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Editorial

Molecular Pathological Epidemiology: An Interdisciplinary Field for Study of Hepatocellular Carcinoma

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Editorial

Hepatocellular Carcinoma (HCC), with a mounting annual incidence of 4.9 per 100 000 persons, accounts for more than 80% of primary liver cancers and ranks globally as the third leading cause of cancer-related deaths [1]. In China, there is a particularly high incidence of 40 per 100 000 persons per year [2]. The prognosis of HCC is still very poor although many advances in diagnosis and treatment have been made. Annual mortality rates of HCC remain comparable to its yearly incidence, making it one of the most lethal varieties of solid-organ cancers [3].

Risk factors for HCC that have been found and confirmed include Hepatitis B Virus (HBV), Hepatitis C Virus (HCV), cirrhosis, heavy alcoholic consumption, aflatoxin exposure, Non-Alcoholic Steatohepatitis (NASH), increasing age, male sex, and positive family history [4]. Diabetes Mellitus (DM) has been suggested as a potential risk factor for HCC and the prognosis after curative therapy can be affected [5]. It is important to clarify how these factors affect the occurrence and development of HCC.

Molecular pathological epidemiology was introduced by Ogino and Stampfer in the year of 2010 [6]. They consolidated this concept mainly based on the researches of Colorectal Cancer (CRC). For a deeper understanding of this concept, we would introduce the prototypical study in the evolving field of molecular pathological epidemiology. Campbell et al. described this case-control study which was designed to evaluate the relationship between Body Mass Index (BMI) and CRC risk in relation to tumor Microsatellite Instability (MSI) status [7]. The authors found that BMI was associated with an increased risk of CRC; however, this excess risk was limited to those patients with MS-stable (for a BMI increment of 5 kg/m^2, adjusted odds ratio/OR = 1.38; 95% confidence interval/CI = 1.24 to 1.54) and MSI-low (OR = 1.33; 95% CI = 1.04 to 1.72) colorectal tumors, but not with the risk of MSI-high tumors (OR = 1.05; 95% CI = 0.84 to 1.31). The results of Campbell et al. suggest that the increased risk of CRC associated with a high BMI might be largely restricted to tumors that display the more common MS-stable phenotype [7]. It may also indicate that colorectal cancer etiology differs by tumor MSI status.

Traditional epidemiology research has typically investigated those factors, including lifestyle, environmental or genetic factors, that might increase or decrease risk of developing carcinomas [8]. Molecular epidemiology has evolved since the 1990s, [9] which refer to a specialized field of epidemiology where researchers investigate the genetic and molecular characteristics in a population and its interaction with lifestyle or environmental factors, to find the association between aetiological factors and tumors. However, the mechanisms remain largely speculative [8].

Traditional molecular pathology research has investigated molecular characteristics in tumor cells to better understand cancer cell behavior and carcinogenic processes. Recently, epidemiology and molecular pathology have converged to better understand how particular exposures influence the carcinogenic and pathologic process. These research efforts create a new interdisciplinary field, which has been introduced as "molecular pathological epidemiology" [6,8]. In this field, somatic molecular changes and biomarkers of tumor initiation or progression have been studied in relation to exposures of interest, for both etiology and prognosis. Molecular pathology plays a central role in this relatively new field, "molecular pathological epidemiology", which is a multidisciplinary investigation of the interrelationship between exogenous and endogenous factors, tumor molecular signatures, and tumor initiation, progression, and response to treatment [6,8]. Molecular pathological epidemiology addresses the question of whether a particular exposure factor is associated with a specific molecular change, as well as the question of whether a specific molecular change can interact with a particular exposure factor to affect tumor cell behavior [8].

Now, please let us look back on the research which was performed by Campbell et al [7]. This study investigated the association between high BMI (exposure factor), risk of CRC (tumor initiation) and tumor MSI status (molecular change). Their results were generally supported by other two case-control studies [10,11]. Because of the critical role of molecular changes and tumor biomarkers, the data from molecular pathological epidemiology may imply that tumors can be classified into distinct subtypes by using these molecular markers, which would be helpful for the treatment.

Considering that most of the molecular pathological epidemiology researches are designed for the CRC, we would like to introduce this relatively new concept into the field of study of hepatocellular carcinoma. As described in the second paragraph, some etiologic factors have been associated with HCC, including diabetes mellitus [12-14]. However, how these etiologic factors affect the occurrence

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and development of HCC remains as yet unclearly understood. Molecular pathological epidemiology may be a promising approach to investigate molecular mechanisms of carcinogenesis. It can be used to determine the effect of these factors on HCC by molecular subtypes.

We should remember that molecular pathological epidemiology is the branch of epidemiology, and its basis is the molecular classification of tumors. Currently, based on our current knowledge, no molecular pathological epidemiology researches are available for HCC. However, those molecular changes and tumor biomarkers of HCC which have been previously identified and described can be used to design such studies and investigate the molecular mechanisms of etiologic factors. For example, Ojanguren et al. found that positive immunostaining of mutant p53 expression was frequently associated with a history of alcohol abuse (42%) and also with viral infection (HBV, 21%; HCV, 7%; non-A/non-B hepatitis, 7%) [15]. Park et al. show that Interleukin (IL)-6 and Tumor Necrosis Factor (TNF) signaling through activation of STAT3 are critical for obesity-promoted HCC development [16]. In obese people, TNF-alpha, IL-1 and IL-6, insulin and insulin-like growth factors, adipokines, plasminogen activator inhibitor-1, adiponectin, and leptin are found to play crucial roles in the initiation and development of some carcinomas, including HCC [17]. On the basis of results of these studies, molecular pathological epidemiology researches can be designed and performed to explore the carcinogenic processes induced by etiologic factors in HCC. Molecular pathological epidemiology can provide useful insights for the pathological processes, although there are challenges which must be overcome.

In summary, molecular pathological epidemiology is to elucidate how exposure factors affect the initiation, transformation and progression of tumor. We believe that it can provide some very important insights on the molecular mechanisms, diagnosis, personalized prevention and treatment for HCC in the future.

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