Commentary

Time for Integrating Clinical, Lifestyle and Molecular Data to Predict Drug Responses

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The study performed by Pottegård and colleagues, published in this issue of EBioMedicine (Pottegård et al., 2016), falls within the clinically relevant scientific field which focuses on the variability in human drug response (Bruno et al., 2014; Fitzgerald, 2005). In some predisposed individuals, treated with a therapeutic dose of a drug, exaggerated responses (serious adverse events) can occur. These responses become evident when drugs, usually marketed at a limited number of doses, are broadly used in the population. Similarly, in some individuals drug therapies can result more effective than in the rest of exposed patients. The sources of heterogeneity among individuals in drug responses involve individual variability in genes, environment and lifestyle for each person. The occurrence of these determinants in drug response has provided the basis for the development of precision medicine, i.e., prevention and treatment strategies that take individual variability into account (FitzGerald, 2015; Collins and Varmus, 2015). While some advances in precision medicine have been made, the practice is not currently in use for most diseases.

Health-care information technology is advancing rapidly, creating new opportunities for the accurate reconstruction of comprehensive drug-exposure histories of individuals. Here, Pottegård et al. (2016) have used this approach to address their hypothesis that pharmaceutical agents may possess long-term carcinogenic or chemopreventive effects. Antiplatelet agents may act as anti-cancer drugs by inhibiting thromboxane A2-dependent platelet activation (Patrignani and Patrono, 2015) but also exhibiting anti-inflammatory and anti-oxidant properties (Weyrich et al., 2005), was inversely correlated with HCC. The protective effect of antiplatelet agents (such as aspirin and clopidogrel) has been demonstrated in a mouse model of hepatitis B virus-associated liver cancer (Sitia et al., 2012). Antiplatelet agents may act as anti-cancer drugs by inhibiting the release of several platelet mediators which may contribute to the development of chronic inflammation associated with HCC.

Several lines of evidence support the chemopreventive effect of the antiplatelet drug low-dose aspirin against colorectal cancer (Patrignani and Patrono, 2015) thus leading the United States Preventive Services Task Force to recommend its use for the primary prevention of cardiovascular disease and colorectal cancer (http://www.uspreventiveservicestaskforce.org/Page/Document/draft-
recommendation-statement/aspirin-to-prevent-cardiovascular-disease-and-cancer). However, this protective signal was not detected in the present study.

Nonsteroidal anti-inflammatory drugs (NSAIDs) have been shown to have a chemopreventive effect in patients with sporadic colorectal adenomas via the inhibitory effect on the biosynthesis of the protumorigenic prostaglandin E\textsubscript{2} (Patrignani and Patrono, 2015). This is confirmed in the present study showing that some individual drugs of the class, i.e., tolfenamic acid and diclofenac, were negatively associated with colon and rectum adenocarcinomas, respectively.

The study by Pottegård et al. (2016) has several points of strength including the detailed stratification according to cancer histology and clinical data collection in large-scale population which allowed evaluation of drug exposure for more rare cancers. However, it is characterized by important weakness related to the fact that this study lacks of adjustment for potential confounding from lifestyle, such as obesity, alcohol consumption, and smoking.

The approach of addressing hypotheses by the analysis of large-scale electronic medical records may capture unexpected responses to drugs in the population; however, the time is ripe to pursue new strategies that will take into account individual variability in genes, environment, and lifestyle for each person (Fitzgerald, 2005, 2015). The new approach integrates electronic medical records with biobank data to identify new disease pathways. Moreover, deep phenotyping of small numbers of patients will allow to elucidate the functional significance of genomic variation (Fitzgerald, 2005, 2015). This change in drug development will permit the use of safer and more efficacious medicines.

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