Review

Etiologic impact of known cancer susceptibility genes

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Abstract

The impact of a gene variant on the population burden of cancer can be measured by the population attributable fraction (PAF), which depends on the risk conferred by the variant, genotype relative risk (GRR), the frequency of the variant in the population and the mode of inheritance. PAF defines the proportion of the disease in the study population due to a gene variant, hence the synonymic term, etiologic fraction. After a review of the literature, 27 confirmed cancer susceptibility genes, groups of genes and loci were selected for analysis on the basis of their prevalence and availability of validated GRR data. The covered variants represent the most common established cancer susceptibility genes; those not included have marginal PAFs on common cancers. The PAF due to known genes at the covered sites was highest for brain hemangioblastoma (19%), conferred by the VHL gene. For colorectal cancer, the PAF estimates amounted to 7.0%. Including genes and identified loci from whole genome scans, PAFs for both breast and prostate cancers summed up to 70%. The derived estimates should rectify common overstatements on the contribution of individual high penetrance genes on common cancers at the population level. More dramatically, the estimates show the large PAFs conferred by the recently discovered breast, prostate and colorectal cancer loci, most of which are not known to alter coding sequences or expression patterns and they thus act through yet unexplained mechanisms. Although of low risk, these common variants appear to explain large proportions of breast and prostate cancers in the population.
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1. Introduction

Studies on cancer susceptibility genes estimate the frequencies of the mutant alleles in the population and their conferred risk in carriers compared to non-carriers. These data are often used in reviews on cancer causes to make statements on the etiologic impact of the particular mutations such as 'the gene accounts for *x%* of cancer *y*'. While potentially useful, it has turned out that such statements are often inaccurate for a number of reasons. First, mutation carrier frequencies may vary extensively between populations, particularly if founder mutations are common, such as BRCA1/2 mutations in Ashkenazi Jews or BRCA2 mutations in Iceland [1–3]. Second, most mutations are rare and data on their population frequencies may be limited. Third, recruitment of patients into mutation detection studies are usually strongly affected by ascertainment bias, not allowing a reliable estimation of the proportion of mutations among unselected cases [4]. For example, although founder mutations related to hereditary nonpolyposis colorectal cancer (HNPCC) have been identified in some populations, these founder mutations may not alone explain the over 20-fold differences in the reported HNPCC prevalence between Caucasian populations [5,6]. The inaccuracies in population estimates of any disease may bias clinical judgment and allocation of diagnostic resources. Such inaccuracies obscure the inferred heritable etiology of that disease, which may misguide search for novel susceptibility genes or other risk factors. Unfortunately, the published inaccuracies tend to persist long in the scientific literature before being rectified.

The population attributable fraction (PAF), the proportion of the disease in the study population due to a gene variant, is a useful concept that permits to quantify the relative importance of known genes in the burden of disease. The PAF merely states the contribution of the studied gene to disease etiology, independent of unmeasured environmental or genetic factors and their interactions with the gene under study [7]. PAF (also called population attributable risk, etiologic fraction) defines the proportion of the particular cancer that would be avoided if the gene variant was not present in the population. PAFs can be calculated based on the genotype relative risk (GRR) and the allele frequency (q) of the harmful variant. Instead of GRR, many genetic association studies use a related measure, the odds ratio (OR) for the risk allele or risk genotypes [7,8]. Reliable PAF estimates will become of ever increasing importance in the assessment of the results from candidate gene studies and results from whole genome association studies, because they provide a unified population measure of risk.

In the present study we evaluate PAFs for confirmed cancer susceptibility genes in the populations where the gene effects were established. Many susceptibility genes are related to a high penetrance at an index site and to a low-penetrance at additional sites. To illustrate the relevance of founder mutations, we report the effects of specific mutations in some genes. Since our aim is to highlight the overall population impact of the known genes, our derivations rely on representative large studies. A thorough review of all mutation specific effects and the exhaustive exploration of all involved cancer sites are beyond the scope of the present article. Furthermore, we do not attempt a comprehensive evaluation of the results from the rapidly expanding field of low-penetrance genes [8–10] mainly because many findings have not been properly validated. However, we will take as examples results on some validated genes in breast cancer [11] and the first positive findings from validated whole genome association studies on breast [12,13] and prostate cancers [14–16]. These examples will illustrate the contrasting population effects of rare high-penetrant genes and common low-penetrant ones [8].

2. Methods

Data on genes with established heritable effects on cancer were collected from the Cancer Genome Project web site (http://www.sanger.ac.uk/genetics/CGP/Census/germline_mutation.shtmli, last modified 3 November 2005) described elsewhere [17] (Supplementary Table 1). In addition, recent literature was reviewed up to June 2007. Genes were selected on the basis of validated GRR data, significant associations in the original studies and replication of results using indepen-