

Title: Genetic risk can be decreased: Quitting smoking decreases and delays lung cancer for smokers with high and low *CHRNA5* risk genotypes - A Meta-analysis

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## ABSTRACT

**Background:** Recent meta-analyses show that individuals with high risk variants in *CHRNA5* on chromosome 15q25 are likely to develop lung cancer earlier than those with low-risk genotypes. The same high-risk genetic variants also predict nicotine dependence and delayed smoking cessation. It is unclear whether smoking cessation confers the same benefits in terms of lung cancer risk reduction for those who possess *CHRNA5* risk variants versus those who do not.

**Methods:** Meta-analyses examined the association between smoking cessation and lung cancer risk in 15 studies of individuals with European ancestry who possessed varying rs16969968 genotypes (N=12,690 ever smokers, including 6,988 cases of lung cancer and 5,702 controls) in the International Lung Cancer Consortium.

**Results:** Smoking cessation (former vs. current smokers) was associated with a lower likelihood of lung cancer (OR=0.48, 95%CI=0.30-0.75, p=0.0015). Among lung cancer patients, smoking cessation was associated with a 7-year delay in median age of lung cancer diagnosis (HR=0.68, 95%CI=0.61-0.77, p=4.9\*10<sup>-10</sup>). The *CHRNA5* rs16969968 risk genotype (AA) was associated with increased risk and earlier diagnosis for lung cancer, but the beneficial effects of smoking cessation were very similar in those with and without the risk genotype.

**Conclusion:** We demonstrate that quitting smoking is highly beneficial in reducing lung cancer risks for smokers regardless of their *CHRNA5* rs16969968 genetic risk status. Smokers with high-risk *CHRNA5* genotypes, on average, can largely eliminate their elevated genetic risk for lung cancer by quitting smoking- cutting their risk of lung cancer in half and delaying its onset by 7 years for those who develop it. These results: 1) underscore the potential value of smoking cessation for all smokers, 2) suggest that *CHRNA5* rs16969968 genotype affects lung cancer diagnosis through its effects on smoking, and 3) have potential value for framing preventive interventions for those who smoke.

**Keywords:** smoking cessation, genetics, meta-analysis, lung cancer

## Highlights:

- *CHRNA5* rs16969968 confers risk for earlier lung cancer diagnosis, but quitting produces benefit regardless of genotype.
- Smokers can cut their risk of lung cancer in half and delay its onset by 7 years among those diagnosed.

