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Molecular Pathological Epidemiology Gives Clues to Paradoxical Findings

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Abstract

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Use of standardized official symbols: Use of standardized official symbols: We use HUGO (Human Genome Organisation)-approved official symbols for genes and gene products, including BRAF, FASN, KRAS, MGMT, and SMAD7; all of which are described at www.genenames.org

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A number of epidemiologic studies have described what appear to be paradoxical associations, where an incongruous relationship is observed between a certain well-established risk factor for disease incidence and favorable clinical outcome among patients with that disease. For example, the “obesity paradox” represents the association between obesity and better survival among patients with a certain disease such as coronary heart disease. Paradoxical observations cause vexing clinical and public health problems as they raise questions on causal relationships and hinder the development of effective interventions. Compelling evidence indicates that pathogenic processes encompass molecular alterations within cells and the microenvironment, influenced by various exogenous and endogenous exposures, and that interpersonal heterogeneity in molecular pathology and pathophysiology exists among patients with any given disease. In this article, we introduce methods of the emerging integrative interdisciplinary field of molecular pathological epidemiology (MPE), which is founded on the unique disease principle and disease continuum theory. We analyze and decipher apparent paradoxical findings, utilizing the MPE approach and available literature data on tumor somatic genetic and epigenetic characteristics. Through our analyses in colorectal cancer, renal cell carcinoma, and glioblastoma (malignant brain tumor), we can readily explain paradoxical associations between disease risk factors and better prognosis among disease patients. The MPE paradigm and approach can be applied to not only neoplasms but also various non-neoplastic diseases where there exists indisputable ubiquitous heterogeneity of pathogenesis and molecular pathology. The MPE paradigm including consideration of disease heterogeneity plays an essential role in advancements of precision medicine and public health.

Keywords

bias; cardiovascular disease; molecular diagnostics; multifactorial diseases; personalized medicine

INTRODUCTION

An apparently paradoxical association, which is occasionally observed in epidemiologic research, refers to the relationship of a well-known risk factor (e.g., obesity) for developing a certain disease (e.g., coronary heart disease) with lower mortality among patients with that disease. Intuitively, we tend to consider that a disease risk factor is likely associated with worse clinical outcomes among patients with that disease, because the risk factor is considered to facilitate the pathogenic process that has led to the disease. In the notorious “obesity paradox” which has been described in various diseases [1–5], obese patients with a given disease in average experience better clinical outcomes than normal-weight patients, despite the fact that obesity is a well-established risk factor for that disease. Possible explanations to the paradox have been proposed, including selection bias, index event bias, collider bias, unmeasured confounding, measurement error, and reverse causation [5–11]. However, possible biological mechanisms which may provide an additional plausible explanation have not been well discussed.

The purpose of this article is to demonstrate that, by means of considering molecular heterogeneity of disease based on pathogenic mechanisms, we can readily decipher some of apparent paradoxical findings. Collapsing two or more heterogeneous disease subtypes into one disease entity would produce a similar problem as unmeasured confounding in the

structure of the association between a risk factor and mortality [12]. This phenomenon (bias due to unmeasured molecular subtypes of disease) has been termed “molecular confounding” though it does not satisfy all of the criteria of typical confounding in an epidemiologic sense [13]. We use examples of studies on colorectal, kidney, and brain cancers, to demonstrate that the inherent nature of inter-personal molecular heterogeneity within a disease can underlie paradoxical observations. These examples attest to the importance of taking disease heterogeneity and pathogenesis into consideration in not only research but also clinical and public health practice [14]. This trend has also been highlighted by the precision medicine initiative of the U.S.A. National Institute of Health [15].

MOLECULAR PATHOLOGICAL EPIDEMIOLOGY (MPE): ANALYSIS METHOD

Accumulating evidence indicates that many traditional disease designations (e.g., lung, breast, or colorectal cancer, heart failure, type 2 diabetes mellitus, hypertension, kidney stones, major depression, stroke, or multiple sclerosis) are umbrella terms for a group of heterogeneous disease processes which share certain common features, such as clinical manifestations and some pathologic characteristics [16]. However, it is increasingly evident that, in each individual, disease processes represent unique sets of molecular changes in cells and microenvironment, and these processes differ from person to person [17]. Furthermore, a disease process is influenced by endogenous and exogenous exposures (e.g., germline genetics, diet, microorganisms, medications, and inhalants) and molecular interactions in the microenvironment [17]. Endogenous and exogenous exposures certainly vary from person to person [17]. Therefore, while there are some similarities between people with a particular disease, each individual has a unique disease process which is different from any other individuals (i.e., the unique disease principle) [17]. The fundamental tenet of MPE is that inherent pathogenic heterogeneity is taken into account when we examine the association between a risk factor and disease incidence. Here, we introduce the emerging field of molecular pathological epidemiology (MPE), and discuss the importance of considering pathogenesis and inherent heterogeneity of disease.

By identifying groups of patients who share similar molecular pathologic signatures, molecular classification of disease plays a key role in integrating the unique disease principle into epidemiologic research [17]. MPE has recently emerged to facilitate this integration of molecular pathology into epidemiology [18]. MPE is defined as epidemiology of molecular pathology and heterogeneity of disease. MPE research emphasizes the importance of considering disease heterogeneity and the complexity of pathogenic mechanisms by examining hypothetic links between exposures and molecular signatures of the disease [19]. The MPE approach can not only uncover associations between exposures and specific molecular subtypes of disease but also refine risk estimates specific for disease subtypes, thereby providing insight into pathogenic mechanisms and contributing to causal inference [17–21]. The MPE approach and concept have been widely accepted and utilized [22–47]. MPE has been a major theme of international symposia [14, 48, 49] and recently-established international meeting series [50].

It is relevant to briefly review molecular pathology of colorectal cancer, because paradoxical findings exist in colorectal cancer and ample data from both conventional epidemiology and MPE research actually give us clues to the paradoxes. Colorectal cancer is a heterogeneous group of neoplasms which arise as a result of accumulation of a differing set of molecular alterations [51–53]. In the initiation and progression of colorectal neoplasia, aberrant cellular genetic and epigenetic changes occur along with stromal microenvironmental changes [51, 54]. Some pathogenic molecular alterations in colorectal cancer including microsatellite instability (MSI), and somatic mutations in *KRAS* and *BRAF* are now routinely tested for clinical use [55]. With these well-established molecular pathology tests, colorectal cancer represents a disease area where MPE research has been quite active. Emerging evidence indicates that specific exposures influence the initiation and progression of different molecular subtypes of colorectal tumor [20]. For example, MPE research has shown that cigarette smoking has been associated with an increased risk for colorectal cancer subtype characterized by high-level CpG island methylator phenotype (CIMP-high) [56–58]. In addition, MPE research has suggested that colonoscopy screening may be less effective in reducing risks of CIMP-high and MSI-high subtypes, compared to non-CIMP-high and non-MSI-high subtypes [59]. These data suggest that optimal colonoscopy screening may vary among individuals with different lifestyle and genetic risk profiles. Hence, MPE research can contribute to the development of more personalized prevention strategies. In essence, “colorectal cancer” is a single disease entity in the conventional research paradigm, but consists of a complex group of conditions when we look deeply into molecular pathological signatures. A better understanding of disease heterogeneity is a prerequisite for accurate assessment of the associations between risk factors and pathologic processes.

In the following section, we analyze and decipher apparent paradoxical findings, utilizing the MPE approach and available literature data.

ANALYSES OF PARADOXES

Lynch syndrome, MSI-high colorectal cancer, and longer survival

Lynch syndrome is the most common form of hereditary colorectal cancer, and is caused by a germline mutation in one of DNA mismatch repair genes [60, 61]. Previous studies have reported that carriage of Lynch syndrome mutations is associated with markedly higher risk of colorectal cancer; but among all colorectal cancer patients, Lynch syndrome patients in average survive longer than other colorectal cancer patients [60, 61]. Studies have shown that Lynch syndrome mutation carriers have a higher risk of the MSI-high subtype of colorectal cancer (but not that of non-MSI subtype), and among colorectal cancer patients, the MSI-high subtype is associated with longer survival (Fig. 1a) [55]. Therefore, the seemingly paradoxical association between colorectal cancer patients carrying Lynch syndrome mutations and superior survival can be readily explained by the association between the specific cancer subtype (MSI-high) caused by Lynch syndrome and better prognosis.

SMAD7 variant, low-stage colorectal cancer, and longer survival

Genome-wide association studies indicate that the rs4939827 single nucleotide polymorphism (SNP) in *SMAD7* (18q21) is a well-validated susceptibility variant for colorectal cancer [62]. The major G allele of the rs4939827 polymorphism has been associated with higher incidence of colorectal cancer; but among colorectal cancer patients, the presence of this major allele is associated with better survival [63, 64]. A recent study has demonstrated that the major G allele of rs4939827 is associated with a high risk of low-stage (indolent and less invasive) colorectal cancer subtype [64]; these findings can explain the apparently paradoxical association of the risk variant with better survival among colorectal cancer patients (Fig. 1b).

Obesity, *FASN* non-upregulated renal cell carcinoma, and longer survival

Renal cell carcinoma (RCC, a specific pathologic type of kidney cancer) is another example where recent MPE data are available to help elucidate paradoxical findings, which fit the "obesity paradox". Obesity has been associated with risk of RCC, but also counter-intuitively with better survival among RCC patients [65]. A study by Hakimi et al. [66] has provided a helpful clue to this paradox; obesity is associated with low-stage RCC and low-grade RCC (less aggressive forms of RCC). Moreover, obesity is associated with a specific molecular subtype of RCC with no upregulation of *FASN* (the official symbol for fatty acid synthase) [66]. The *FASN* protein is a key enzyme in fatty acid metabolism [67]. Compared to RCCs with *FASN* upregulation, RCCs without *FASN* upregulation are associated with longer survival [66]. Thus, obesity is associated with low-stage, low-grade, and *FASN* non-upregulated subtypes of RCC; all of which are features associated with longer survival in RCC patients (Fig. 1c).

MGMT promoter variant, loss of *MGMT* expression, and longer survival in glioblastoma

The paradoxical observation in the association between a *MGMT* promoter variant, a risk factor for glioblastoma, and longer patient survival was explained by MPE studies. *MGMT* is DNA repair enzyme, and functions as a tumor suppressor. In some cancers, *MGMT* expression is lost, through DNA hypermethylation at its promoter CpG island. Loss of *MGMT* expression is causally linked to mismatch repair deficiency and carcinogenesis [68]. The minor T allele of the rs16906252 SNP in the *MGMT* promoter is associated with longer patient survival in glioblastoma (a common pathologic type of brain cancer) [69]. This is paradoxical, because the minor T allele of this SNP has been causally linked to carcinogenesis, through *MGMT* promoter methylation and loss of expression [70, 71]. However, this paradox can be easily explained, as studies have shown that *MGMT* promoter CpG island methylation and loss of *MGMT* expression are associated with longer survival in glioblastoma [68, 69]. Essentially, the minor T allele of the SNP is a cause of the indolent tumor molecular subtype with *MGMT* promoter CpG island methylation and loss of *MGMT* expression in glioblastoma. Thus, the apparent paradoxical association can be explained by disease heterogeneity in glioblastoma (Fig. 1d).

DISCUSSION

The above analyses illustrate how inherent heterogeneity of disease can readily explain paradoxical findings, utilizing the molecular pathological epidemiology (MPE) approach and available literature data. Under the MPE paradigm, a risk factor for a disease likely facilitates specific pathogenic processes, thereby influencing occurrence of a specific disease subtype, which is often associated with clinical outcome among patients with the disease (consisting of the specific subtype and other subtypes). Without considering heterogeneous disease subtypes, the associations depicted in Fig. 1 can appear as paradoxes. In another setting, if a disease risk factor is linked with occurrence of an aggressive disease subtype, the risk factor is most likely associated with both disease occurrence and adverse prognosis among disease patients; hence, there is no paradox.

MPE research has been mostly applied to neoplastic diseases where tumor molecular tests have been widely available in research as well as clinical practice [16, 72]. In contrast, for most non-neoplastic diseases, disease molecular pathology data remain scanty, and the emerging MPE paradigm has not yet been widely applied. However, accumulating evidence indicates that, in many non-neoplastic diseases (including obesity, metabolic diseases, cardiovascular diseases, respiratory diseases, infectious diseases, immunity-related diseases, neurological diseases, psychiatric diseases, etc.), there exists inherent heterogeneity of pathogenesis [16]. Therefore, the relevance of the MPE paradigm in non-neoplastic diseases has been increasingly recognized [16, 73–75]. Hence, we speculate that, perhaps together with the other recognized causes of paradoxes, disease heterogeneity can contribute to some of reported paradoxical findings in not only neoplastic diseases but also non-neoplastic diseases. For example, recently, Lajous et al. [6] have suggested that type 2 diabetes mellitus may consist of different subtypes, and that the paradoxical finding on better survival among diabetic patients could result from the heterogeneity of the disease. As we do not generally consider subtypes of type 2 diabetes mellitus in practice, analysis limited to cases with type 2 diabetes mellitus (as one entity) will be conditioned on a collider, and then introduces selection bias [6]. Heart failure is another example of a complex disorder that results from diverse biological processes. Patients with heart failure comprise a heterogeneous group, and pathologic processes of heart failure are influenced by many factors, including hypertension, structural disorders of the pericardium, myocardium, endocardium or heart valves, vascular abnormalities, diabetes mellitus, other metabolic abnormalities, cigarette smoking, alcohol consumption, and kidney disease [76].

With the advent of molecular pathology tests and precision medicine [15, 77–79], molecular classification systems can be used to subgroup patients with similar pathogenic characteristics, to better predict disease evolution and response to intervention. As biomedical and public health sciences advance, modern epidemiology and clinical medicine should more explicitly take into account disease pathogenesis and inherent heterogeneity of disease [80–82]. The MPE concept and research can substantially contribute to the acceleration of precision medicine. We emphasize that a full assimilation of the MPE concept requires a change in mindsets of clinicians and researchers. Furthermore, the MPE concept has been expanding for recent years. The MPE field has recently been integrated with pharmacoepidemiology (to form pharmaco-MPE) [16], and with immunology (to form

immuno-MPE) [83]. In order to keep up epidemiology to advancement of biomedicine, we must address various challenges, which include difficulty in characterizing the complex nature of many multifactorial diseases, paucity of data on their molecular subtyping, and paucity of interdisciplinary experts who can conduct MPE-type research on complex diseases. Interdisciplinary education which fully integrates pathology and epidemiology has been proposed to transform epidemiology into modern integrative population health science [80, 81, 84]. We stress the importance of considering heterogeneity in disease pathogenesis and mechanisms in not only enhancing causal inference but also advancing medicine and public health.

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Abbreviations

CIMP	CpG island methylator phenotype
MPE	molecular pathological epidemiology
MSI	microsatellite instability
RCC	renal cell carcinoma
SNP	single nucleotide polymorphism.

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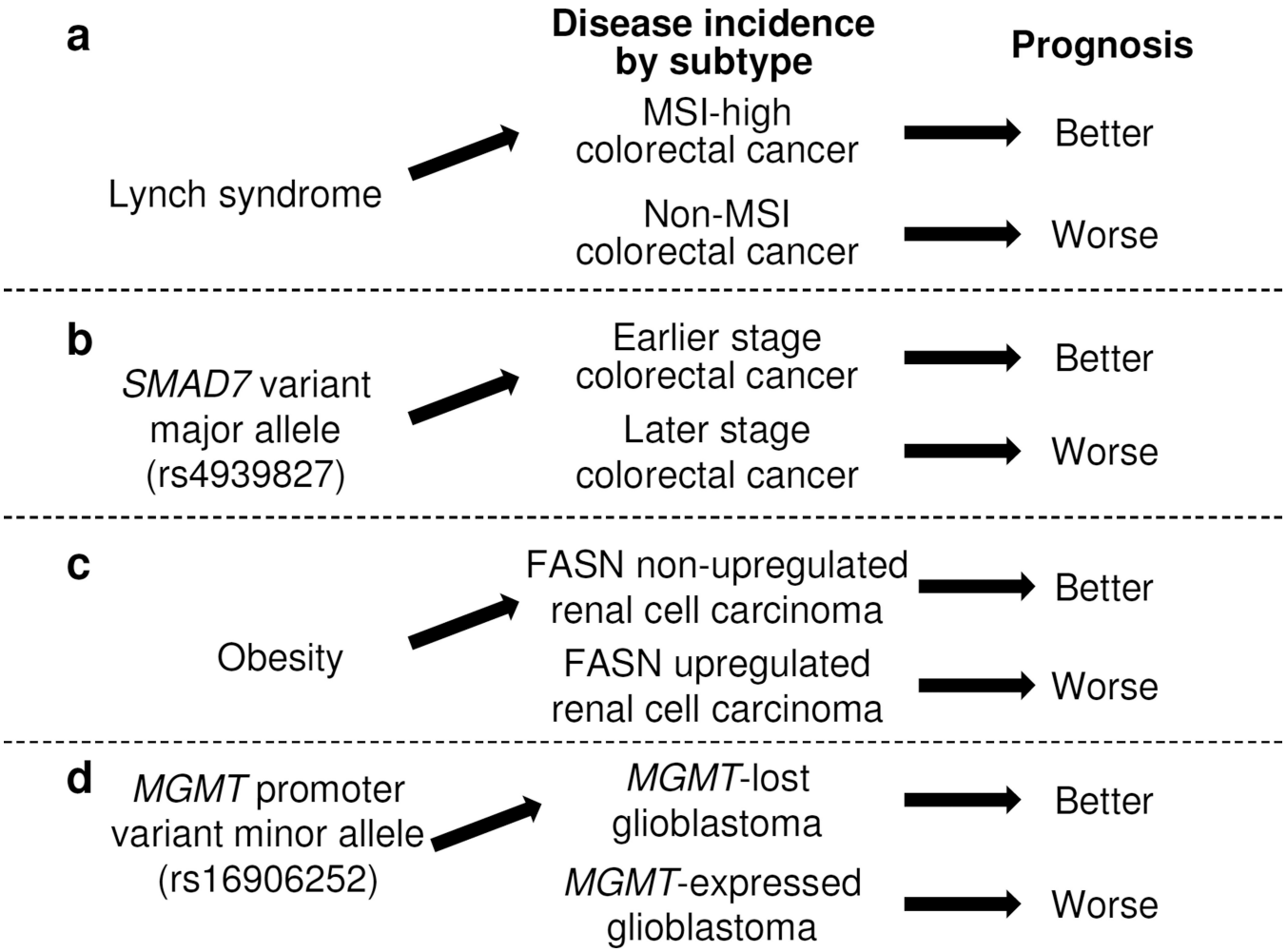

Fig. 1.

The apparent paradoxical associations in colorectal cancer, renal cell carcinoma, and glioblastoma (malignant brain tumor), utilizing molecular pathological epidemiology (MPE) approach and literature data. a. Lynch syndrome is associated with incidence of colorectal cancer with high levels of microsatellite instability (MSI-high), and MSI-high cancer is associated with better prognosis among patients with colorectal cancer. Hence, the carrier status of Lynch syndrome mutation is associated with higher colorectal cancer risk, but with better prognosis among colorectal cancer patients. b. The major G allele of the rs4939827 *SMAD7* polymorphism is associated with colorectal cancer with earlier stage, and earlier cancer stage is associated with better prognosis among patients with colorectal cancer. The major G allele of the rs4939827 *SMAD7* polymorphism is associated with higher colorectal cancer risk, but with better prognosis among colorectal cancer patients. c. Obesity is associated with a subtype of renal cell carcinoma (RCC) characterized by low-stage, low-grade, and *FASN* non-upregulation, and all of these features are associated with better prognosis among RCC patients. Hence, obesity is associated with higher RCC risk, but with better prognosis among RCC patients. d. The minor T allele of the rs16906252 polymorphism in the *MGMT* promoter region is associated with loss of *MGMT* expression in glioblastoma, and loss of *MGMT* expression is associated with better prognosis among

patients with glioblastoma. Hence, the minor T allele of rs16906252 polymorphism contributes to pathogenesis of glioblastoma, but is associated with better prognosis among glioblastoma patients.

MSI, microsatellite instability.