EDITORIAL
Moving from one to many: insights from the growing list of pleiotropic cancer risk genes

Pleiotropy, a phenomenon in which a single gene affects multiple phenotypes, is becoming very common among different cancer types and cancer-related phenotypes, such as those in hormonal, cardiometabolic and inflammatory/immune conditions. The discovery of pleiotropic associations can improve our understanding of cancer and help to target investigation of genes with greater clinical relevance.

British Journal of Cancer (2019) 120:1087–1089; https://doi.org/10.1038/s41416-019-0475-9

MAIN
Closely following heart disease, cancer is the second leading cause of death in westernised populations. The complex biology of cancer is underscored by the discovery of more than 1000 low-penetrance cancer risk variants. Estimates of shared genetic penetrance cancer risk variants. The number of publications involving Mendelian randomisation studies has rapidly increased as of late; most likely, this

Despite the fact that pleiotropy is pervasive throughout the human genome, investigations to characterise the shared genetic basis of common cancers and other cancer-related phenotypes remain limited, but the plethora of pleiotropy findings revealed through ad hoc analyses (Fig. 1) suggest that many additional shared genetic risk genes exist. Here we highlight key examples of the insights gained from comprehensive and systematic cross-cancer GWAS analyses. Pleiotropic discoveries can (1) identify shared biologic pathways and prioritise probable causal relationships, (2) reveal unexpected links between phenotypes and aid in aetiological disease classification, (3) test key assumptions for Mendelian randomisation studies, (4) inform repurposing of drugs and predict adverse drug reactions, and (5) increase the statistical power.

SHARED BIOLOGICAL PATHWAYS AND UNEXPECTED PHENOTYPIC LINKS
Pleiotropy has for long been described in monogenic diseases because high-penetrance mutations often cause a constellation of seemingly unrelated clinical features. As an example, PTEN hamartoma tumour syndrome (PHTS), which is caused by mutations in PTEN, predisposes to multiple cancers. PHTS is characterised by multiple hamartomas – benign tumour-like malformations comprising an abnormal mixture of cells and tissues – that can arise in any organ. Although PTEN is a tumour suppressor, it is also involved in non-canonical pathways, meaning that individuals with PHTS can also suffer from severe disfigurement and intellectual disability. This is referred to as biological pleiotropy (e.g. cancer → GPTEN → intellectual disability). By contrast, pleiotropic associations can also arise when one phenotype influences another. Take, for instance, CHRNA5, a gene that associates with lung cancer, chronic obstructive pulmonary disease (COPD) and smoking behaviours. Associations with lung cancer could be due to the profound effects of CHRNA5 variants on smoking intensity, either directly or indirectly through effects on COPD, in a phenomenon referred to as mediated pleiotropy (GCHRNA5 smoking → COPD → lung cancer). Systematic analysis of possible pathways between GCHRNA5 and lung cancer risk suggests that both direct and mediated effects contribute, with approximately 40% attributed to smoking (directly or through COPD). Systematic investigations can provide critical new insight into shared disease mechanisms, causal relationships or novel biological pathways. However, little attention has been given to the study of pleiotropy in complex phenotypes, as opposed to in Mendelian disease. GWAS have provided ample evidence that complex traits are highly polygenic, which has led to the establishment of very large case-control studies and encouraged super-consortia usually focusing on a single disease. The rapid discovery of variant associations by these ‘disease-specific’ consortia has, however, detracted from efforts to find pleiotropic key regulator genes with far-reaching aetiological influences, and hindered the ability to readily perform cross-trait analyses.

GWAS have identified many genetic risk factors that are shared between cancers and other related phenotypes, such as cardiometabolic (CDKN2B-AS1, HNF1B), inflammatory/immune (CDKN1B, FADS1), obesity (FTO), or hormonal (LGR5) conditions. Some of these associations initially seemed rather surprising, such as the positive link between prostate cancer and HNF1B, which also showed a reduced risk for type 2 diabetes; however, this result is consistent with the observation that individuals with type 2 diabetes are at decreased risk for prostate cancer – an unexpected association that had previously been given limited attention.

MENDELIAN RANDOMISATION
The number of publications involving Mendelian randomisation studies has rapidly increased as of late; most likely, this
reflects their purported ability to estimate causal effects in observational settings. In this capacity, Mendelian randomisation has been proposed as a pharmacovigilance and drug-repurposing tool to help identify treatment targets and to prioritise (or deprioritise) major investments in randomised controlled trials (RCTs). In this setting, Mendelian randomisation involves finding genetic variants associated with a modifiable target (e.g. plasma selenium and dietary supplement), and then testing the association between those variants and the outcome (e.g. prostate cancer). However, the absence of pleiotropy is a core assumption that underlies Mendelian randomisation studies, and violation of this assumption can cause severe bias. For example, if the genetic variants used as a proxy for an intended target are associated with decreasing cancer risk through an alternative pathway, the drug or supplement in question could be completely ineffective, or even harmful, despite support from Mendelian randomisation. The extent of pleiotropy among complex traits and diseases is only beginning to be appreciated. As we typically only assess pleiotropy in the context of variants that have already been reported, more comprehensive cross-trait studies are needed before we continue to replace true RCTs with an imperfect statistical approach.

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