Letter to the Editor

Clinical Cancer Research

Replication of Genetic Polymorphisms Reported to Be Associated with Taxane-Related Sensory Neuropathy in Patients with Early Breast Cancer Treated with Paclitaxel—Letter

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We have with great interest read the pharmacogenetic study by Abraham and colleagues (1) reporting SNPs associated with paclitaxel-induced neuropathy. The identification of markers predictive of sensory neuropathy is an important clinical problem for taxanes, vinca-alkaloids, platinum compounds, bortezomib, and thalidomide, among other anticancer drugs. In this respect, the study by Abraham and colleagues is a remarkably large study investigating 73 SNPs previously associated with taxane-related sensory neuropathy (TRSN) in 1,303 European individuals treated with paclitaxel (1). The authors found significant results for nine SNPs, including *EPHA6*-rs301927. Two genome-wide association studies (GWAS; refs. 2, 3) suggest *EPHA5*-rs7349683 as a neuropathy marker (meta-analysis *P* value of 1.4×10^{-9}), and in our study, other members of the Eph receptor family members were also associated with paclitaxel-induced neuropathy (3).

To follow up our initial results suggesting that ephrin type A receptors are important factors influencing TRSN, we analyzed detailed neuropathy data, recorded cycle by cycle using the NCI-CTCAE, from 146 patients treated with first-line paclitaxel. Patients had either ovarian (72%) or breast cancer; 57 (39%) were prospectively recruited in Spain and 89 patients were from a previously described Danish cohort (4). The study was approved by the corresponding ethical review committees and was carried out in accordance with the Helsinki declaration. We genotyped 4 SNPs in *EPHA4*, *EPHA5*, *EPHA6*, and *EPHA8* genes (rs17348202, rs7349683, rs301927, and rs209709, respectively) and 3 SNPs in *XKR4*, *PIK3IP1*, and *SGCG* genes (rs4737264, rs5749248, and rs1753097, respectively), all top signals in our GWAS (3). When tested against TRSN using a cumulative dose analysis, all SNPs in *EPHA* genes, except for *EPHA4*-rs17348202 (minor allele frequency = 0.05, indicating low statistical power), were associated with an increased neuropathy risk (Fig. 1). When analyzing the SNPs using maximum neuropathy grade, only *EPHA6*-rs301927 showed a trend toward increased toxicity ($P = 0.069$), suggesting

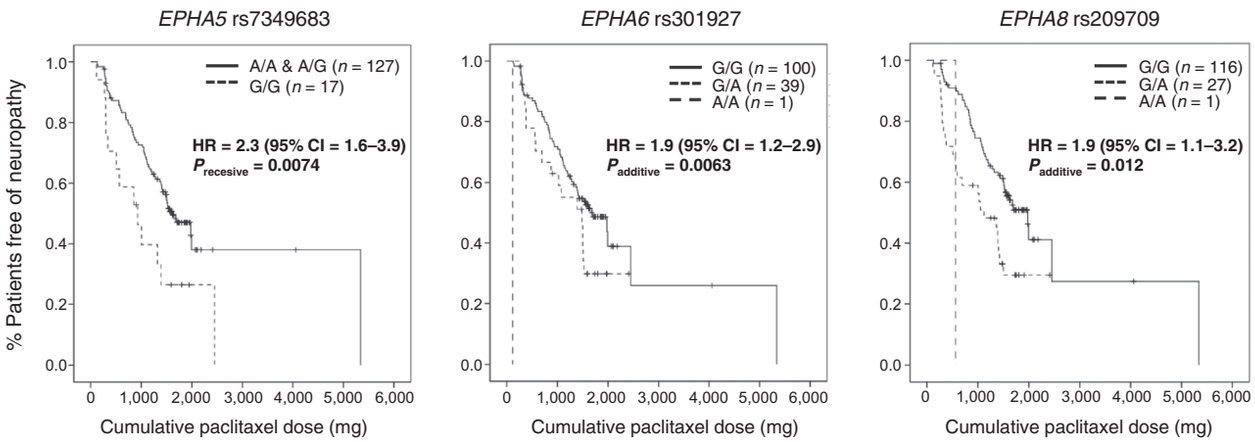

Figure 1.
Kaplan–Meier comparisons by *EPHA* SNPs. Paclitaxel-treated patients grouped according to *EPHA5*-rs7349683, *EPHA6*-rs301927, and *EPHA8*-rs209709 and compared with the cumulative dose of paclitaxel up to the development of grade 2 peripheral sensory neuropathy. *P* values correspond to Cox regression analysis including country as covariate; results from rs7349683 correspond to recessive genetic model.

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that cumulative dose analysis is more sensitive to detect differences in neuropathy. No evidence of association was found for SNPs in other genes.

From a biologic perspective, Eph receptors represent a family of receptor kinases, involved in axon guidance and other neural-related functions, such as neuronal regeneration following nerve injury (5). Thus, this prospective study, together with that from Abraham and colleagues and previous reports, supports an increased TRSN risk for *EPHA5*-rs7349683 (2, 3), *EPHA6*-rs301927 (1, 3), and *EPHA8*-rs209709 (3). Furthermore, because EPHA proteins mediate neural injury repair, these SNPs could act as broad-spectrum neuropathy risk markers relevant for many neurotoxic drugs. Abraham and colleagues performed an exhaustive study of SNPs previously associated with TRSN; however, in view of these results, it would be interesting if the authors could further investigate these potentially clinically relevant markers (e.g., *EPHA8*-rs209709 and *EPHA5*-rs7349683 under different genetic models).

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Correction: Replication of Genetic Polymorphisms Reported to Be Associated with Taxane-Related Sensory Neuropathy in Patients with Early Breast Cancer Treated with Paclitaxel—Letter

In this letter (Clin Cancer Res 2015;21:3092–3), which was published in the July 1, 2015, issue of *Clinical Cancer Research* (1), the A/A and G/G labeling in each panel of Fig. 1 is incorrect—the labels should be reversed. A corrected version of the figure is shown below. The figure legend and main text remain unchanged. The error does not affect the conclusions set forth in the letter. The authors regret this error.

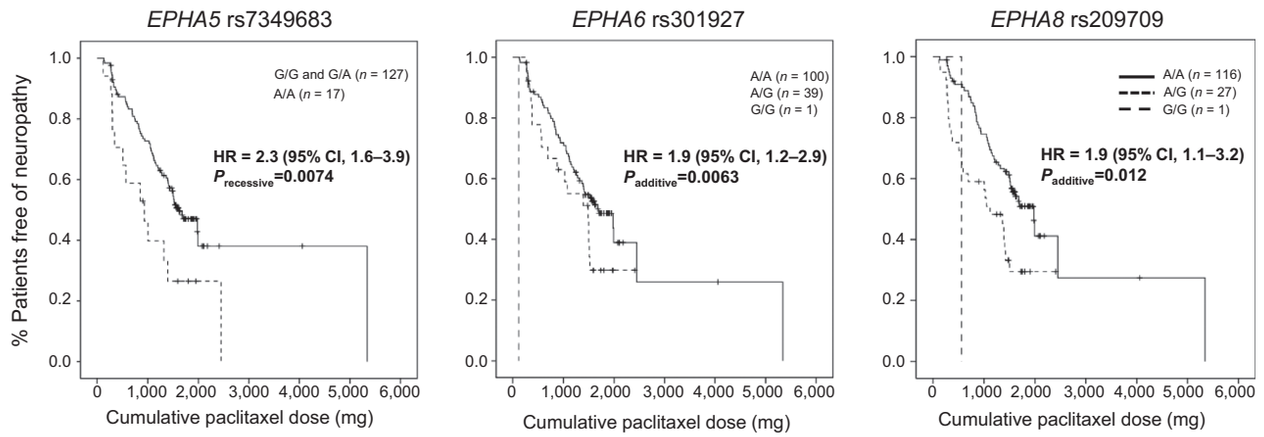

Figure 1.

Reference

1. Apellániz-Ruiz M, Sánchez-Barroso L, Gutiérrez-Gutiérrez G, Sereno M, García-Donás J, Åvall-Lundqvist E, et al. Replication of genetic polymorphisms reported to be associated with taxane-related sensory neuropathy in patients with early breast cancer treated with paclitaxel—letter. Clin Cancer Res 2015;21:3092–3.

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