disclosure
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references

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**KRT81 miR-SNP rs3660 is associated with risk and survival of NSCLC**

We read with great interest the study by Lee et al. [1] recently published in *Annals of Oncology*, in which the association of *KRT81* rs3660 (G/C) with survival of nonsmall-cell lung cancer (NSCLC) was reported. Specifically, Lee and colleagues found that patients with the rs3660 GC + CC genotype had a significantly better overall survival compared with those with the GG genotype [1]. To the contrary, an earlier paper by Campayo et al. [2] reported that the *KRT81* rs3660 CC genotype was associated with shorter time to NSCLC recurrence compared with CG + GG.

Single-nucleotide polymorphisms in miRNA binding sites (miR-SNPs) can strengthen or reduce binding between a miRNA and its target [3]. Our laboratory has focused on the association of miR-SNPs with lung cancer risk [4]. As an extension of that latest study, we genotyped rs3660 in 312 NSCLC cases and 311 population controls frequency matched to cases by age and gender. Consistent with Campayo et al. [1] we found that rs3660 GG (and CG) were associated with reduced risk of cancer-associated mortality compared with CC. However, we observed this association only in men [hazard ratio (HRGG versus CC): 0.51, 95% confidence interval (CI) 0.29–0.89, \( P = 0.018 \); HRGG versus CG: 0.50, 95% CI 0.26–0.98, \( P = 0.043 \)] and not in women (HRGG versus CC: 1.34, 95% CI 0.73–2.44, \( P = 0.260 \); HRGG versus CG: 1.17, 95% CI 0.61–2.24, \( P = 0.752 \)) (adjusted for age, gender, race, smoking status, pack-years of smoking, stage and histology) (Figure 1). Additionally, we found that rs3660 GG was associated with reduced risk of NSCLC, again only in men (ORGG versus CC: 0.43, 95% CI 0.21–0.87, \( P = 0.020 \)) compared with women (ORGG versus CC: 1.82, 95% CI 0.80–4.14, \( P = 0.154 \)) (adjusted for age, gender, race, smoking status and pack-years of smoking).

We note with interest that both the Discovery and Validation cohorts analyzed by Lee et al. comprise 76% and 71% male cases, respectively [1]. In addition, we note that the study population in the study by Campayo et al. was 88% male [2]. Thus, we hypothesize that gender is a modifying factor of the association between rs3660 and NSCLC, which became apparent upon stratification of our samples by gender in the context of a well-matched case-control study. Further, we present additional insight suggesting that this gender-specific association also extends to cancer risk.

Regarding the discrepancy with Lee et al. [1], we also note that the studies in agreement both comprised participants with similar ethnic background, i.e. Caucasian, in which the allelic frequencies of rs3660 C are 47% (our study) and 49% (Campayo et al.), whereas the new study comprises participants of Asian ethnicity, in which the frequency of rs3660 C is 24%.

![Figure 1. Kaplan–Meier survival analysis of rs3660 in (A) men and (B) women with NSCLC.](image-url)
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Reply to the letter to the editor
‘KRT81 miR-SNP rs3660 is associated with risk and survival of NSCLC’ by Robles et al.

We thank to Robles and Ryan for the interest in our study [1]. They suggested the possibility that gender is a modifying factor of the association between KRT81 rs3660 and non–small cell lung cancer (NSCLC) based on the stratified analysis of their study population, comprising 312 NSCLC cases and 311 controls, by gender. In their study [2], the association between rs3660 and non–small cell lung cancer (NSCLC) survival was significant in men [adjusted hazard ratio (aHR)CG versus CC = 0.51, 95% confidence interval (CI) 0.29–0.89; aHRGG versus CC = 0.50, 95% CI 0.26–0.98], but not in women (aHRCG versus CC = 1.34, 95% CI 0.73–2.44; aHRGG versus CC = 1.17, 95% CI 0.61–2.24). In addition, they reported that the association between rs3660 and the risk of NSCLC was also significant in men [adjusted odds ratio (aOR)GG versus CC = 0.43, 95% CI 0.21–0.87], but not in women (aORGG versus CC = 1.82, 95% CI 0.80–4.14).

As they noted, our discovery and validation cohorts comprised 76% and 71% of male patients [1]. Therefore, we conducted stratified analysis by gender to see if the association between KRT81 rs3660 and survival of NSCLC is gender specific. Furthermore, we also stratified our population by tumor histology and smoking status. In our combined cohort comprising 836 NSCLC cases, there was no significant difference of the associations in male and female subgroups (aHRGC+CC versus GG = 0.66, 95% CI 0.50–0.89 and aHRGC+CC versus GG = 0.68, 95% CI 0.37–1.26, respectively), as evidenced by the test for heterogeneity to evaluate whether HRs are different across subgroups [test for heterogeneity, P (PH) = 0.93]. Although the association was not significant in the female subgroup probably because of the small number of cases, the effect size was similar and the association was in the same direction compared with male cases (Figure 1).

Neither was there any difference of the associations in squamous cell carcinoma and adenocarcinoma (aHRGC+CC versus GG = 0.65, 95% CI 0.44–0.96 and aHRGC+CC versus GG = 0.69, 95% CI 0.48–1.00, respectively; PH = 0.82), nor in smokers and never smokers (aHRGC+CC versus GG = 0.71, 95% CI 0.53–0.96 and aHRGC+CC versus GG = 0.54, 95% CI 0.32–0.91, respectively; PH = 0.37). We say that our stratified analyses suggest the association is consistent over varied subgroups.

As in the discrepancy of the association between KRT81 rs3660 and NSCLC among studies [1–3], the discrepancy of gender-specific association among studies may also be attributable to ethnic difference. However, it is possible that stratified analysis may lead to type II error due to the reduced number of subjects in subgroups. Therefore, the modifying effect of gender on the association between KRT81 rs3660 and NSCLC survival is to be confirmed in a larger population.

S. Y. Lee1,2,†, J. E. Choi3* & J. Y. Park1,2,3,†
†Lung Cancer Center, Kyungpook National University Medical Center, Daegu, Republic of Korea;
Departments of 2Internal Medicine;
3Biochemistry and Cell Biology, Kyungpook National University, Daegu, Republic of Korea
*These authors contributed equally to this paper.
(*E-mail: jechoi.9711@gmail.com)

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