

## GENETIC PREDISPOSITION TO LUNG CANCER

### Introduction

This idea was discussed in the 1950's-60's particularly by Sir Ronald Fisher and Professor Philip Burch, both of whom are now deceased. Their ideas found little general support largely because Sir Richard Doll claimed epidemiology demonstrated that environmental carcinogens, including tobacco smoke, were responsible for nearly all cancer deaths. During August 1990, five scientific papers and one conference presentation (U.I.C.C. Cancer Meeting, Hamburg, August 1990) have addressed the genetic issue either directly or indirectly, (but not independently of environmental risk factors). Furthermore one of the scientific papers is from a group in the USA (Caporaso and colleagues) who are close to a group supported by the BAT Scientific Research Group (Idle and colleagues, University of Newcastle) while another paper by Sellers and colleagues is partly supported by the Council for Tobacco Research USA.

### Comments on Papers

The paper by Sellers (Evidence for Mendelian Inheritance in the Pathogenesis of Lung Cancer) addresses the broadest issues. It is based on the use of the Segregation Analysis, a rare specialist statistical technique that is currently being examined by one of our consultants. Further comments on the validity or otherwise of this statistical technique will be made in due course, although it does appear to conflict in some ways with the age-distribution analysis which was so much a feature of Burch's work. However, as published, the claims made by Sellers are quite startling, and are based on an age x genetic x smoking interaction analysis. There are three genetic variants (genotypes):

- AA Susceptible
- AB Partly Susceptible
- BB Not Susceptible.

The following matrix of relative risk v. age, smoking status and genotype is given in the paper.

Age	Tobacco Exposure	Relative Risk* (Genotype) of Developing Lung Cancer		
		AA	AB	BB
50	0	2246	15	1
	Average (A)	327	14	1
	Heavy (H)	63	12	1
60	0	618	14	1
	A	56	12	1
	H	11	7	1
70	0	112	13	1
	A	10	6	1
	H	3	2	1

\* Unfortunately this table is misleading because for each horizontal line the risk is only compared to the BB genetic group. It is not, therefore, an absolute measure of the chance of getting lung cancer - merely the risk relative to the BB Group. Far more 70 year olds die of lung cancer than do 50 year olds.

502558316

Equally, the figures do not mean that 2246 non-smokers die relative to 63 heavy smokers (lines 1 and 3).

It is claimed in the paper that AA smokers have a 27.2% probability of developing lung cancer by age 50, this probability apparently not increasing greatly with age, and it can be calculated from the paper that of the non-smokers who die by age 50, the vast majority are of the AA genetic disposition:

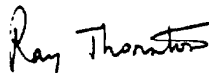
$$\frac{2246}{2245+15+1} = 99.3\%$$

However, the analysis gives smoking an ever increasing role with age, genetic predisposition being claimed to be less important for old persons and, for heavy smokers age 70, it is claimed only 50% are of the AA genotype.

Sellers is not able to identify the nature of the genetic variation but some scientists believe it to be associated with mutations on a specific human gene (CYP2D6), active in the metabolism of drugs and potential carcinogens, and the enclosed editorial by Bonney discusses this. One part of this gene is responsible for metabolising a drug, debrisoquine, and genetic variations can be identified by following the metabolism of this drug. This is Professor Idle's view, although it seems more likely that this is just a marker for some closely related gene of greater importance, such as the adjacent CYP1A1 gene known to be anomalous in some lung cancer cases.

#### Conclusion

While nothing definitive has yet emerged from this area and the present paper is clearly speculative, it will nevertheless provoke much further research and it is imperative to monitor the Scientific Research as it progresses. If genetic predisposition is subsequently validated for lung cancer and other major diseases, the implications for Society in identifying people at risk could be enormous. This identification could be achieved within the next 5-10 years.



Dr. R.E. Thornton

RET/SC  
12th September, 1990

502558317