

Respiragene™ Research Update - Oct 2009

Prepared by Dr Robert Young
Chief Scientific Officer – Synergz BioScience Ltd.
Associate Professor of Medicine and Molecular Medicine
School of Biological Sciences, University of Auckland

Summary

A recently published study by independent researchers from the NIH (Sanderson, et al, Cancer Epidemiology, Biomarkers & Prevention) ¹ has highlighted current smokers' interest in, and responsiveness to, genetic information allows them to better understand their personal risk of developing lung cancer. The study also found that such knowledge of “increased lung cancer risk may increase uptake of effective smoking cessation services”. The study surveyed a relatively small group of people (N=44), and it used a single genetic marker that provides relatively weak association with disease. However, I believe it strongly supports our views that smokers are interested in ², and benefit from, taking gene-based risk tests for lung cancer ³. Equally, the study found that no patient harm was identified from the testing process.

Abstract: <http://cebp.aacrjournals.org/cgi/content/abstract/1055-9965.EPI-08-0620v1>

The findings of this study support those of a previously published randomised control trial using the same gene based risk test for lung cancer susceptibility (CM McBride et al, 2002), where smoking quit rates were improved by 1.5-2 fold in those getting the genetic test in addition to a counselling based programme ³.

Emerging Trend

The Sanderson study is consistent with a strengthening trend in the scientific literature in this field. A brief summary of the scientific literature to date includes the following points:

1. Between 80%-90% of smokers are interested in knowing their genetic predisposition for lung cancer (Ostroff and Sanderson have both showed this)
2. Fear of lung cancer is the most cited reason smokers quit ⁴.
3. Despite the well publicised link between smoking and lung cancer, over 50% of smokers do not think they are personally at risk of lung cancer.
4. Smokers taking genetic risks tests for lung cancer are not de-motivated from trying to quit (this article ¹ and work we have submitted for publication confirms this). To date, data shows that testing improves motivation to quit.
5. The significant drop in smoking prevalence in the 1960s followed widely published links between smoking and lung cancer (long before public health measures were instituted) and the recent drop in coronary mortality has come, to a large degree, from widespread uptake of individualised coronary heart risk assessment and risk reduction with effective treatments.

These conclusions come from published research and should counter the views, primarily taken by non-smokers, that people smoking today are (a.) not interested in learning their personal risk or (b.) not able to be helped through the personalised engagement and treatment approaches prompted by Respiragene™ (which are comparable to those that have helped reduced heart disease mortality). Put simply, until governments ban or regulate the sales of tobacco, public health measures alone will not be sufficient to change the attitudes of smokers today – something new is needed to augment existing public health messages.

While non-smokers believe lung cancer is due to smoking, they don't know that they carry 'lung cancer' related genes that are never "expressed" or realised in the absence of smoking exposure. Smokers, on the other hand understand that genetic factors largely explain why only 10-15% of smokers get lung cancer. This highlights the point that smokers actually understand gene-environment risks better than non-smokers (see Ostroff comments in linked article: (<http://www.sciencedaily.com/releases/2009/06/090630132003.htm>)).

My comment: "The view depends on which window you're looking out from".

I attach a table below which sets out why our lung susceptibility tests meets public health criteria for widespread use.

Criteria for instituting a screening programme: The possible role of gene based risk testing for lung cancer		
Disease	Serious	Lung Cancer: <ul style="list-style-type: none"> • preventable (rare before 1900) • 30% of all cancer deaths, 30% of all smoking related deaths per annum , leading cause of death after heart attack and stroke • No.2 and No.3 cancer killer in men and woman respectively • 10% 5 year survival with late presentation (survival improves to 70-80% with diagnosis in Stage 1).
	High prevalence of preclinical stage	90% of lung cancer occurs in those over 50 years of age after 30-35 years of smoking exposure. Risk for lung cancer in smokers and non-smokers does not diverge until after age 40 years of age.
	Natural history understood	See above. 70% of lung cancer occurs in those with pre-existing COPD – mostly mild (target group).
	Long period between first signs and overt disease	For a predictive test, this is not relevant. This refers to a diagnostic test. Peto et al. showed lung cancer risk reduction with quitting about age 40 yrs equates to similar lifetime risk as a non-smoker.
Diagnostic test	Sensitivity and specificity	This is a susceptibility test with similar performance to Framingham score and Gail score for breast cancer.

Criteria for instituting a screening programme: The possible role of gene based risk testing for lung cancer		
	Simple and cheap	This test is a one-off test. Use of government tobacco taxes to subsidise this test would seem appropriate here (see article in the Sun). This test may improve outcomes in funded smoking cessation programmes (reduce relapse). The test requires a cheek swab for DNA analysis and can be processed in 3 days.
	Safe and acceptable	The testing procedure is non-invasive and safe for patients. We have conducted surveys in our intended patients group (smokers over 40 yo) and find no reduction in intention to quit at the average risk and increased intention in those at higher than average risk.
	Reliable	Genotyping is being done with 99% accuracy in an approved lab. The non-genetic variables include age, COPD and family history, all independently associated with lung cancer. Over half the SNPs have been associated with lung cancer by other groups and several appear in NIH genome websites.
Diagnosis and treatment	Facilities are adequate	Testing is done through an approved lab and in association with GP and or specialist advice. Smoking cessation is the single best intervention a doctor can achieve.
	Effective, safe and acceptable treatment available	Smoking cessation is effective and can be improved with a number of readily available medicines. Statin therapy may be shown to be effective in this group of patients (see my articles).
Educative tool		Studies show that over 50% of smoker/ex-smokers with lung cancer did not think they were at risk (optimistic bias = denial which is huge here). This test will tell that 50% that they are, at best, average risk.

Conclusion

The Sanderson study, while small, found that providing genetically based personal risk information to smokers prompted greater interest in quitting and generated no harm for patients. The test utilized a single genetic marker which is responsible for a 1.2 fold increased risk among those who have it compared to those who don't.

We believe a test that identifies approximately 20 percent of the population as having a 10-fold increase in risk for developing lung cancer compared to the average smoker will prove an even more powerful tool in smoking cessation.

References

1. Sanderson S, et al. *Cancer Epidemiol Biomarkers Prev* 2009; 18: 1953-1961.
2. Ostroff JS, et al. *Preventive Medicine* 2001; 33: 613-621.
3. McBride CM, et al. *Cancer Epidemiology, Biomarkers & Prevention* 2002; 11:521-528.
4. Orleans CT, et al. *Cancer* 1994; 74:2055-2061.