

Molecular epidemiology: Linking molecular scale insights to population impacts

Paul A. Schulte, Nathaniel Rothman, Pierre Hainaut, Martyn T. Smith, Paolo Boffetta, and Frederica P. Perera

Summary

In a broad sense, molecular epidemiology is the axis that unites insights at the molecular level and understanding of disease at the population level. It is also a partnership between epidemiologists and laboratory scientists in which investigations are conducted using the principles of both disciplines. A key trait of molecular epidemiology is to evaluate and establish the relationship between a biomarker and important exogenous and endogenous exposures, susceptibility, or disease, providing understanding that can be used in future research and public health and clinical practice. When potential solutions or interventions are identified, molecular epidemiology is also useful in developing and conducting clinical and intervention

trials. It can then contribute to the translation of biomedical research into practical public health and clinical applications by addressing the medical and population implications of molecular phenomena in terms of reducing risk of disease. This chapter summarizes the contributions and research endeavours of molecular epidemiology and how they link with public health initiatives and clinical practice.

Introduction

This is a unique and exciting period in the health sciences. For the first time, it is possible to look at both nature and nurture with sophisticated and molecular-level tools (1–12). The promise

of using these and other tools to prevent, control, and treat chronic and infectious diseases stimulates the imagination and creativity of medical and health scientists and practitioners. The challenge is to effectively apply these tools, and knowledge from genetics, exposure assessment, population health and medicine, to health problems that afflict 21st century people. The means of meeting that challenge is the widespread conduct of molecular epidemiologic research. Driven by discoveries of basic biological phenomena at the molecular and genetic levels, molecular epidemiology is able to translate discovery of essential scientific knowledge into determination and quantification of hazards and risks, and then to

investigate useful approaches for prevention, control, and treatment of disease and dysfunction (9,12–15).

To fully appreciate the potential contributions of molecular epidemiology, it is important to understand how it fits into the context of epidemiology and public health. Molecular epidemiology is a partnership between epidemiologists and laboratory scientists that conducts investigations using the principles of both laboratory and population research (1,2,16). This is a message that merits restatement as powerful genetic and analytic technologies become available to epidemiologists. Historically, molecular epidemiology was derived from those disciplines that made contributions to relating biological measurements to health and disease (1,2). These include bacteriology, immunology and infectious disease epidemiology; pathology and clinical chemistry; carcinogenesis and oncology; occupational medicine and toxicology; cardiovascular disease epidemiology; genetics, molecular biology, and genetic epidemiology; and traditional epidemiology and biostatistics. The term “molecular epidemiology” was first used in the infectious disease literature by Kilbourne to describe the “molecular determinants of epidemiologic events” (17). In 1977, Higginson used the term in the context of pathology in a paper entitled “The role of the pathologist in environmental medicine and public health” (18). Lower’s landmark 1979 publication introduced genetic effect modifiers and brought attention to the importance of external exposure, individual susceptibility and biologic markers in terms of phenotype (19). In a seminal paper in 1982, Perera and Weinstein coined the term “molecular cancer epidemiology” and first proposed a formal and

comprehensive framework for the use of biomarkers of internal dose, biologically effective dose, early biologic effect and susceptibility within a molecular epidemiological framework (2). In 1987, the National Research Council (NRC) adopted this basic conceptual framework for molecular epidemiology and subsequently published a series of reports on biological markers (20–22). In the 1980s through the mid-1990s, a series of important papers and books were published describing the evolution and progress of molecular epidemiology (1,17,23–36). More recently, the changing face of epidemiology in the genomics and epigenetic eras has been described (9,12,36–39).

In the past, molecular epidemiology was sometimes viewed as one of epidemiology’s many subspecialties. Some subspecialties focus on the disease type (e.g. chronic, infectious, reproductive or cardiovascular), some on the origin of the hazard (e.g. occupational, environmental or nutritional), and still others focus on the approach to the disease (e.g. clinical, serological or analytical). Viewed in this context, molecular epidemiology may best fit into the category of subspecialty defined by the approach that is applicable to all of these areas. Molecular epidemiology is the use of all types of biological markers in the investigation of the cause, distribution, prevention and treatment of disease, in which biological markers are used to represent exposures, intervening factors, susceptibility, intermediate pathological events, preclinical and clinical disease, or prognosis.

More broadly, molecular epidemiology can be viewed as a hub that links various aspects of health research. Even the term molecular epidemiology is a linking term

which brings together molecular-level thinking and population-level understanding. These insights can be useful in characterizing a health problem, conducting mechanistic research (at the molecular and population levels), understanding the solutions, and contributing to the clinical and public health practice. These four functions and the research that supports them are illustrated in Figure 1.1.

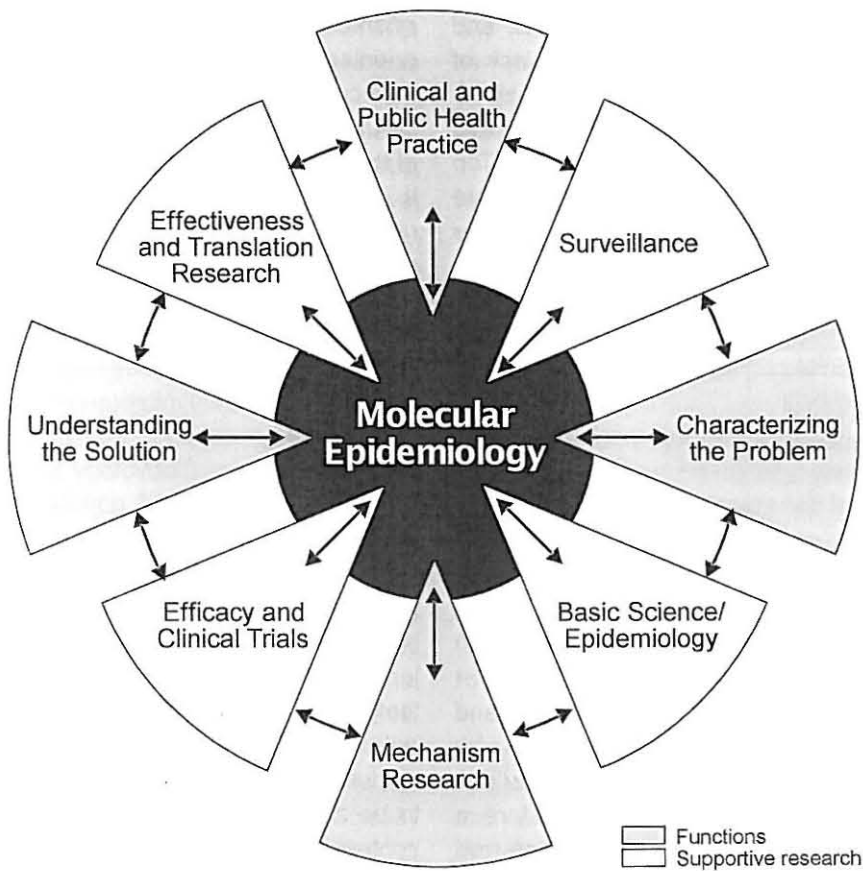
Characterizing a public health problem

Surveillance, the sentinel activity of public health and clinical practice, is the ongoing collection, analysis and interpretation of data on rates and trends of disease, injury, death and hazards. Molecular epidemiology plays an important role in surveillance by identifying the frequency of biological markers of exposure, disease or susceptibility in various population groups and in monitoring trends of biomarkers over time. Examples are population monitoring of blood lead concentrations, neonatal screening for genetic disease, and molecular typing of viruses in a geographical area. The validation of those biomarkers and the analysis of the data involve molecular epidemiologic skills and knowledge. Increasingly, biological specimen banks are being used as public health surveillance systems (40) and can play an important role in etiologic research (41).

Mechanistic research

Establishing the relationship between a biomarker and exposure, disease or susceptibility is the hallmark of molecular epidemiology, and leads to developing the knowledge that will eventually be used in further research and in clinical and public health practice.

Figure 1.1. Molecular epidemiology can serve as a hub for other components of health research and practice. Adapted from (74).



To achieve this progression, there is a need for parallel laboratory and population research to understand the mechanisms through which environmental exposures interact with host susceptibility factors to increase the risk of disease. The key mechanisms can then be blocked by interventions, such as exposure reduction, behaviour modification, chemoprevention or prophylaxis.

Understanding the solutions

When potential solutions or interventions are identified, molecular epidemiological knowledge is useful in the development and conduct of clinical and intervention trials, and monitoring the efficacy of policy interventions. Following

assessment in trials, there is a need for research on the translation of findings to clinical and public health practitioners. This involves identifying the potential uses of the findings, the plan for communicating and disseminating this information, and ways to measure the impact of their use. Epidemiologists have a long history of providing the evidence base for demonstrating the efficacy and effectiveness of clinical and population interventions moved into practice (42). Molecular epidemiologic knowledge can be used in impact assessments to determine changes in incidence of the biomarkers as surrogates for disease or as indicators of disease risk.

Clinical and public health practice

Translation of biomedical research to useful clinical and public health applications is clearly a major challenge (15,42–44). Molecular epidemiologists can accept that challenge and contribute to the translation of knowledge from research endeavours. This entails a more expansive view of molecular epidemiology beyond a tool in etiologic research to a discipline that addresses the medical and population ramifications of molecular phenomena in terms of reducing risk of disease (45). Translation is a multifaceted process that has been described as involving four phases: 1) discovery to candidate health application; 2) health application to evidence-based practice guidelines; 3) practice guidelines to health practice; and 4) practice to population health impact (44).

At times, molecular epidemiology has been portrayed as a reductionist approach that merely identifies molecular risk factors and indicators in individuals. However, molecular epidemiology is first and foremost a means to gain sufficient biological understanding at the molecular and biochemical level of the process of disease causation to protect public health. From its outset, molecular epidemiology has had the vision that biological marker data can be used to prevent or reduce morbidity and mortality (1,2,21,22,46). Consequently, molecular epidemiology is the means to obtain molecular- and biochemical-level understanding in a population context.

The term molecular epidemiology is compelling. It inspires the scientific imagination, compelling thinking of incorporating the new resolving powers of

molecular biology, genetics and analytical chemistry into epidemiology, and it stimulates hypothesis development and testing over a broader range of genetic and environmental factors. The term also focuses on the population distributions and implications of molecular events.

On the face of it, the fact that molecular epidemiology is focused both on biological processes in individuals and their distribution in populations makes the term sound contradictory (47). Yet this tension between identifying causal pathways at an individual biological level and understanding the causes of disease in populations has always been present in epidemiology. This seemingly contradictory nature of the molecular epidemiological endeavour may be most familiar as articulated by Geoffrey Rose, in that epidemiologists' efforts are concerned with unraveling both the determinants of individual cases and the determinants of incidence rates (48). Although this tension may be exemplified by molecular epidemiology, there is nothing inherent in the actions of molecular epidemiologists *per se* that limits the utility of their activities for public health. Of greater importance is that this tension itself, this struggle to reconcile two seemingly contradictory objectives, has been productive and inspiring (49). In this vein, some have argued that the integration of genomics into epidemiology can be seen as a further challenge to epidemiologists to take seriously the contextual factors that bear on biological processes (37,50).

In short, the relevance and usefulness of molecular epidemiologic research to public health depends on how successfully practitioners address challenges that face epidemiology

and research in general. These issues—lack of biological realism or theoretical basis for research, lack of consistency in results, and worse still, in some cases lack of scientific rigor—are threats of which all epidemiology, indeed all scientific research, must be wary (51,52). Too often the attempt to substantiate molecular epidemiologic results by post-hoc searching through the scientific literature has led to finding biologic information that is not truly corroborating but only appears to be so (53).

Similarly, the criticism that molecular epidemiologic results are not consistent between studies, and are even sometimes contradictory, is partly due to the media and public misinterpretation of the nature of scientific investigations, but it is also partly due to the failure of molecular epidemiologists to say loud and clear that their studies must be repeated and confirmed in various populations and settings before a causal link can be strongly inferred (54,55). This is especially true when strong causal claims are made following small studies.

To continue to serve as a hub for health research, molecular epidemiology will need to continue expanding its contribution to surveillance, mechanistic research, efficacy trials, translational research and health policy. Critical for this holistic approach is the ability to assemble and communicate information, and, ultimately, evidence to decision-makers, medical and health professionals, and the public. This will involve fostering an evidence-based approach to research and adopting vigorous and stringent criteria for systematic integration of confirmation from many disciplines (e.g. genomics, biochemistry, exposure assessment, pathology, medicine and public health)(43).

Specifically, this expansive view means not only thinking of causal mechanisms and being problem-oriented, but also being solution-oriented. How can the findings of molecular epidemiologic research be used to address a problem both at the patient and population levels? It is critical to focus on credibility, rather than statistical significance of research findings; encourage rigorous replication, not just discovery; and build public trust by communicating results honestly and acknowledging the limitations of the evidence (43).

If molecular epidemiology is to make a major impact on population health, it must have a global focus as well as a local one. Too often, the findings of research on genetic biomarkers have been seen as leading to expensive sophisticated tests and treatments for a few rather than for the many. Molecular epidemiologic researchers need to be aware of this concern in the context of their work. The result should be research and strategies to help develop affordable population-wide tools for combating common diseases (56).

Nomenclature, taxonomics and approaches

Other disciplines and terms overlap with molecular epidemiology. The terms genomics, population genomics, population genetics, and human genome epidemiology all can involve molecular epidemiologic approaches. Critical in all of these approaches is the use of valid epidemiological study designs, methodologies, and perspectives with valid and reliable indicators of susceptibility, genotype and phenotypes.

Another term that merits discussion and definition is "biomarker." The term biologic

marker, or biomarker, is broadly defined to include any type of measurement made in a biologic sample and includes measurements of exogenous and endogenous exposures, as well as any phenomena in biologic systems at the biochemical, molecular, genetic, immunologic or physiologic level (1,20).

Historically, biomarkers have been used for many decades in etiologic and clinical research, beginning with seminal studies of infectious diseases followed by research on chronic diseases, such as cardiovascular disease (1,57–59). Over time, an appreciation of the heterogeneity in biomarkers developed with regard to the different aspects of the disease process reflected by them. Emerging from the seminal works in the 1980s and 1990s, three types of biomarkers were defined: biomarkers of exposure/dose (internal and biologically effective dose), biomarkers of effect (generally indicators of damage, alteration in homeostatic mechanisms, molecular or biochemical dysfunction, preclinical effects of early disease, and clinically apparent disease), and biomarkers of susceptibility (either inherited or acquired) (2,20–22,29,30). These have been linked in a continuum that is applicable to many exposure-disease relationships and have been further characterized with regard to the advantages and limitations of their application within the spectrum of epidemiologic studies (1,2,33,39).

The discovery of new biomarkers for medical, environmental and epidemiologic research is of growing importance. The global biomarkers market is projected to reach about \$20.5 billion by 2014 (60). Increasingly, there are developments in a broad range of areas that include: biomarkers as

tools in decision-making, regulation, diagnostics, personalized medicine, therapeutics, pharmacology, public and environmental health, and as dependent and independent variables in molecular epidemiologic research.

Implicit in biomarker-based research is the collection of biological specimens from individuals within an epidemiologic framework, analysis of those specimens and the amassing of the results in databases. The emergence of large-scale networks, multicentre collaborations and formal consortia has increasingly been observed and has been advanced as an approach to complex disease research efforts (12,61–63). Although there is a strong rationale for using consortia for exploring the role of environmental exposures and genetic variants in disease, this does not mean that smaller, single investigative approaches are without merit. Such studies still may provide useful leads, hypotheses, mechanistic insights and identification of risk factors; they are also helpful for validation of biomarkers. Nonetheless, large-scale consortia provide a powerful approach to achieve adequate statistical power (particularly in studies of individual genetic variants and gene-environment interactions) to identify effects and avoid false-positive reports and to address complex research problems (64–69). One unique, global collaboration, the Human Genome Epidemiology Network (HuGE Net), combines the traditional methodology of population-level investigation with molecular and genetic epidemiology data. HuGE Net is focused on the post-gene discovery phase and interpretation of epidemiologic information on human genes for the purpose of health promotion (70,71). This is one example of

the convergence of classical and molecular epidemiology applications in a practical approach for disease prevention.

On the horizon

The great investment in biomedical research made in the past 50 years could yield many benefits in the next 50 years if the results of that research can be used and translated into practical advances (see the following chapters that discuss these advances). The skills, tools and insights of molecular epidemiology can contribute to that effort. Knowledge is the basis of action. Serving as the linking hub for laboratory and population research, molecular epidemiology can help translate it to practice. To do this, there will be a need to maintain current trends in the discipline and establish new ones. Continuation of the trend towards large-scale networks and biobanks, use of bioinformatics, and attention to individual and collective ethical issues will serve to move the field forward. But more powerful effects will be achieved by incorporating epigenetic and biological systems theory in research, expanding skill sets and professional knowledge to complement translation research and risk communication, and by fostering public health perspectives (35,72,73). A broad population-wide vision for using biological markers is required to leverage the power of molecular scale insight to give beneficial macro-scale impacts on public health.

Disclaimer: The findings and conclusions in this chapter are those of the author and do not necessarily represent the views of the Centers for Disease Control and Prevention.

References

- Schulte PA, Perera FP, editors. Molecular epidemiology principles and practices. San Diego (CA): Academic Press Inc; 1993.
- Perera FP, Weinstein IB (1982). Molecular epidemiology and carcinogen-DNA adduct detection: new approaches to studies of human cancer causation. *J Chronic Dis*, 35:581–600. doi:10.1016/0021-9681(82)90078-9 PMID:6282919
- Khoury MJ (1999). Human genome epidemiology: translating advances in human genetics into population-based data for medicine and public health. *Genet Med*, 1:71–73. PMID:11336455
- Pittinger CA, Brennan TH, Badger DA *et al.* (2003). Aligning chemical assessment tools across the hazard-risk continuum. *Risk Anal*, 23:529–535. doi:10.1111/1539-6924.00333 PMID:12836845
- Waters MD, Olden K, Tennant RW (2003). Toxicogenomic approach for assessing toxicant-related disease. *Mutat Res*, 544:415–424. doi:10.1016/j.mrrev.2003.06.014 PMID:14644344
- Weis BK, Balshaw D, Barr JR *et al.* (2005). Personalized exposure assessment: promising approaches for human environmental health research. *Environ Health Perspect*, 113:840–848. doi:10.1289/ehp.7651 PMID:16002370
- National Research Council. Human biomonitoring for environmental chemicals. Washington (DC): The National Academies Press; 2006.
- Ward MH, Wartenberg D (2006). Invited commentary: on the road to improved exposure assessment using geographic information systems. *Am J Epidemiol*, 164:208–211. doi:10.1093/aje/kwj183 PMID:16707652
- Wild C, Vineis P, Garte S, editors. Molecular epidemiology of chronic diseases. Chichester (England): John Wiley & Sons; 2008.
- Jayjock MA, Chaisson CF, Arnold S, Dederick EJ (2007). Modeling framework for human exposure assessment. *J Expo Sci Environ Epidemiol*, 17 Suppl 1:S81–S89. doi:10.1038/sj.jes.7500580 PMID:17505502
- National Research Council. Applications of toxicogenomic technologies to predictive toxicology and risk assessment. Washington (DC): The National Academies Press; 2007.
- Vineis P, Perera FP (2007). Molecular epidemiology and biomarkers in etiologic cancer research: the new in light of the old. *Cancer Epidemiol Biomarkers Prev*, 16:1954–1965. doi:10.1158/1055-9965.EPI-07-0457 PMID:17932342
- Perera FP (2000). Molecular epidemiology: on the path to prevention? *J Natl Cancer Inst*, 92:602–612.
- Riley LW, editor. Molecular epidemiology of infectious diseases: principles and practices. Washington (DC): ASM Press; 2004.
- Schulte PA (2005). The use of biomarkers in surveillance, medical screening, and intervention. *Mutat Res*, 592:155–163. PMID:16051280
- McMichael AJ (1994). Invited commentary—"molecular epidemiology": new pathway or new travelling companion? *Am J Epidemiol*, 140:1–11. PMID:8017398
- Kilbourne ED (1973). The molecular epidemiology of influenza. *J Infect Dis*, 127:478–487. doi:10.1093/infdis/127.4.478 PMID:4121053
- Higginson J (1977). The role of the pathologist in environmental medicine and public health. *Am J Pathol*, 86:460–484. PMID:836677
- Lower GM Jr, Nilsson T, Nelson CE *et al.* (1979). N-acetyltransferase phenotype and risk in urinary bladder cancer: approaches in molecular epidemiology. Preliminary results in Sweden and Denmark. *Environ Health Perspect*, 29:71–79. doi:10.2307/3429048 PMID:510245
- National Research Council (1987). Biological markers in environmental health research. *Environ Health Perspect*, 74:3–9. doi:10.1289/ehp.87743 PMID:3691432
- National Research Council. Biologic markers in pulmonary toxicology. Washington (DC): National Academy Press; 1989.
- National Research Council. Biologic markers in reproductive toxicology. Washington (DC): National Academy Press; 1989.
- Perera FP, Poirier MC, Yuspa SH *et al.* (1982). A pilot project in molecular cancer epidemiology: determination of benzo[a]pyrene-DNA adducts in animal and human tissues by immunoassays. *Carcinogenesis*, 3:1405–1410. doi:10.1093/carcin/3.12.1405 PMID:6295657
- Miller JR (1983). International Commission for Protection against Environmental Mutagens and Carcinogens. ICPEMC working paper 5/4. Perspectives in mutation epidemiology: 4. General principles and considerations. *Mutat Res*, 114:425–447. PMID:6835244
- Tannenbaum SR, Skipper PL (1984). Biological aspects to the evaluation of risk: dosimetry of carcinogens in man. *Fund Appl Toxicol*, 4:S367–S373. doi:10.1016/0272-0590(84)90264-1 PMID:6745554
- Harris CC, Vahakangas K, Autrup H *et al.* Biochemical and molecular epidemiology of human cancer risk. In: Scarpelli D, Craighead J, Kaufman N, editors. The pathologist and the environment. Baltimore (MD): Williams and Wilkins; 1985. p. 140–67.
- Wogan GN, Gorelick NJ (1985). Chemical and biochemical dosimetry of exposure to genotoxic chemicals. *Environ Health Perspect*, 62:5–18. PMID:4085448
- Perera FP (1987). Molecular cancer epidemiology: a new tool in cancer prevention. *J Natl Cancer Inst*, 78:887–898. PMID:3471998
- Hulka BS, Wilcosky TC (1988). Biological markers in epidemiologic research. *Arch Environ Health*, 43:83–89. doi:10.1080/0003986.1988.9935831 PMID:3377561
- Schulte PA (1989). A conceptual framework for the validation and use of biologic markers. *Environ Res*, 48:129–144. doi:10.1016/S0013-9351(89)80029-5 PMID:2647488
- Hulka BS, Wilcosky TC, Griffith JD. Biological markers in epidemiology. New York (NY): Oxford University Press; 1990.
- Groopman JD, Skipper PL, editors. Molecular dosimetry and human cancer: analytical, epidemiological, and social considerations. Boca Raton (FL): CRC Press; 1991.
- Rothman N, Stewart WF, Schulte PA (1995). Incorporating biomarkers into cancer epidemiology: a matrix of biomarker and study design categories. *Cancer Epidemiol Biomarkers Prev*, 4:301–311. PMID:7655323
- Carrington M, Hoelzel R, editors. Molecular epidemiology. New York (NY): Oxford University Press; 2001.
- Wild CP (2005). Complementing the genome with an "exposome": the outstanding challenge of environmental exposure measurement in molecular epidemiology. *Cancer Epidemiol Biomarkers Prev*, 14:1847–1850. doi:10.1158/1055-9965.EPI-05-0456 PMID:16103423
- Rebbeck TR, Ambrosone CB, Shields PG, editors. Molecular epidemiology: applications in cancer and other human diseases. New York (NY): Informa Healthcare; 2008.
- Millikan R (2002). The changing face of epidemiology in the genomics era. *Epidemiology*, 13:472–480. doi:10.1097/00001648-200207000-00017 PMID:12094104
- Jablonka E (2004). Epigenetic epidemiology. *Int J Epidemiol*, 33:929–935. doi:10.1093/ije/dyh231 PMID:15166187

39. Garcia-Closas M, Vermeulen R, Sherman ME *et al.* Application of biomarkers. In Schottenfeld D, Fraumeni JF Jr, editors. *Cancer epidemiology and prevention*. 3rd ed. New York (NY): Oxford University Press; 2006. p.70–88.
40. Brand AM, Probst-Hensch NM (2007). Biobanking for epidemiological research and public health. *Pathobiology*, 74:227–238. doi:10.1159/000104450 PMID:17709965
41. Pukkala E, Andersen A, Berglund G *et al.* (2007). Nordic biological specimen banks as basis for studies of cancer causes and control—more than 2 million sample donors, 25 million person years and 100,000 prospective cancers. *Acta Oncol*, 46:286–307. doi:10.1080/02841860701203545 PMID:17450464
42. Hiatt R, Samet J, Ness RB; American College of Epidemiology Policy Committee (2006). The role of the epidemiologist in clinical and translational science. *Ann Epidemiol*, 16:409–410. doi:10.1016/j.annepidem.2006.02.002 PMID:16647631
43. Ioannidis JPA (2006). Evolution and translation of research findings: from bench to where? *PLoS Clin Trials*, 1:36. doi:10.1371/journal.pctr.0010036 PMID:17111044
44. Khoury MJ, Gwinn M, Yoon PW *et al.* (2007). The continuum of translation research in genomic medicine: how can we accelerate the appropriate integration of human genome discoveries into health care and disease prevention? *Genet Med*, 9:665–674. doi:10.1097/GIM.0b013e31815699d0 PMID:18073579
45. Grodsky J (2005). Genetics and environmental law: redefining public health. *Calif Law Rev*, 93:171–270.
46. Harris CC (1993). p53: at the crossroads of molecular carcinogenesis and risk assessment. *Science*, 262:1980–1981. doi:10.1126/science.8266092 PMID:8266092
47. Castiel LD (1999). Apocalypse...now? Molecular epidemiology, predictive genetic tests, and social communication of genetic contents. *Cad Saude Publica*, 15 Suppl 1:S73–S89. doi:10.1590/S0102-311X1999000500009 PMID:10089550
48. Rose G (2001). Sick individuals and sick populations. *Int J Epidemiol*, 30:427–432, discussion 433–434. doi:10.1093/ije/30.3.427 PMID:11416056
49. Parodi A, Neasham D, Vineis P (2006). Environment, population, and biology: a short history of modern epidemiology. *Perspect Biol Med*, 49:357–368. doi:10.1353/pbm.2006.0044 PMID:16960306
50. Shostak S (2003). Locating gene-environment interaction: at the intersections of genetics and public health. *Soc Sci Med*, 56:2327–2342. doi:10.1016/S0277-9536(02)00231-9 PMID:12719185
51. Taubes G (1995). Epidemiology faces its limits. *Science*, 269:164–169. doi:10.1126/science.7618077 PMID:7618077
52. Gori GB (1998). Presentation: epidemiology and public health: is a new paradigm needed or a new ethics? *J Clin Epidemiol*, 5:637–641.
53. Muscat JE (1996). Epidemiological reasoning and biological rationale. *Biomarkers*, 1:144–145. doi:10.3109/13547509609088683.
54. Gallo V, Egger M, McCormack V *et al.* (2011). Strengthening the Reporting of Observational studies in Epidemiology - Molecular Epidemiology (STROBE-ME): An Extension of the STROBE Statement. *PLoS Med*, 8:e1001117. doi:10.1371/journal.pmed.1001117 PMID:22039356
55. Ioannidis JPA (2007). Genetic and molecular epidemiology. *J Epidemiol Community Health*, 61:757–758. doi:10.1136/jech.2006.059055 PMID:17699527
56. Brand A (2005). Public health and genetics—a dangerous combination? *Eur J Public Health*, 15:114–116. doi:10.1093/eurpub/cki090 PMID:15941755
57. Kannel WB, McGee D, Gordon T (1976). A general cardiovascular risk profile: the Framingham Study. *Am J Cardiol*, 38:46–51. doi:10.1016/0002-9149(76)90061-8 PMID:132862
58. Epstein FH, Napier JA, Block WD *et al.* (1970). The Tecumseh study. *Arch Environ Health*, 21:402–407. PMID:5504438
59. Lipid Research Clinics Program (1984). The Lipid Research Clinics Coronary Primary Prevention Trial results. *JAMA*, 251:351–364. doi:10.1001/jama.251.3.351 PMID:6361299
60. Markets and Markets (2009). Available from URL: <http://www.marketsandmarkets.com/PressReleases/global-biomarker-market-worth-US-20.5-billion-by-2014.asp>.
61. Boffetta P, Armstrong B, Linet M *et al.* (2007). Consortia in cancer epidemiology: lessons from InterLymph. *Cancer Epidemiol Biomarkers Prev*, 16:197–199. doi:10.1158/1055-9965.EPI-06-0786 PMID:17301250
62. Hunter DJ, Thomas G, Hoover RN, Chanock SJ (2007). Scanning the horizon: what is the future of genome-wide association studies in accelerating discoveries in cancer etiology and prevention? *Cancer Causes Control*, 18:479–484. doi:10.1007/s10552-007-0118-y PMID:17440825
63. Seminara D, Khoury MJ, O'Brien TR *et al.*; Human Genome Epidemiology Network; Network of Investigator Networks (2007). The emergence of networks in human genome epidemiology: challenges and opportunities. *Epidemiology*, 18:1–8. doi:10.1097/01.ede.0000249540.17855.b7 PMID:17179752
64. Epidemiology and Genetics Research Program (EGRP). Supported Epidemiology Consortia. Available from URL: <http://epi.grants.cancer.gov/Consortia/>.
65. Psaty BM, O'Donnell CJ, Gudnason V *et al.*; CHARGE Consortium (2009). Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium: Design of prospective meta-analyses of genome-wide association studies from 5 cohorts. *Circ Cardiovasc Genet*, 2:73–80. doi:10.1161/CIRCGENETICS.108.829747 PMID:20031568
66. Chinese SARS Molecular Epidemiology Consortium (2004). Molecular evolution of the SARS coronavirus during the course of the SARS epidemic in China. *Science*, 303:1666–1669. doi:10.1126/science.1092002 PMID:14752165
67. Truong T, Sauter W, McKay JD *et al.*; EPIC-lung (2010). International Lung Cancer Consortium: coordinated association study of 10 potential lung cancer susceptibility variants. *Carcinogenesis*, 31:625–633. PMID:20106900.
68. Furberg H, Kim YJ, Dackor J *et al.*; Tobacco and Genetics Consortium (2010). Genome-wide meta-analyses identify multiple loci associated with smoking behavior. *Nat Genet*, 42:441–447. doi:10.1038/ng.571 PMID:20418890
69. Tuberculosis Epidemiologic Studies Consortium (TBESC) Centers for Disease Control and Prevention. Available from URL: <http://www.cdc.gov/tb/topic/research/TBESC/>.
70. Khoury MJ (1999). Human genome epidemiology: translating advances in human genetics into population-based data for medicine and public health. *Genet Med*, 1:71–73. PMID:11336455
71. Khoury MJ. Human Genome Epidemiology Network (HuGENet™). Available from URL: <http://www.cdc.gov/genomics/huogenet/>.
72. Sutherland JE, Costa M (2003). Epigenetics and the environment. *Ann N Y Acad Sci*, 983:151–160. doi:10.1111/j.1749-6632.2003.tb05970.x PMID:12724220
73. Wade PA, Archer TK (2006). Epigenetics: environmental instructions for the genome. *Environ Health Perspect*, 114:A140–A141. doi:10.1289/ehp.114-a140 PMID:16507439
74. Narayan KM, Benjamin E, Gregg EW *et al.* (2004). Diabetes translation research: where are we and where do we want to be? *Ann Intern Med*, 140:958–963. PMID:15172921