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## **Epidermal growth factor (*EGF*) gene polymorphism, gastroesophageal reflux disease (GERD), and esophageal adenocarcinoma (EAC) risk.**

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**Background:** Single nucleotide polymorphisms (SNPs) of key cancer genes, such as *EGF A61G*, are associated with an elevated risk of EAC, but the lack of full penetrance indicates that the effects of these SNPs on esophageal carcinogenesis are modified by additional genetic or environmental variables. Since GERD is an established risk factor for EAC, we evaluated whether the association between *EGF* polymorphism and EAC development is altered by the presence of GERD. **Methods:** *EGF* genotyping of DNA samples was performed and GERD history was collected for 309 EAC patients and 275 matched healthy controls. Associations between genotypes and EAC risk were examined with adjusted logistic regression. Genotype-GERD relationships were explored using analyses stratified by GERD history and joint effects models that considered severity and duration of GERD symptoms. **Results:** Baseline characteristics were comparable between cases and controls except that *EGF* variants (*A/G* or *G/G*) were more common ( $p=0.02$ ) and GERD was more prevalent ( $p<0.001$ ) in cases than in controls. When compared to the *EGF* wild type *A/A* genotype, the *G/G* variant was associated with an increased risk of EAC (OR 1.9; 95% CI, 1.2-3.0;  $p=0.007$ ). Stratified analyses revealed that the *G/G* variant contributed to a substantial increase in EAC risk among individuals with GERD, but a slight decrease in risk for GERD-free individuals (see table). In the joint effects models, the odds of EAC was also highest for *G/G* patients who either experienced frequent GERD of more than once per week (OR 21.8; 95% CI, 5.1-94.0;  $p<0.001$ ) or suffered GERD for longer than 15 years (OR 22.4; 95% CI, 6.5-77.6;  $p<0.001$ ). There was a highly significant interaction between the *G/G* genotype and the presence of GERD ( $p<0.001$ ). **Conclusions:** *EGF A61G* polymorphism exerts its effect on EAC susceptibility through an interaction with GERD. Performing *EGF* genotyping for patients with severe or longstanding GERD can help to identify individuals at the greatest risk of EAC.

### **Odds of EAC stratified by *EGF A61G* polymorphism and GERD status**

	Number of cases/controls	Adjusted odd ratios of EAC by <i>EGF A61G</i> polymorphism			
		<i>A/G</i> vs <i>A/A</i> genotype		<i>G/G</i> vs <i>A/A</i> genotype	
		OR (95% CI)	p value	OR (95% CI)	p value
Overall study cohort	309/275	1.2 (0.8 - 1.8)	0.298	1.9 (1.2 - 3.0)	0.007
GERD subset	150/62	3.6 (1.7 - 7.7)	0.001	9.7 (3.8 - 25.0)	< 0.001
GERD-free subset	159/213	0.7 (0.4 - 1.1)	0.126	0.4 (0.2 - 0.9)	0.024

EAC = esophageal adenocarcinoma; GERD = gastroesophageal reflux; OR = odds ratio; CI = confidence interval.