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Editorial

Next Generation Epidemiology: The Bridge for Translational Cancer Research and Personalized Medicine

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EDITORIAL

US biomedical research including epidemiology research has been criticized that a majority of the research findings are not translational. That is, researches have limited direct impact on improving patient care and public health [1]. In a move to expedite the process for impact, NIH has newly established the National Center for Advancing Translational Sciences (NCATS).

As we all know, epidemiologists investigate research questions at macro-environment level, individual level and molecular or biology level. It seems that epidemiology has natural advantages to be the pivotal for translational cancer research. However, current epidemiology research tends to focus on social and environmental hypotheses, thus limits its ability to integrate clinical and biologic factors. Recently, there are enormous efforts in the epidemiology community trying to bridge the gaps [2], to leverage epidemiology and clinical studies of cancer outcomes [3], and finally to transform epidemiology for 21st century medicine and public health [4]. Therefore, the prototype for translational epidemiology is emerging. There are at least four driver research areas that epidemiology studies can speed up this transition:

Pan life-span epidemiological study

There are increasing number of huge cohort studies and cohort consortiums with long term follow-up. Many cohorts provide unique opportunities to address the effect of various demographic, lifestyle, genomic, molecular, clinical, as well as psychosocial factors on cancer outcomes. For example, the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial is a large population based randomized trial with extensive follow-up. By collecting biologic materials and risk factor information from trial participants before the diagnosis of disease, an ongoing PLCO component, the Etiology and Early Marker Studies (EEMS) is being added. Efforts can be undertaken to link the epidemiologic data with electronic medical and health records to further address the patient's outcomes. These efforts can thus enable systemically study research questions along the whole life-span of cancer patients from cancer susceptibility, gene–environment interaction (GXE) in cancer initiation, promotion, and progression to treatment and finally the survival. Therefore a single study can be used to estimate cancer risk, evaluate treatment selection, and predict treatment response and survival outcomes. The findings can be extremely translational and will impact cancer prevention and management directly.

Pharmaco-genetic-epidemiology study

Pharmaco-genetic-epidemiology studies can be nested on these life span cohorts. Recent advances in genomic research have demonstrated a substantial role for genomic factors in predicting response to cancer therapies. As the numbers of cancer survivors in those cohorts and many large clinical trials for chemotherapy continue to grow, researches investigating the factors that affect cancer outcomes are maturing. These outcomes include but not limit to cancer treatment response, side effects, disease recurrence, survival outcomes as well as the late effects of cancer treatments. Researchers can seek to understand why individuals respond differently to drug therapy, in terms of both adverse effects and treatment efficacy [5]. To advance the fields of cancer pharmaco-genomics and Pharmacogenetics, it may be a good start to first genotype and analyze the association of outcomes with single nucleotide polymorphisms (**SNPs**) in 139 drug metabolism genes identified through the PharmGKB database (http://www.pharmgkb.org/). Of course, novel tools for gene–drug interactions should be also developed and utilized.

Clinical/molecular phenotype subset study

Personalized medicine is a rapidly advancing field that is informed by each person's unique clinical, molecular, genomic, and environmental information [6]. All these areas are broadly fall in the domain of epidemiology. Hence, epidemiology can serve a pivotal role in personalized medicine. The key for finding targets for personalized cancer prevention and treatment is to identifying clean phenotype and distinct genotype. Cancers are heterogeneous, for example colorectal cancer is not a single disease but a complex multifactorial disease [7]. As a result, the genotype–phenotype relationship is complicated by significant heterogeneity, which largely because gene–gene, GXE and environment–environment interactions factor in all phases of

carcinogenesis, progression and also management. Traditional cancer epidemiology studies do not fully take account of this heterogeneity because when it comes to subset analysis, sample size is always an issue. Recently established cohort consortiums make subset analysis a reality. Further, most common cancers are known to arise neither exclusively from genetic nor environmental factors, but through a combination of the two [8,9]. But genome-wide association studies (GWAS) studies mostly did not include environmental/risk factors. Thus, It will be rewarding to thoroughly investigate the interaction of both factors for of all clinical/molecular subsets of a specific cancer to identify new targets for personalized cancer prevention and treatment.

Mendelian randomization analysis (MRA) studying gene-environment interactions

One annoying obstacle prevents epidemiological findings from translating into intervention is that a large proportions of the findings of observational studies are associations rather than causations. To put findings to intervention, novel tools for proof of causation have been becoming the bottle-neck. MRA, based on the principle of Mendel's law of independent assortment, is developed for this purpose [10,11]. It combines genetic and classical epidemiological analysis exposures to reduce or even eliminate potential biases in the associations thus infer causality [12]. However, the application of MRA in epidemiology has substantial limitations, which is predominantly owing to the lack of good genetic factors as proxies for environmental exposures of interest. To overcome this limitation, there have been some novel approaches in which combined genetic risk categories based on the putative genetic pathways were used as the proxies [13,14].

Translational cancer research is interdisciplinary and trans-disciplinary by nature. Numerous suggestions and recommendations have been making for multidisciplinary collaborations and partnerships to identify and fill the knowledge gaps. Much less attention has been paid to how to prepare the scientists for trans-disciplinary research [15,16]. In fact, multidisciplinary training is a prerequisite for the next generation researchers who want to be fully capable to conduct translational cancer research. The next generation epidemiologists (NGEs) may have to obtain comprehensive knowledge of cancer epidemiology, molecular/genetic biology, statistics, and oncology or pathology [15]. Thus an ideal NGE might be an oncologist with rigorous training in molecular-genetics and epidemiology. Of course, there should be many kinds of NGEs for whom different multi-disciplinary expertise is required. Nonetheless, knowledge integration is the key [16]. Although the requirement of this kind of cross-training sounds prohibitive, this is a dynamic time for the NGEs to play a critical role in personalized medicine and translational research. We may have to embark upon the exciting challenges to be NGEs and function fully as translational researchers.

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