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Special Article

Interdisciplinary Education to Integrate Pathology and Epidemiology: Towards Molecular and Population-Level Health Science

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In recent decades, epidemiology, public health, and medical sciences have been increasingly compartmentalized into narrower disciplines. The authors recognize the value of integration of divergent scientific fields in order to create new methods, concepts, paradigms, and knowledge. Herein they describe the recent emergence of molecular pathological epidemiology (MPE), which represents an integration of population and molecular biologic science to gain insights into the etiologies, pathogenesis, evolution, and outcomes of complex multifactorial diseases. Most human diseases, including common cancers (such as breast, lung, prostate, and colorectal cancers, leukemia, and lymphoma) and other chronic diseases (such as diabetes mellitus, cardiovascular diseases, hypertension, autoimmune diseases, psychiatric diseases, and some infectious diseases), are caused by alterations in the genome, epigenome, transcriptome, proteome, metabolome, microbiome, and interactome of all of the above components. In this era of personalized medicine and personalized prevention, we need integrated science (such as MPE) which can decipher diseases at the molecular, genetic, cellular, and population levels simultaneously. The authors believe that convergence and integration of multiple disciplines should be commonplace in research and education. We need to be open-minded and flexible in designing integrated education curricula and training programs for future students, clinicians, practitioners, and investigators.

education, public health professional; health care reform; individualized medicine; interdisciplinary communication; molecular epidemiology; pathology

Abbreviations: MPE, molecular pathological epidemiology; STROBE, Strengthening the Reporting of Observational Epidemiology.

Editor's note: *An invited commentary on this article appears on page 668, and the authors' response appears on page 672.*

Education is a crucial mission of the academic community. Excellence in research and education requires the combined efforts of many different disciplines (1, 2). As fundamental disciplines of biomedical and public health sciences, both pathology and epidemiology are fields of study of the entire spectrum of human diseases—the former focused on disease mechanisms in individual cases, the latter on patterns of disease in populations. The importance of these fields is well exemplified by the universal presence of pathology in medical school curricula and that of epidemiology in public health school curricula. Because of advances in both laboratory technologies and epidemiologic methods, pathology and epidemiology have become compartmentalized in schools of medicine and public health, respectively. By virtue of our training in both pathology and epidemiology, we can appreciate that knowledge, skills, and concepts from both fields can be integrated and synergized to advance biomedical, public health, and population sciences. In this era of personalized medicine (3), we need integrated, convergent scientific disciplines, which will enable us to decipher the characteristics of diseases simultaneously at both the individual and population levels (4–6).

Table 1. Examples of Molecular Pathological Epidemiology Studies Which Have Shown Consistent Links Between Etiologic Factors and Cellular Molecular Changes[a]

First Author, Year (Reference No.)	Disease (as in Traditional Epidemiology)	Study Design	Sample Size (No. of Participants)	Putative Etiologic Factor	Tumor Molecular Changes (Subtypes)	Direction of Association
Chen, 2007 (31)	Colorectal cancer	Case-case	383	*MLH1* rs1800734 SNP	*MLH1* methylation	Positive
Chen, 2007 (31)	Endometrial cancer	Case-case	498	*MLH1* rs1800734 SNP	*MLH1* methylation	Positive
Raptis, 2007 (32)	Colorectal cancer	Case-control	766 cancer cases, 1,098 controls	*MLH1* rs1800734 SNP	MSI	Positive
Samowitz, 2008 (33)	Colon cancer	Case-control	795 cancer cases, 1,968 controls	*MLH1* rs1800734 SNP	*MLH1* methylation, CIMP, *BRAF* mutation	Positive
Allan, 2008 (34)	Colorectal cancer	Case-case	1,392	*MLH1* rs1800734 SNP	*MLH1* loss of expression	Positive
Campbell, 2009 (35)	Colon cancer	Case-control	1,211 cancer cases, 1,972 controls	*MLH1* rs1800734 SNP	MSI	Positive
Oyama, 2004 (36)	Colon cancer (proximal)	Case-case	194	1-carbon metabolism (*MTHFR* rs1801131 SNP)	*CDKN2A* (p16) methylation	Positive
Curtin, 2007 (37)	Colon cancer	Case-control	916 cancer cases, 1,972 controls	1-carbon metabolism (*MTHFR* rs1801131 SNP)	CIMP	Positive
Jensen, 2008 (38)	Colorectal cancer	Case-case	130	1-carbon metabolism (plasma homocysteine)	MSI	Positive
de Vogel, 2009 (39)	Colorectal cancer	Case-cohort	373 cancer cases, 4,774 in subcohort	1-carbon metabolism (*MTHFR* rs1801131 SNP)	CIMP	Null
Schernhammer, 2010 (40)	Colon cancer	Prospective cohort	609 incident cancer cases, 136,056 participants	1-carbon nutrients (folate, B vitamins), alcohol	LINE-1 hypomethylation	Lack of folate and excess alcohol are associated with increased incidence of LINE-1 hypomethylated cancer but not that of LINE-1 methylation-high cancer.
Hazra, 2010 (41)	Colorectal cancer	Case-case (in prospective cohort studies)	182	1-carbon metabolism (*MTHFR* rs1801131 SNP)	CIMP	Positive
Van Guelpen, 2010 (42)	Colorectal cancer	Nested case-control (in prospective cohort study)	190 cancer cases, 380 controls	1-carbon metabolism (*MTHFR* rs1801131 SNP)	CIMP	Negative (inverse)
Curtin, 2011 (43)	Rectal cancer	Case-control	671 cancer cases, 1,205 controls	1-carbon metabolism (*MTHFR* rs1801131 SNP and folate intake)	CIMP	*MTHFR* rs1801131 SNP and folate intake interact to modify an association with CIMP-positive rectal cancer
Ogino, 2007 (44)	Colorectal cancer	Case-case (in prospective cohort studies)	182	*MGMT* rs16906252 SNP	*MGMT* methylation	Positive

Table continues

Table 1. Continued

First Author, Year (Reference No.)	Disease (as in Traditional Epidemiology)	Study Design	Sample Size (No. of Participants)	Putative Etiologic Factor	Tumor Molecular Changes (Subtypes)	Direction of Association
Hawkins, 2009 (45)	Colorectal cancer and normal individuals (colon mucosa)	Case-case	1,039 cancer cases, 97 normal samples from cancer patients, 20 normal mucosa samples from persons without cancer	*MGMT* rs16906252 SNP	*MGMT* methylation in cancer and normal colon mucosa	Positive
Candiloro, 2009 (46)	Normal individuals (peripheral blood cells)		89	*MGMT* rs16906252 SNP	*MGMT* methylation (in peripheral blood cells)	Positive
Leng, 2011 (47)	Lung adenocarcinoma	Case-case	179	*MGMT* rs16906252 SNP	*MGMT* methylation	Positive
Kristensen, 2011 (48)	Malignant pleural mesothelioma	Case-case	95	*MGMT* rs16906252 SNP	*MGMT* methylation	Positive
Pedroni, 1999 (49)	Colorectal cancer		78 (all synchronous cancer patients and 0 solitary tumors)	Tumor synchronicity/ metachronicity	MSI	Concordant pattern of MSI status in synchronous/ metachronous tumor pairs
Velayos, 2005 (50)	Colorectal cancer		110 (all synchronous/ metachronous cancer patients and 0 solitary tumors)	Tumor synchronicity/ metachronicity	MSI	Concordant pattern of MSI status in synchronous/ metachronous tumor pairs
Nosho, 2009 (51)	Colorectal cancer	Case-case (in prospective cohort studies)	1,113 (29 synchronous cancer patients)	Tumor synchronicity	CIMP, MSI, *BRAF* mutation, LINE-1 hypomethylation	Positive; concordant pattern of LINE-1 hypomethylation in synchronous tumor pairs
Konishi, 2009 (52)	Colorectal cancer	Case-case	97 (28 synchronous cancer patients)	Tumor synchronicity	CIMP	Positive
Gonzalo, 2010 (53)	Colorectal cancer	Case-case	82 (37 synchronous cancer patients)	Tumor synchronicity/ metachronicity	Methylation in *MGMT, RASSF1*	Positive
Slattery, 2000 (54)	Colon cancer	Case-control	1,510 cancer cases, 2,410 controls	BMI	MSI	Obesity is associated with MSS cancer but not MSI-high cancer
Satia, 2005 (55)	Colon cancer	Case-control	486 cancer cases, 1,048 controls	BMI	MSI	Obesity is associated with MSS cancer but not MSI-high cancer
Slattery, 2007 (56)	Colon cancer	Case-control	1,154 cancer cases, 2,401 controls	BMI	CIMP	Obesity is associated with CIMP-negative cancer but not CIMP-high cancer
Campbell, 2010 (57)	Colorectal cancer	Case-control	1,250 cancer cases, 1,880 controls	BMI	MSI	Obesity is associated with MSS cancer but not MSI-high cancer
Sinicrope, 2010 (58)	Colon cancer	Case-case	2,222	BMI	MSI	Negative (inverse)

Table continues

Table 1. Continued

First Author, Year (Reference No.)	Disease (as in Traditional Epidemiology)	Study Design	Sample Size (No. of Participants)	Putative Etiologic Factor	Tumor Molecular Changes (Subtypes)	Direction of Association
Kuchiba, 2012 (59)	Colorectal cancer	Prospective cohort	536 cancer cases, 109,051 participants	BMI	*FASN* expression	Obesity is associated with *FASN*-negative cancer but not with *FASN*-positive cancer
Slattery, 2000 (54)	Colon cancer	Case-control	1,510 cancer cases, 2,410 controls	Smoking	MSI	Smoking is associated with MSI-high cancer but not MSS cancer
Wu, 2001 (60)	Colon cancer	Case-case	276	Smoking	MSI	Positive
Lüchtenborg, 2005 (61)	Colorectal cancer	Case-cohort	650 cancer cases, 2,948 in subcohort	Smoking	*APC* mutation	Negative (inverse)
Chia, 2006 (62)	Colorectal cancer	Case-control	1,792 cancer cases, 1,501 controls	Smoking	MSI	Smoking is associated with MSI-high cancer but not MSS cancer
Samowitz, 2006 (63)	Colon cancer	Case-control	1,315 cancer cases, 2,392 controls	Smoking	CIMP, *BRAF* mutation	Smoking is associated with CIMP-high cancer and *BRAF*-mutated cancer but not CIMP-negative or *BRAF*-wild-type cancer
Poynter, 2009 (64)	Colorectal cancer	Case-control	1,564 cancer cases, 4,486 controls	Smoking	MSI	Smoking is associated with MSI-high cancer but not MSS cancer
Rozek, 2010 (65)	Colorectal cancer	Case-control	1,297 cancer cases, 2,019 controls	Smoking	*BRAF* mutation	Positive
Limsui, 2010 (66)	Colorectal cancer	Prospective cohort	540 cancer cases, 41,528 participants	Smoking	MSI, CIMP, *BRAF* mutation	Smoking is associated with CIMP-high cancer, MSI-high cancer, and *BRAF*-mutated cancer but not CIMP-negative, MSS, or *BRAF*-wild-type cancer

Abbreviations: BMI, body mass index; CIMP, CpG island methylator phenotype; MSI, microsatellite instability; MSS, microsatellite stability; SNP, single nucleotide polymorphism.

[a] The official symbols approved by the Human Genome Organization's Gene Nomenclature Committee are used for genes and gene products (*APC, BRAF, CDKN2A, FASN, MGMT, MLH1,* and *MTHFR*).

The importance of integration of divergent disciplines has repeatedly been discussed (7–10). As an initial step toward such integrated scientific disciplines, our discussion is primarily focused on the integration of molecular pathology and epidemiology—that is, molecular pathological epidemiology (MPE) (4–6). This integrated field improves understanding of human diseases and may provide a model for future integrations of other subspecialties. Thus, this article will help foster an interdisciplinary integration of a wide variety of other fields in biomedical, public health, population, and social science and an establishment of hybrid disciplines.

PATHOLOGY EDUCATION IN PUBLIC HEALTH SCHOOLS

Epidemiology is a core component of public health school curricula, reflecting its pivotal role in the health sciences. However, in public health schools, most students get little, if any, opportunity to study pathology, resulting in limited understanding of disease pathogenesis. Recently, integration of pathology into epidemiologic studies has become increasingly common (4, 6, 11), because many diseases are being defined by molecular pathogenic mechanisms. As current disease classification schemes become more reflective of pathobiology (4, 6, 11), epidemiologists must appreciate the rationale behind disease classifications and subtyping in their study designs. Possibilities for pathology training include: lectures by pathologists, rotations at clinical pathology laboratories, and participation in MPE research.

EPIDEMIOLOGY EDUCATION IN PATHOLOGY AND MEDICAL SCHOOLS

Pathology is a core component of medical school curricula, reflecting its central role in medical education. In addition, training in pathology as a medical specialty occurs as a part of postgraduate medical education. Unfortunately, most pathologists and other physicians have limited knowledge of epidemiology. Education in epidemiology can provide knowledge of proper study design, data interpretation, and statistical and causal inferences, which are necessary in correlative pathology research. However, neither epidemiology nor biostatistics is a common component of pathology training (12). Only a minority of pathologists and physicians have sufficient understanding of epidemiology to apply relevant principles to their investigations. Epidemiology can provide ideas about potential etiologic factors and can teach pathologists proper study design and conduct in terms of population selection, sample size determination, statistical methods, causal inference, assessment of generalizability, and validation of findings. In our opinion, pathology training and medical school programs should be encouraged to include formal epidemiology courses or lectures, preferably as a mandatory requirement.

Substantial concerns have been raised about the validity of much of published scientific research (13–17). Published studies are often called into question for inappropriate study design, biased sample selection, inadequate sample size, inappropriate statistical methods, etc. Studies conducted by pathologists and other clinical investigators are commonly biased, because cases typically come from tertiary referral medical centers. Those common problems in study design and analysis should be considered, and the best attempts to improve study design must be made.

MPE AS AN INTERDISCIPLINARY SCIENCE

MPE is a recently established interdisciplinary and transdisciplinary field (4–6). Traditional epidemiology (including molecular epidemiology and genome-wide association studies) has the substantial limitation of treating pathogenically heterogeneous diseases (e.g., hypertension, diabetes mellitus, major depression, breast cancer) as a single entity. In contrast, from the MPE viewpoint (4–6), any human disease entity is fundamentally heterogeneous from person to person (18), just as each individual is unique. Nonetheless, by classifying disease according to its pathogenic mechanisms, we can better predict the course of a disease in a given individual (6). In fact, there exists heterogeneity of risk factors as well as heterogeneity of molecular pathogenesis in any given disease (4–6).

A growing body of literature (see Web Appendix (http://aje.oxfordjournals.org/)) supports this MPE paradigm (4–6), with evidence suggesting that carcinogenic or protective effects of lifestyle, dietary, environmental, and genetic factors differ according to specific molecular characteristics in neoplastic cells. The MPE concept is gaining widespread adoption (19–30). As Table 1 shows, MPE studies have improved our understanding of pathogenesis by demonstrating consistent links between etiologic factors and molecular subtypes of diseases (31–66). Furthermore, recent evidence suggests that host factors can interact with tumor molecular changes to modify cancer cell behavior (67–74). Thus, the MPE approach, unlike the traditional epidemiologic research design, allows insights into etiologic factors and pathogenic mechanisms.

NECESSITY FOR MPE GUIDELINES AND INTERDISCIPLINARY SCIENTISTS

MPE is a relatively new field of science, and no standard research guidelines have yet been established, as they have been for observational epidemiology (STROBE, which stands for Strengthening the Reporting of Observational Epidemiology) (16, 17, 75) and molecular epidemiology (STROBE-ME) (76). For MPE, there are specific caveats in addition to the typical limitations in observational epidemiology (6). We plan to develop international guidelines for MPE research (STROBE-MPE) as a logical extension of STROBE. To develop and implement guidelines, we need to produce more scientists with cross-disciplinary training and expertise in molecular pathology and epidemiology.

INTEGRATED EDUCATIONAL PROGRAMS IN PUBLIC HEALTH AND MEDICAL SCHOOLS

Pathology and epidemiology are inherently complementary disciplines. Both fields encompass the entire spectrum

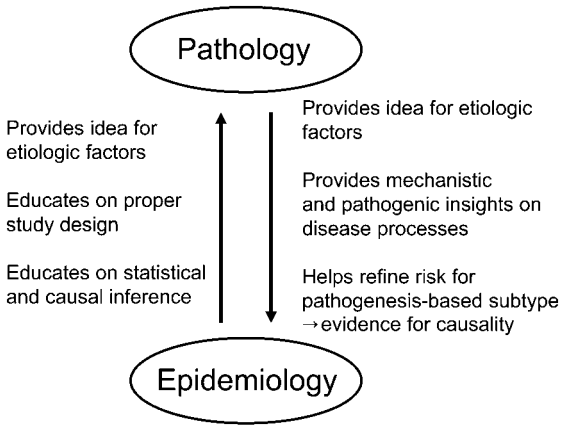

Figure 1. Collaborative relation between pathology and epidemiology. Both pathology and epidemiology are method-based disciplines and fields of study covering the entire spectrum of human diseases. The methods of pathology and those of epidemiology can complement each other and can be synergized to create an integrated science: molecular pathological epidemiology. In the integrated interdisciplinary environment, pathologists and epidemiologists can help each other and benefit from educating each other as illustrated.

of human diseases, generate hypotheses from observations, and attempt to elucidate disease etiologies. This shared scientific framework is the foundation of the field of MPE (4, 6) and should serve as the underpinning for integrated pathology and epidemiology educational programs.

Eventually, there will be a universal collaborative relation between pathology and epidemiology (Figure 1), which will facilitate high-quality health science at the molecular, cellular, and population levels. Pathology is capable of providing detailed insights into pathogenic mechanisms and improving understanding of disease processes. In comparison, epidemiology can identify novel potential etiologic factors for pathologic processes. Pathologists also often contribute to early recognition of new exposure-disease associations, such as those among microbiota, inflammation, and cancers (77–86). Another crucial component of the discipline of epidemiology is expertise in study designs, statistical methods, and causal inference, all of which are of utmost importance in correlative clinicopathologic and translational research.

As an integrated discipline, MPE will draw on the knowledge base of pathology and epidemiology. A scientist with integrated MPE training would have the skills to consider pathogenic hypotheses, design and conduct studies, analyze data, make inferences, and validate/generalize findings in populations. This type of researcher can work well with other investigators in diverse disciplines and can "translate" between collaborators who do not share this scientific background.

For these reasons, it is desirable to establish integrated educational programs of pathology and epidemiology. In the current system, such educational opportunities will require the merger of resources held by medical schools, public health schools, and hospitals with pathology training programs. We acknowledge that dual-degree Doctor of Medicine/Master of Public Health programs exist, but they are not standardized and do not systematically offer training in epidemiology and biostatistics. We hope that institutions will adopt integrated educational programs across medical and public health schools and hospitals to meet these interdisciplinary research and educational needs.

SUBSTANTIAL ROLE OF FUNDING AGENCIES

Most biomedical and public health research projects are funded by governments or nongovernment organizations. Currently, relatively few funded projects integrate molecular pathology and epidemiology or population health science. There exists a significant knowledge gap between various etiologic factors and cellular and molecular changes that occur during disease evolution, and interdisciplinary investigations in these areas are needed. Funding agencies need to increase career development grants in order to nurture the next generation of scientists who can fully integrate the fields of molecular pathology and epidemiology.

CONCLUSIONS AND FUTURE DIRECTIONS

Over the last century, biomedical and public health sciences have been practiced in a highly compartmentalized way, typically missing the value of the perspectives gained through integration of divergent scientific fields. MPE (4–6) is an example of the integration of molecular biologic and population health science in order to gain insights into disease etiology and pathogenesis. MPE research stands to benefit both individuals and the population at large. To advance integrated MPE research, appropriate interdisciplinary educational programs are needed. This will require reforms in medical and public health education as well as postgraduate pathology training. We need to be open-minded and flexible in designing optimal education and training programs at various levels. We believe that convergence and integration of scientific disciplines should become more commonplace in the future, as MPE will prove to be a successful field.

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