

Hypothesis/Commentary

Cancer Epidemiology in the 21st Century

"Drivers" of Translational Cancer Epidemiology in the 21st Century: Needs and OpportunitiesTram Kim Lam¹, Margaret Spitz^{1,2}, Sheri D. Schully¹, and Muin J. Khoury^{1,3}**Abstract**

Cancer epidemiology is at the cusp of a paradigm shift—propelled by an urgent need to accelerate the pace of translating scientific discoveries into health care and population health benefits. As part of a strategic planning process for cancer epidemiologic research, the Epidemiology and Genomics Research Program (EGRP) at the National Cancer Institute (NCI) is leading a "longitudinal" meeting with members of the research community to engage in an on-going dialogue to help shape and invigorate the field. Here, we review a translational framework influenced by "drivers" that we believe have begun guiding cancer epidemiology toward translation in the past few years and are most likely to drive the field further in the next decade. The drivers include: (i) collaboration and team science, (ii) technology, (iii) multilevel analyses and interventions, and (iv) knowledge integration from basic, clinical, and population sciences. Using the global prevention of cervical cancer as an example of a public health endeavor to anchor the conversation, we discuss how these drivers can guide epidemiology from discovery to population health impact, along the translational research continuum. *Cancer Epidemiol Biomarkers Prev*; 22(2); 181–8. ©2013 AACR.

"Knowledge is not enough; we must apply. Willing is not enough; we must do." This quote by Goethe encapsulates the overarching goal of cancer epidemiology, which is to apply knowledge gained through scientific discovery to improve population health. John Snow and his Broad Street Pump cholera's investigation in 1854 presents a historical illustration of the transcendent role of epidemiology across the translational research continuum—as a scientific field and a methodologic approach not only to identify disease-related risk factors, but also to influence effective policy for improved health outcomes at both the individual and population levels. Snow's testimonies to policymakers, buttressed by strong epidemiologic evidence that cholera is transmitted by water, led to the removal of the Broad Street Pump and the eventual reform of English public health legislation (1, 2). In cancer epidemiology, there are notable achievements in discovery and prevention (3). Yet as a discipline, cancer epidemiol-

ogy has been too focused on etiologic research centered on the discovery and early characterization phase to have broader public health impact. In fact, a wide chasm exists in the field between discoveries and applications. Epidemiologists should broaden their perspective and extend a wider reach of epidemiologic methods and approaches across the entire translational research continuum to avoid this "translational valley of death" (4).

Needless to say, the movement from scientific discovery to public health impact across the research translational continuum in today's complex environment is slow, challenging, and arguably messy. The first decade of the 21st century brought about dramatic changes in epidemiology—accentuated by the sequencing of the human genome. Shpilberg and colleagues commented toward the end of the 20th century that "the sequencing of the human genome offers the greatest opportunity for epidemiology since John Snow discovered the Broad Street Pump" (5). In the era of postgenome-wide association studies (GWAS), cancer epidemiology is at the cusp of a significant paradigm shift—influenced by a cacophony of factors including: technologic and methodologic advancements, high dimensional and complex data and bioinformation, transdisciplinary and multidisciplinary innovations and discoveries, and demographic and ecologic shifts. And thus 21st century epidemiologists will need to evolve to meet this changing landscape.

In the face of these rapid changes, the Epidemiology and Genomics Research Program (EGRP) at the National Cancer Institute (NCI) is engaging in a strategic

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planning effort to address the monumental public health burden of cancer. As an initial step, EGRP is hosting a "longitudinal" meeting, "Trends in 21st Century Epidemiology: From Scientific Discoveries to Population Health Impact" in December 2012 and calling for an active on-going engagement, both online and at a workshop, from both epidemiologists and related disciplines to help reshape the field of cancer epidemiology (6). To facilitate the ongoing dialogue, we have created an online forum blog-epi.grants.cancer.gov/2012. To further frame the conversation, we have identified at least 4 "drivers" of the cancer epidemiology to accelerate the translation of scientific discoveries into health care and population health benefits. This framework, by no means, is complete or sufficient, but is presented as a starting point. We envision that it will evolve to incorporate new ideas, insights, and commentaries from leaders of the field.

In this commentary, we briefly review the 4 "drivers" within a translational framework that are likely to influence the field in the next decade and discuss their relevance and caveats. We also use the global prevention of cervical cancer as an example of a tangible future public health endeavor to anchor the discussion of how cancer epidemiology can be the engine that drives the movement from discovery to population health impact.

Drivers of Translational Cancer Epidemiology: Needs, Opportunities, and Challenges

Khoury and colleagues described a framework of "translational epidemiology" as involving multiple phases (T0–T4), beginning with scientific discoveries and ending with population health impact (7). Using the framework (Fig. 1), epidemiologists have played a crucial role in discovery (T0 example: cigarette smoking and lung cancer; ref. 3), population characterization (T1 example: quantifying the magnitudes of genetic risk factors in cancer; ref. 8), evaluation (T2 example: randomized clinical trials of β -carotene in lung cancer prevention (9), implementation science (T3 example: evaluating provider practices on BRCA testing; ref. 10); and outcomes and surveillance research (T4 example: monitoring rates and determinants of lung cancer incidence at the population level; ref. 11). While most epidemiologists focus their research on discoveries and early translational work, there is an increasing trend of publications in the latter phases of translation (7), both in prevention as well as treatment and survivorship. Epidemiology also has a critical role in the translation of scientific evidence into policy and practice (12).

In the next decade, we anticipate that at least 4 "drivers" will influence the translational process: (i) collaboration and team science, (ii) technology, (iii) multilevel analyses and interventions, and (iv) knowledge integration from basic, clinical, and population sciences. These drivers

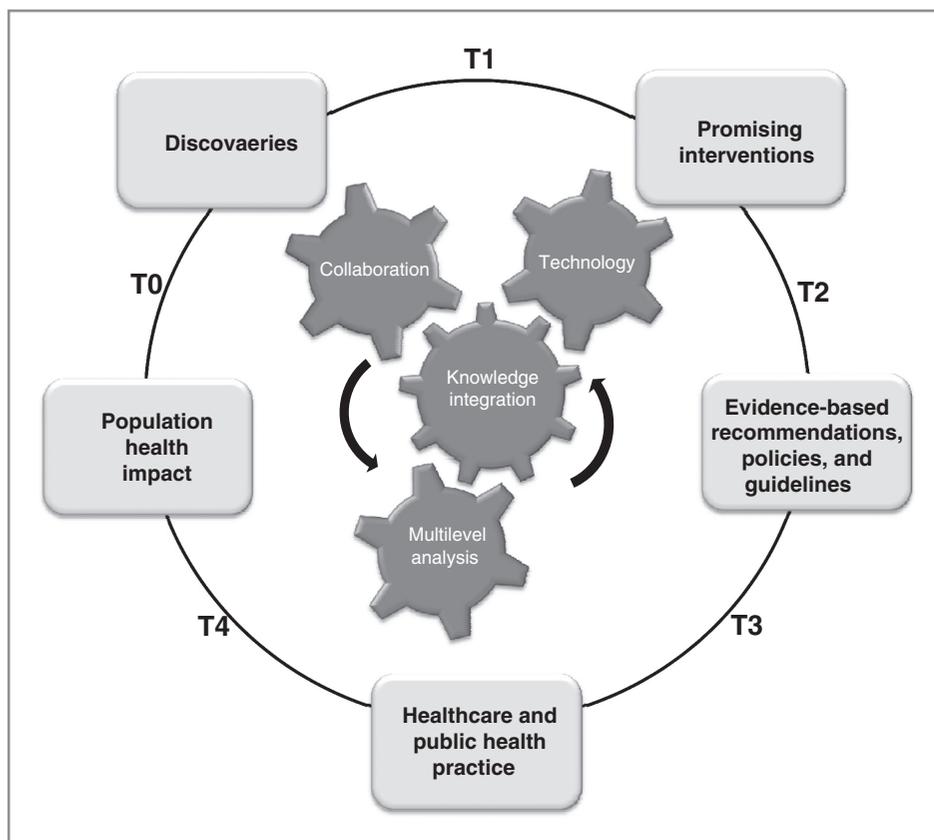


Figure 1. Translational research framework influenced by 4 "drivers" of epidemiology. Phases of translation: T0, discovery; T1, characterization; T2, evaluation; T3, implementation and health services; and T4, outcome research. Figure adapted from Khoury and colleagues (7).

complement one another and work in concert to accelerate epidemiologic findings through the translational research continuum to impress a true impact on cancer prevention and population health (Fig. 1).

Collaboration and team science

Given the complexity of cancer, a concerted effort is needed to unravel the mechanisms underlying carcinogenesis, characterize risk factors, promote prevention and treatment efforts, and influence outcomes of cancer care. This approach requires thoughtful team science initiatives across a growing list of disciplines (e.g., epidemiology, clinical medicine, statistics, environmental health, genomics, behavioral and social science, and health economics). The concepts of team science and related scientific approaches (e.g., multidisciplinary, interdisciplinary, and transdisciplinary) have been previously defined and described (13). At the NCI's Division of Cancer Control and Population Sciences, the Science of Team Science Initiative, for example, was specifically established to advance our understanding of cross-disciplinary research to accelerate progress in cancer control, prevention, and treatment (14). In epidemiology, consortia of well-characterized cohort studies are needed to enable epidemiologists to address scientific questions that require large sample sizes for statistical precision (15). While the need for collaboration seems obvious, there are technical and methodologic challenges that require the collective cooperation from experts to address, including data harmonization, population heterogeneity, and imprecise measurements of exposures across studies. A forum to discuss the opportunities and challenges of consortia and large-scale cohorts was held in 2006 and summaries of the conversations have been published (16).

Technology

A single technological advancement or innovation, such as affordable high-throughput genomic sequencing, can revolutionize a field. Likewise, "omics" technologies (e.g., proteomics, metabolomics, and epigenomics) are changing the landscape of epidemiologic research (17–20). Beyond "omics," emerging technologies could facilitate better characterization of the exposome and gene–environment interactions (21), digital epidemiology via the transformative development of communication technologies [smart phones, social media (22), and infodemiology and infosurveillance (23)]. Other innovative technologies include advances in imaging and biostatistical and bioinformatics tools and more precise and reliable methods to measure exposures such as diet/nutrition (24).

The promises and the potential rewards of a new technology can be intoxicating, but one should be mindful of the pitfalls of adapting a new technology too early and too soon. The relationship between technologies and epidemiology is bidirectional. While the former may provide the tools to delve into the "Big Data" deluge (25) and better measurements of exposures and outcomes, the latter is needed to inform, test, and validate the

application for usage in real settings. Technologies are tools that epidemiologists use to test a hypothesis and answer a scientific question; epidemiologic principles, concepts, and methods therefore should not be abandoned amidst the allure of a new technology.

Multilevel analysis and interventions

To fulfill the promise of epidemiologic findings making a population impact, epidemiologists need to fully understand the "macro" levels of influence and their interactions with personal and biologic factors throughout the cancer care continuum. For example, in the context of discoveries of biologic mechanisms and etiology of cancer, the construct of gene–environment interactions has been integrated into epidemiologic studies of various cancers (26). Environmental factors are broadly defined to include exposures ranging from personal to behaviors to social constructs. A similar ecologic model of health and the need to examine multiple levels and interaction applies throughout translational phases. In the context of implementation and evaluation, Taplin and colleagues (27) described a multilevel analysis model for the cancer care continuum, which is firmly rooted in an epidemiologic foundation. The model includes interactions between the person (e.g., the biologic, risk factors, and sociodemographic characteristics), the provider (e.g., the functioning of the provider or care team), the family and social supports (e.g., family interactions and social networks), the organization or practice setting (e.g., existing resources and processes), the local community environment (e.g., the physical environment and local health care markets; local public health campaigns), the state environment (e.g., state reimbursement policies, taxation, and state public health or cancer programs), and the national environment (e.g., national health reform, reimbursement policies, and national public health campaigns or cancer programs). Cancer epidemiologists should look beyond individual level factors (and even the person's immediate environment) to incorporate the influence of the physical/social/structural environment if their discoveries are to truly have a population-level impact.

Knowledge integration

Central among the drivers is knowledge integration. Knowledge integration is the process of combining information from many sources (and disciplines) to accelerate the translation of scientific discoveries into health benefits for both individuals and populations (28). We recently published a commentary on how knowledge integration can be applied in cancer epidemiology (29). Briefly, knowledge integration involves 3 components: knowledge management (selecting, storing, curating, and tracking relevant information), knowledge synthesis (applying technical methods, including meta-analyses, for the systematic review of published and unpublished data using *a priori* rules of evidence, as well as tools for modeling and

decision analysis), and knowledge translation (using synthesized information to broker stakeholder discussion and influence policy, guideline development, practice, and research). As depicted in Fig. 1 and discussed in our recent article (29), knowledge integration is at the center of translational cancer epidemiology. At any given point within the continuum, it provides methodologic guidance and applications to evaluate the robustness and accuracy of existing scientific discoveries, assess their implications for cancer care and prevention, and identify scientific gaps that warrant further research.

Case Study: Cervical Cancer Control and Prevention

Cervical cancer is a common disease worldwide (WHO, last accessed September 21, 2012) with striking inequities among resource-poor regions and racial/ethnic populations (GLOBOCAN, 2008). The infectious nature of cervical carcinogenesis, coupled with available vaccination and efficacious screening programs, offer a foreseeable scenario of global eradication of this disease (12). Nevertheless, significant challenges and research gaps exist in the areas of etiology, screening, prevention, treatment, and policy development. Experts have extensively discussed the nuances of the issues associated with these areas (23, 24). Moreover, 5 articles (30–34) in the September 2012 special issue of *Cancer Epidemiology, Biomarkers, and Prevention* (CEBP) focused on existing obstacles relating to cervical cancer burden worldwide. The welcomed coincidence of this CEBP Focus, as we were drafting this commentary using cervical cancer to illustrate our argument, underscores the timeliness of the driver-driven translational framework we outlined. Here, we highlight selected challenges in cervical cancer to illustrate how the cancer epidemiology drivers can be applied to accelerate progress to reduce the burden of cervical cancer worldwide (Table 1).

Cervical cancer etiology

The identification of human papillomavirus (HPV) as a necessary cause of invasive cervical cancer (35) and its precursors is a shining achievement of discovery in epidemiologic research—an epidemiologic evolution of scientific progress, dating as far back as 1842 (36) and reaching critical mass in the late 1960s with early indications that sexual behaviors played an etiologic role in cervical cancer risk (37–39). Technologic advances in HPV-DNA testing provided molecular epidemiologists with the tools to sort through the plurality of HPV types and to identify oncogenic strains associated with cervical cancer. Infections of HPV 16 and HPV 18 have been shown to account for approximately 70% of cervical cancer cases worldwide (40). Nevertheless, our understanding of cervical carcinogenesis remains incomplete. For example, although HPV-infection is a necessary etiologic factor for cervical cancer, it is not a sufficient factor (41). The role of cofactors (e.g., host/viral/envi-

ronmental) in the etiology of invasive cervical cancer is unclear (41–44). HPV infection is highly prevalent in the population, yet little is known about its natural history (45). Basic scientists along with molecular epidemiologists can help provide critical information about the mechanism(s) underlying HPV persistence and clearance. Strong evidence about HPV-associated cancers in men may be critical in providing scientific justification (s) for implementation of a widespread male-HPV vaccination policy (46, 47). Consortia are needed to gather adequate sample sizes to study less common HPV-associated cancers (e.g., penile) and cancers that affect both genders (e.g., anal canal and oropharyngeal; ref. 48), as the current body of evidence on the etiology for some of these HPV-associated cancers is equivocal (49, 50).

In addition, collaboration with behavioral epidemiologists/scientists, public health care workers, social/community workers, and health communication specialists can help curtail the spread of HPV infections, and identify the most effective behavioral interventions to promote protective sexual practices. The 3 components of knowledge integration are essential to synthesize existing knowledge from distinct fields to identify research gaps. For example, a Cochrane review of 23 randomized control trials on behavioral interventions and transmission of sexually transmitted diseases in young women concluded that these type of interventions are effective, but identified gaps, including the need for greater emphasis on education about HPV and cervical cancer risk as well as focused research on resource-poor countries (51). The translation of these "discovery" findings into clinical and public health practices, and policy recommendations can have tremendous health impact. For example, characterization of the natural history of HPV may inform the decision models for policy development-relating cervical cancer prevention (45).

Cervical cancer screening and vaccination programs

Widespread implementation of Pap tests has averted an epidemic of cervical cancer over the past several decades (52). Recently, technologic advances in HPV-DNA testing have transformed the conventional cytology-based screening protocol. The U.S. Preventive Services Task Force has adapted new screening guidelines to include the combination of cytology and HPV testing as a primary screening (53). Other transformative events driven by technologies include the availability of 2 HPV vaccines (Cervarix for HPV types 16 and 18; Gardasil for HPV types 6, 11, 16, and 18) against cervical intraepithelial neoplasia (CIN). The current U.S. Food and Drug Administration (FDA)-approved vaccines and HPV-DNA tests, however, offer partial protection against oncogenic HPV strains. Moreover, they are expensive and thus limit access, particular for high-risk populations.

Improved methods will continue to shape the landscape of cervical cancer vaccination and screening (54).

Table 1. Selected influence(s) of the 4 "drivers" of cancer epidemiology on cervical cancer research and prevention

Drivers	Needs	Translational impact on population health
Collaboration (Consortia and Team Science)	<ul style="list-style-type: none"> • Characterization of HPV natural history • Etiology of other HPV-associated cancers • Curtailment of high-risk sexual behaviors (e.g., behavioral interventions and health education) • Cost-benefit analyses of HPV testing 	<ul style="list-style-type: none"> • Inform decision models for policy development • Provide scientific justification(s) for implementation of widespread male-HPV vaccination policy • Prevent spread of HPV infection at a global scale
Technology	<ul style="list-style-type: none"> • Improved and affordable second/third generation HPV-DNA tests (e.g., self-administered) and vaccines (e.g., single dose) • Alternative HPV tests (e.g., HPV viral load, epigenetic changes, self-sampling) 	<ul style="list-style-type: none"> • Reduce implementation costs and increased screening/vaccine uptake and efficacy • Improve screening methods • Reduce cervical cancer disparities
Multilevel analysis	<ul style="list-style-type: none"> • Infrastructure supports to provide care for HPV/CIN positive women • Incorporation of risk factors into decision-making model • Evidence on long-term efficacy of HPV vaccine • Policies to provide structural and implementation support 	<ul style="list-style-type: none"> • Accelerate implementation of screening, vaccination, and education programs • Facilitate development of individualized screening recommendations • Establish optimal screening strategies for HPV-vaccinated cohort • Establish sustainable health care infrastructure
Knowledge integration	<ul style="list-style-type: none"> • Synthesis of scientific evidence to overcome barriers to screening and vaccination • Identification of scientific/interventional gaps (e.g., research on underserved populations) and best-practice interventions (e.g., cultural appropriate education on risks and prevention) to overcome socioeconomic/racial-ethnic inequities • Sustainable support in resources and man-power 	<ul style="list-style-type: none"> • Implement universal vaccination against HPV • Develop comprehensive cervical cancer screening program • Provide accessible, equitable, and affordable health care programs • Establish national/international evidence-based guidelines for prevention, screening, and vaccination • Develop appropriate targeted interventions to promote: (i) sexual behavioral risk-reduction; (ii) screening and vaccination initiation and uptake

Proximally, technologic advances can address the issues of cost and oncogenic HPV coverage by developing improved and affordable second/third generation HPV vaccines and HPV-DNA tests. For example, careHPV, a rapid, affordable, and self-administered assay that can detect 14 oncogenic HPV types, has recently been introduced as a primary screening method for poor women in El Salvador (54). More distally, innovations in other screening methods, HPV genotyping assays, detection of HPV viral load, and epigenetic changes, have the potential to impact screening programs (55). Likewise, an approved single-dose HPV vaccine that can target a wider range of oncogenic HPV strains has the possibility of significantly impacting a spectrum of issues including programmatic implementation costs and vaccine uptake/efficacy.

Despite the transformative impact of HPV testing on cervical cancer screening, there are considerable limitations to the current evidence. Epidemiologic studies with validation design components (56), are needed to evaluate, and/or compare these tests and various screening strategies that incorporate HPV testing in multiple populations and resource settings. In addition, multilevel analyses at different junctions can answer some of the "macro" level questions that require thoughtful and critical consideration: (i) what are the socioeconomic and political infrastructure needs to address the care of women who test positive for HPV or CIN; (ii) how can individual risk factors be incorporated to tailor screening recommendations; or (iii) how to best screen the anticipated HPV-vaccinated cohort (57). The application of knowledge integration is critical

to manage, synthesize, and translate the incoming scientific evidence from distinct disciplines. Hence, knowledge integration coupled with multilevel analyses can solidify the scientific evidence on vaccines, HPV-DNA tests, and screening/vaccination strategies. The translation of this collective knowledge across different areas of cervical cancer research can consequently inform decision making and policy recommendation, and lead to the development of national/international guidelines for cervical screening and prevention.

Disparities in cervical cancer

Significant disparities in cervical cancer incidence and mortality exist in the United States and worldwide, despite strong evidence that screening via Pap smear is efficacious and effective. A lack of sustainable large-scale prevention programs contributes to the vast disparities observed in some low- and middle-income countries. Barriers to access, acceptability, and adoption of preventive services have been identified as outstanding issues (58). The uptake of HPV vaccination among low-income, racial/ethnic, and special populations is hampered by lack of awareness, knowledge, acceptability (due to social/cultural barriers), and access (due to cultural/socioeconomic and structural barriers; ref. 59). Affordable technologies may help alleviate some of the disparities in screening/vaccination. Beyond the aid of technologies, multilevel analyses and knowledge integration that span the translational research continuum can drive the research to identify best practices and targeted interventions to overcome identified barriers to preventive services, especially among high-risk populations. As the synthesized evidence matures to show that HPV-DNA testing (especially with improved and affordable tests) is comparatively better than Pap smears, implementation of HPV-DNA testing as a primary screening strategy (60, 61), will have significant impact in addressing cervical cancer disparities in resource-poor countries and underserved/high-risk populations.

Limited resources in developing countries mandate focused, deliberate, and thoughtful conversations among various stakeholders (policy makers, health care providers, community leaders and organizers, social networks, and individuals) as part of a collaborative, multilevel effort to garner and distribute precious resources. The identified drivers, therefore, complement each other throughout the translational research continuum and cancer care. Certainly, the translation of scientific evidence into clinical

and public health practices, and policy recommendations can have tremendous overarching impact and must extend beyond just policy implementation.

Summary

At the heart of a global prevention of cervical cancer is a committed and invigorated effort that spans disciplines, states, nations, and populations. Accordingly, epidemiologists need to recognize the transcendent role they can play to contribute to this global effort and across the translational research continuum (12). The driver-catalyzed translational framework described in this commentary, illustrated with the cervical cancer example, is a start to engage epidemiologists in the reshaping of cancer epidemiology to further our mission to reduce the burden of cancer and impact population health. There are already discussions on an interdisciplinary epidemiologic education and training of the 21st century epidemiologist (62, 63) as well as the types of dynamic collaborative research needed to move cancer epidemiology forward. We believe that the perception of epidemiology as a discipline focused only on etiologic research at the individual level must be broadened to adopt an ecologic model of population health and tackle issues of health care and survivorship. In fact, epidemiologists should reclaim the role that John Snow epitomized in the next decade. By organizing the "longitudinal" meeting and with the compilation of commentaries to provide supporting materials, EGRP hopes to engage the scientific community to join the conversation, reshape the framework, and prepare the field of cancer epidemiology for a paradigm shift.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: T.K. Lam, S.D. Schully, M.J. Khoury

Development of methodology: T.K. Lam, M.J. Khoury

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): T.K. Lam

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): T.K. Lam, M.J. Khoury

Writing, review, and/or revision of the manuscript: T.K. Lam, M. Spitz, S. D. Schully, M.J. Khoury

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): T.K. Lam, M.J. Khoury

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