Smokers with gene defect have one in four chance of developing lung cancer

June 1 2014

Credit: Vera Kratochvil/public domain

Around a quarter of smokers who carry a defect in the BRCA2 gene will develop lung cancer at some point in their lifetime, a large-scale, international study reveals.

Scientists announce a previously unknown link between lung cancer and a particular BRCA2 defect, occurring in around 2 per cent of the

population, in research published in *Nature Genetics* today.

The defect in BRCA2 - best known for its role in breast cancer - increases the risk of developing lung cancer by about 1.8 times.

Smokers as a group have a high lifetime risk of around 13 per cent (16 per cent in men and 9.5 per cent in women). The new study therefore suggests around one in four smokers with the BRCA2 defect will develop lung cancer. Around 10 million adults in Great Britain smoke, which means that up to around 200,000 adult smokers could have the specific BRCA2 defect, known as BRCA2 c.9976T.

The researchers, led by a team at The Institute of Cancer Research, London, compared the DNA of 11,348 Europeans with lung cancer and 15,861 without the disease, looking for differences at specific points in their DNA. The team was mainly funded by the US National Institute of Health, with additional support from Cancer Research UK.

The link between lung cancer and defective BRCA2 – known to increase the risk of breast, ovarian and other cancers – was particularly strong in patients with the most common lung cancer sub-type, called squamous cell lung cancer. The researchers also found an association between squamous cell lung cancer and a defect in a second gene, CHEK2, which normally prevents cells from dividing when they have suffered damage to their DNA.

The results suggest that in the future, patients with squamous cell lung cancer could benefit from drugs specifically designed to be effective in cancers with BRCA mutations. A family of drugs called PARP inhibitors have shown success in clinical trials in breast and ovarian cancer patients with BRCA mutations, although it is not known whether they could be effective in lung cancer.

Study leader Professor Richard Houlston, Professor of Molecular and Population Genetics at The Institute of Cancer Research (ICR), said: "Our study showed that mutations to two genes, BRCA2 and CHEK2, have a very large effect on lung cancer risk in the context of smoking. Mutated BRCA2 in particular seems to increase risk by around 1.8 times.

"Smokers in general have nearly a 15 per cent chance of developing lung cancer, far higher than in non-smokers. Our results show that some smokers with BRCA2 mutations are at an enormous risk of lung cancer – somewhere in the region of 25 per cent over their lifetime.

"Lung cancer claims more than a million lives a year worldwide and is by far the biggest cancer killer in the UK. We know that the single biggest thing we can do to reduce death rates is to persuade people not to smoke, and our new findings make plain that this is even more critical in people with an underlying genetic risk."

Professor Paul Workman, Deputy Chief Executive of The Institute of Cancer Research, said:

"These findings indicate that around a quarter of smokers with a specific defect in their BRCA2 gene will develop lung cancer – a disease which is almost invariably fatal. All smokers are taking a considerable risk with their health, regardless of their genetic profile, but the odds are stacked even more heavily against those with this genetic defect who smoke."

More information: Paper: Rare variants of large effect in BRCA2 and CHEK2 affect risk of lung cancer, DOI: 10.1038/ng.3002

Provided by Institute of Cancer Research