials of lung cancer screening are critical to determine the most effective ways to reduce lung cancer mortality. However, harms as well as benefits need to be measured.

The benefits of the NLST have received wide attention in the press; the NLST found a 20% decrease in lung cancer deaths after 6.5 years of follow-up. However, that decrease is perhaps not as hopeful as it seems as only 4% of the 26,722 high risk individuals were found to have lung cancer. After 34 and 58 months of follow-up, there have been no statistically significant differences found in two other randomized trials of LDCT that are still ongoing: the Danish Lung Cancer Screening Trial (3) and the DANTE trial (4). Using NLST data, it is estimated that 320 individuals at high risk will need to be screened to prevent one death from lung cancer. This is actually a far better cost-benefit ratio than for breast cancer screening by mammography (1339 women invited to screen to prevent 1 breast cancer death with 11-20 years of follow up; refs. 5, 6) or colorectal cancer screening with sigmoidoscopy (817 screened to prevent one colon cancer death; ref. 7). There are different estimates as to the economic costs of LDCT. According to one estimate, LDCT will add \$2 billion dollars to the annual health care budget if the uptake is as high as 75% (8). However, 8,100 premature lung cancer deaths would be avoided. The additional cost of screening to avoid one lung cancer death was estimated at \$240,000.

Harms associated with LDCT, however, have also received attention. The false positive rate among LDCT use was very high (2,5). Furthermore, the costs of identifying and treating a lung nodule are high. In the NLST, the false positive rate was 90%; i.e., 90% of lesions identified as potentially cancerous were actually benign. These need to be followed up with more imaging, i.e., radiation, and although the management of follow-up was inconsistently reported, it is likely that many individuals received high doses of radiation for benign lesions. Radiation doses for lesions, benign or malignant, are difficult to evaluate from the current data. Dose varies by body weight, CT detector and manufacturer, and the number of images obtained (5). Bach and coauthors evaluated the risk of death or a major complication following diagnosis for what were benign nodules as 4.1 and 4.5 per 10,000 for LDCT and 1.1 and 1.5, respectively, per 10,000 for CXR (2). As such risks are not minor, it would be valuable to have some way to identify very high risk individuals who might benefit more directly from screening for lung cancer with LDCT and who are less likely to have benign lesions.

Sevilya and colleagues in Israel have been working for at least 10 years to develop functional DNA repair assays that might separate high risk and low risk individuals (9). Beginning with 8-oxoguanine DNA glycosylase (OGG1) functional assays, adding methylpurine DNA glycosylase (MPG) and now AP endonuclease 1 (APE1), the authors have developed an integrated DNA repair OMA (OGG1, MPG & APE1) score using a population-based analysis of risk for lung cancer with a very high odds ratio (9.7, 95% CI = 3.1, 29.8)). Due to the relatively small population of 96 cases and 96 controls, it is imperative that this finding (with wide confidence intervals) be replicated in a much larger dataset. However, although the wide confidence intervals belie the robustness of the finding, the very fact that the biological significance is strong in addition to the strength of the

association, presents a strong rationale for moving forward with automation of these assays and their use in a new study.

In 1994, the DNA repair enzyme was elected as Molecule of the Year (10), and for many years since, DNA repair has been considered the “guardian of the genome” (11). DNA repair enzymes, such as APE1, now have wider applicability – not just for specific repair but also for effects on RNA expression, among other factors (12). No longer can we think of DNA repair as a “one size fits all” behavior, such that diminished DNA repair could account for negative health outcomes, but similar to many body processes, the “balance” in DNA repair must be taken into account. When we reviewed DNA repair in 2000 (13), most of the studies had limitations that Sevilya et al. have overcome: small sample sizes, the use of convenience controls rather than population-based controls, the use of cells that had no relationship to the target organ and the use of mutagens that do not occur in the natural environment. Although some of the studies did have larger sample sizes and very high risk estimates with quite wide confidence intervals, almost all suffered from selection bias of one type or another; none had a population-based sampling frame. This point is critical because such studies lack generalizability.

Since 1998, the end of the time frame for those analyses, many advances have been made in the area of measurement of DNA repair capacity and in the understanding of the process and its biological effects. The use of genetic tests of DNA repair capacity have been fraught with problems and do not yet appear to be reliable enough to use in risk prediction. A search of review articles on DNA repair polymorphisms found 65 such papers, focusing on risk and response to therapies. However, even in 2006 it was clear that studies of single polymorphisms would not provide a simple answer in relationship to lung cancer risk (14). Unfortunately, although many investigators believe that DNA repair polymorphisms can affect risk and response to therapy (15), no review to date is consistent (16). Furthermore, GWA studies do not show strong associations between DNA repair gene variants and lung cancer risk. Therefore, we need, as suggested by Weiss et al. (17) “larger, well designed functional and epidemiologic studies...to clarify these relationships.” Clearly, using work similar to that of Sevilya et al. (1) in well-designed population-based or cohort studies with functional assays, we may be able to make progress in preventing mortality from lung cancer – certainly more than is currently available. Adding the integrated DNA repair OMA score would clearly improve the ability to predict who might benefit from screening.

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