Precision Oncology – Translating Discovery to the Clinical Practice

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ABSTRACT

Under-representation of non-European populations in the development of breast cancer polygenic risk scores (PRS) has hindered its broader clinical implementation. In this study, we aimed to (1) develop PRSs using the largest available studies of Asian ancestry and (2) to assess the transferability of the best PRS across Asian ethnic subgroups.

The development dataset comprised 58,759 women from 17 case-control studies. PRSs were generated using Asian-specific single-nucleotide polymorphisms (SNPs) or SNPs selected for European 313-SNP PRS but re-weighted using Asian weights. These PRSs were evaluated in 89,898 Asian women from three prospective studies. We evaluated the predictive performance of the best PRS across three ethnic subgroups in Asia – Malay, Chinese and Indian-ancestry women and compared the PRS distribution across women from seven Asian countries.

For the best PRS, the hazard ratio for breast cancer per unit standard deviation in prospective cohorts was 1.50 (95% confidence interval (CI) = 1.35 - 1.65), with area under the receiver operating curve = 0.61 (95% CI = 0.59 – 0.62). The predictive ability of the best PRS was similar across the three ethnic subgroups in Asia. However, the distribution of this PRS was different across seven Asian countries, with the magnitude of differences consistent with genetic distance between these ethnic groups.

This Asian-specific PRS may aid development of risk-stratified screening or prevention programmes for women of Asian ancestry. Importantly, the differences in distribution of the same PRS across different ethnic groups demonstrate that population-specific calibration is important for valid PRS interpretation.

Precision Medicine in Diabetes Mellitus and Cardiovascular Health

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ABSTRACT

Chronic heart failure (CHF) and type 2 diabetes (T2D) frequently coexist and are associated with a poor outcome. Insulin resistance is often unrecognized in HF patients and is associated with poor outcome. The development of diabetic heart failure (HF) may involve genetic and metabolic factors.

Treating patients with concomitant HF and T2D can be challenging as it has been difficult to outline an evidence-based diabetic treatment strategy because there have been no randomized trials that have adequately explored the risks and benefits of diabetic therapies in this population. Intensive glucose lowering does not appear to impact on HF and outcomes. Until recently, most guidelines recommended metformin as the first-line choice based largely on observational data that show that metformin is associated with lower mortality rates when compared to sulphonylureas or insulin.

The newer incretin-based therapies (GLP agonists and DPP-4 inhibitors) are generally not associated with any HF interaction. The sodium-glucose co-transporter-2 (SGLT2) inhibitors have been shown to reduce HF hospitalization in patients with established cardiovascular disease or at risk of cardiovascular disease. The beneficial effect of this class of drug is reported in HF patients with or without T2D. There is intense interest in the mechanisms underlying these observed HF benefits as insight into this mechanism may help define drug therapeutic strategies for HF.

My research has helped change practice as it has been used as underpinning evidence for treatment recommendations in clinical practice guidelines across the world.