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Editorial:

INTERACTION OF GENETIC VARIANTS TOWARDS INCREASED CANCER RISK

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More than 300 associations between genetic variants and common diseases have been identified in recent years (Hindorff et al., 2009; Golka et al., 2009, 2011, 2012; Kiemeney et al., 2010; Binder et al., 2012).

For cancer, most variants, also called single nucleotide polymorphism (SNP), confer only a moderate risk with odds ratios less than 1.5 (Lichtenstein et al., 2000; Selinski et al., 2012a, b, 2011; Lehmann et al., 2010; Ovsiannikov et al., 2012; Rafnar et al., 2011). Until recently, it was unknown whether interaction among the high-risk alleles of several genetic variants would lead to an increased cancer risk (Bolt, 2013a, b; Stewart and Marchan, 2012). This was addressed in a recent study by Holger Schwender and colleagues who investigated the interaction among SNPs known to be associated with bladder cancer and risk. Their results clearly show increased overall risk, causing much excitement in the field (Schwender et al., 2012).

In their work, the group from Dortmund, Germany, showed that for single SNPs, for example rs1014971 and rs9642680, the odds ratio are 1.63 and 1.48, respectively. However, combining both SNPs resulted in an increased odds ratio of 1.91 (Schwender et al., 2012) – a ratio larger than the individual effects but smaller than additive (1.63 + 1.48 = 3.11). Including a third SNP also increased the odds ratio, but only by a further 0.07 (Schwender et al., 2012). Using an elegant statistical approach and testing stability by bootstrapping, the authors demonstrate that stable combinations of up to three high-risk alleles result in odds ratios of up to 2.0 in non-smokers. This is clearly higher than the influence of individual high-risk alleles, but also less than the additive risk.

Although the study of Schwender (Schwender et al., 2012) represents remarkable progress, one important question remains open. What would happen if more high-risk variants were added to the three-way interactions? Would there be a relevant further increase in the cancer risk? Or, would odds ratios asymptotically approach a 'natural' upper limit of 2.0 or slightly above? Schwender and colleagues could not answer this question due to the limited case numbers (1,593 urinary bladder cases and 1,760 controls). Therefore, four-way or even higher interactions could not be evaluated because the combination results were no longer stable after bootstrapping.

In conclusion, there is a definite need to bring together all data on genetic variants that is available world-wide. The increased statistical power will facilitate studies of interactions, and advance our understanding on how genetic variants interact to cause increased cancer risk.

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