Editorial

Cancer Epidemiology in the 21st Century

Bridging the Gap between Biologic, Individual, and Macroenvironmental Factors in Cancer: A Multilevel Approach

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Abstract

To address the complex nature of cancer occurrence and outcomes, approaches have been developed to simultaneously assess the role of two or more etiologic agents within hierarchical levels including the: (i) macroenvironment level (e.g., health care policy, neighborhood, or family structure); (ii) individual level (e.g., behaviors, carcinogenic exposures, socioeconomic factors, and psychologic responses); and (iii) biologic level (e.g., cellular biomarkers and inherited susceptibility variants). Prior multilevel approaches tend to focus on social and environmental hypotheses, and are thus limited in their ability to integrate biologic factors into a multilevel framework. This limited integration may be related to the limited translation of research findings into the clinic. We propose a “Multi-level Biologic and Social Integrative Construct” (MBASIC) to integrate macroenvironment and individual factors with biology. The goal of this framework is to help researchers identify relationships among factors that may be involved in the multifactorial, complex nature of cancer etiology, to aid in appropriate study design, to guide the development of statistical or mechanistic models to study these relationships, and to position the results of these studies for improved intervention, translation, and implementation. MBASIC allows researchers from diverse fields to develop hypotheses of interest under a common conceptual framework, to guide transdisciplinary collaborations, and to optimize the value of multilevel studies for clinical and public health activities. Cancer Epidemiol Biomarkers Prev; 22(4); 485–95. ©2013 AACR.

Motivation

Cancer is etiologically complex and its causes are multifactorial. Risk factors associated with cancer development have been identified that represent a variety of levels of influence on health and disease (Table 1). Macroenvironment factors including health system, neighborhood, or community characteristics, have increasingly been linked to cancer incidence and mortality (1, 2). In addition, social determinants and processes (1, 3, 4) have been identified as cancer risk factors, including socioeconomic status or self-reported race (5–8). Environmental exposures at the level of the individual (5) including cigarette smoking (9), radon (10), asbestos (11), diet (12), and physical activity (13) are causally associated with some cancers. Applied and fundamental investigations have identified a wide array of biologic factors mechanistically involved in carcinogenesis including those of the tumor microenvironment, metabolome, proteome, transcriptome, and genome. For example, hundreds of novel genetic susceptibility loci have been identified through candidate and genome-wide association studies (GWAS; ref. 14).

Studies of factors at a single level have provided a great deal of insight into the etiology of disease. Despite successes in identifying cancer risk factors, these approaches are limited and at some point the information obtained from these single-level studies reach a saturation point, and have provided as much information as they can. It is clear that the factors reported to date do not fully explain cancer incidence in the general population. For example, while smoking is strongly associated with lung cancer (15), most smokers will not be diagnosed with lung cancer, whereas some nonsmokers will (16). While BRCA1 or BRCA2 mutation carriers have a greatly increased lifetime risk of developing breast cancer (17), some BRCA1/2 mutation carriers are never diagnosed with breast or ovarian cancer, even at an advanced age. GWAS have identified a wealth of susceptibility genes, but the identification of novel genes using this approach is unlikely to continue ad infinitum. Therefore, risk factors studied in...
Overview of Current Multilevel Approaches

To address the complex nature of cancer etiology, multilevel approaches have been developed to simultaneously assess the role of 2 or more etiologic agents within a hierarchical or nested structure (18). A number of conceptual frameworks have been proposed that integrate information across levels of disease etiology, including the “web of disease” of MacMahon and Pugh (19), the “wheel” of Mausner and colleagues (20), “systems epidemiology” (21), and more recent models of multifactorial etiology (22–27). Multilevel approaches are generally characterized by 3 main levels: (i) macroenvironment, referred to elsewhere as “eco-level” (23, 24); (ii) individual; and (iii) biology (Table 1). Each of these levels is further characterized by sublevels (Table 1) that define domains of variables involved in cancer etiology or outcomes. Multilevel conceptual frameworks are based on the premise that factors affecting disease act within and across levels to collectively affect disease. These approaches generally hypothesized that cancer outcomes can result from the complex relationship of factors at multiple levels in at least 2 ways (Table 1). First, factors at the macroenvironment and individual levels can directly affect the biologic events and result in cancer. Second, factors may confer risk in a hierarchal fashion, such that biologic-level effects are affected by behaviors or exposures of the individual, and individual level effects are affected by the macroenvironment (28).

The relationships described earlier in the context of a multilevel model refer to both statistical and biologic interactions. Here, we use the term “interaction” generically to refer to any nonadditive statistical structure that can be constructed between 2 or more factors. This concept includes that of effect modification, mediation (29), as well as biologic structures that may be defined between 2 or more factors (e.g., epistasis among genetic loci). The goal of the multilevel framework we will present here is not to define a specific form for interaction. A variety of statistical approaches have been developed to guide implementation of hierarchal, longitudinal, or multilevel models (18, 30–32). Instead, we hope to provide a framework around which a researcher can generate hypotheses about the relationship among etiologic agents in a consistent manner. When results of these hypothesis tests are known, investigators using our proposed framework may be better able to compare and combine their results to form coherent multilevel inferences.

Most multilevel approaches lack a detailed focus on mechanisms that can be used to frame the relationships between macroenvironment or individual-level factors. In part, the limited incorporation of mechanistic hypotheses stems from the early multilevel frameworks having evolved from research focused on social factors. Thus, multilevel conceptual approaches have tended to take a “top-down” approach that is focused on the role of social determinants at the macroenvironment level (Table 2). Only more recently has a detailed consideration of the biologic level been included in multilevel studies. For instance, the model of Warnecke and colleagues (22) centers on health disparities as the outcome of interest and defines macroenvironment level factors by policies, institutions, and social or physical factors. They also include a single level including biologic factors. Similarly, the models of Taplin and colleagues (23) and Gorin and colleagues (24) focus on improved cancer care, subdividing the macroenvironment level by national and state health policy, local community environment, organization or practice setting, health care provider teams, and family/social support. Across proposed multilevel frameworks, the traditional individual level risk factors for cancer (e.g., smoking, race, diet, etc.) are also considered, whereas biologic

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<td>Defined by factors: allostatic load (e.g., combination of stress markers or other biomarkers), metabolic processes, genetic mechanisms</td>
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factors in these constructs remain broadly defined by genes, proteins, enzymes, and other somatic changes in the cellular environment (23, 24, 33). In these models, all biologic processes are treated in a manner similar to those of other levels without accounting for the extensive knowledge of biologic processes, pathways, and etiologic relationships that are involved in carcinogenesis.

Approaches that focus on macroenvironment have had an impact on the conceptual advancement of our understanding of disease etiology. While the NIH has increasingly recognized and encouraged the use of multilevel approaches to go beyond investigating individual level factors to include macroenvironment level exposures (34, 35), many of the current approaches (34, 35), come from the perspective of social and environmental research, and the full integration of biologic level factors has yet to be realized. A search of PubMed for the term “cancer” and “multilevel analysis” or “multilevel model” resulted in 55 articles published between 2002 and 2012, although the majority of these (26 of 55, 47%) were published since 2010. Most of these studies focused on individual-level and macroenvironmental factors, and few incorporated biologic factors. Thus, work is needed to improve the understanding of which factors at each level are relevant to the disease, the hierarchical nature of the relationship of those factors, and the effective application of integrative multilevel approaches to achieve meaningful etiologic inferences.

Multilevel Biologic and Social Integrative Construct (MBASIC)

To the degree that a researcher has knowledge of biologic mechanisms of human cancer, multilevel models could be used to harness this information and to generate hypotheses that link macroenvironment or individual level factors with mechanisms of carcinogenesis. Current multilevel conceptual approaches, while created to promote multidisciplinary research, often lack detailed descriptions of the biologic level that could be used to unite traditionally distinct fields (e.g., molecular biology and social epidemiology).

MBASIC defines the multilevel framework (construct) to include 3 main hierarchical levels that contribute to cancer etiology and levels of carcinogenesis (i.e., macroenvironment, individual, and biologic factors; Fig. 1), where the biologic level is more specifically defined. This multilevel etiologic model is then placed in the context of interventions, and translation/implementation (i.e., T0-T4; refs. 36, 37; Fig. 1). This framework allows researchers from the fields of public health, health policy, prevention, behavioral sciences, sociology, epidemiology, biology, clinical medicine, and others to test hypotheses of interest under a common conceptual framework, to address the dynamic nature of carcinogenesis, to facilitate translation of multilevel studies to clinical and public health strategies, and to support multidisciplinary collaborations.

The primary goal of MBASIC is to consistently and systematically frame complex hypotheses about cancer etiology. As may be expected with any comprehensive conceptual framework, the full range of MBASIC components is not meant to be implemented in any one study. Instead, MBASIC is meant to aid the researcher in stating hypotheses for individual studies that address a part of the complete framework. Thus, MBASIC provides the framework for hypotheses that allow comparison and compilation of individual study results using formal
Multilevel Approach in Cancer

Predictive and mechanistic links between and among hierarchical levels of etiology

A primary goal of the MBASIC is to guide researchers to consistently and systematically incorporate biologic mechanisms into a multilevel framework. Despite the substantial limitations in our ability to generate meaningful statistical or epidemiologic models of mechanism and biologic events (38, 39), knowledge of existing biologic pathways emerging from animal, tumor, and other in vivo studies can be used to improve generation of hypotheses about how each of the 3 hierarchal levels relates with the others to frame questions about the complexity of cancer etiology (40). The well-known molecular epidemiology paradigm (41–45) provides a useful structure into which biology can be incorporated into a multilevel framework. As shown in Fig. 2 and defined later, the effect of exposures can be measured by biomarkers of biologically effective dose (BED), early biologic effects (EBE), and altered structure and function (ASF) that are predictive of disease (42–45). The formation of these biomarkers can be influenced by inherited genotypes. These factors can give rise to somatic genomic changes involved in carcinogenesis. Note that while prior constructs include markers of internal dose, which have great value as biomarkers for research, clinical, or screening purposes, we exclude these in the present framework to emphasize biologic and mechanistic effects in the multilevel etiology of cancer. While spontaneous mutation may give rise to the biomarkers of disease and effect shown in Fig. 2, the multilevel construct assumes that each of the biomarkers occur in response to an initial macroenvironment or individual level exposure, even though that exposure may not be known or measurable.

We adapt the traditional molecular epidemiology approach (42–45) in 2 ways: by considering the nested hierarchical nature of the multilevel model (Fig. 2); and by expanding the definition of “exposure” to include both macroenvironment level and individual level exposures. As noted in Table 1, relevant etiologic factors can be measured by biomarkers (i.e., BED, EBE, and ASF) of exposure or disease at the biologic level. These biomarkers reflect somatic changes and are often measured at the tissue or cellular level. For example, biomarkers of exposure to cigarette smoking at the individual level can be measured by exposure biomarkers such as DNA adducts (42–45) in blood; prostate-specific antigen (PSA) levels or chromosomal instability (45) measured in blood can serve as markers of disease. Thus, these factors may be framed as both processes leading to disease and as intermediates reflecting the relationship between macroenvironmental and individual factors, separately, and disease (Table 1). For instance, macroenvironment level variables can induce a psychologic response, which can be directly measured at the biologic level. Witnessing a crime in a neighborhood environment can lead to flight or fight cellular responses that cause increases in cortisol levels. Thus, cortisol is a biomarker of a macroenvironment exposure. An example of a linkage between the individual level and the biologic level is that of the human exposome (46). The exposome is defined by environmental exposures (including lifestyle factors) that represent combined exposures from all sources, from the prenatal period onward (46). The exposome can be measured by biomarkers at the cellular level via bodily fluids or tissue that can serve as surrogates for exogenous or endogenous environmental exposures. For instance, exposure to organophosphate pesticides can be measured by certain metabolites, and dietary factors, such as vitamin intake, can be measured by antioxidant metabolites. Like the GWAS approach, epidemiology has used environment-wide association studies (EWAS; refs. 46, 47) that use an agnostic approach to identifying environmental factors involved in disease. Future EWAS studies in cancer are warranted to provide practical evidence for a link between individual level exposures and the biologic level. While EWAS and GWAS share some conceptual similarities, there are numerous methodologic differences between the 2 approaches (48). However, the results of each can provide information that may promote the development of multilevel hypotheses in cancer etiology.

While the examples earlier show how macroenvironment and the individual level factors can each separately affect the biologic level as an exposure, we can also show the hierarchal effect among exposures at multiple levels on the biologic level. For example, exposure to a group of friends who smoke cigarettes could prompt an individual to change her behavior and also start to smoke cigarettes. This change in behavior at the individual level influences
molecular carcinogenesis at the biologic level (i.e., DNA adducts; BED) and chromosomal damage (ASF). Despite symptoms of decreased lung function over the course of 15 to 20 years, the individual is genetically predisposed to nicotine dependence, is unable to quit smoking, and ultimately ends up developing lung cancer. Here, the behavior change served as an intermediate between the macroenvironment and biologic events involved in carcinogenesis. Thus, this example shows the biologic plausibility of how a macroenvironmental factor can impact an individual, affecting her biologic environment, ultimately resulting in disease. When the macroenvironment, individual, and biologic factors are collectively considered to predict or explain a cancer outcome, statistical methods will need to be determined which levels or which risk factors within each level are most relevant to the cancer outcome under study. Thus, it is possible for intermediates to serve as surrogates of exposure and disease, but the importance of each level and each factor within each level will need to be determined statistically based on available methods.

Biology in a Multilevel Framework

Starting with the levels of etiology (Fig. 1), the biologic level can be subdivided into sublevels with a hierarchical order based on our knowledge of biology and carcinogenesis: tissues are composed of cells, which contain genes. Somatic mutations and cellular events (e.g., DNA replication) may be involved in carcinogenesis. In the following sections, we build the framework around which the biologic level can be optimally incorporated into multilevel analysis (Fig. 2).

Tissues

Tissues warrant consideration as a unique biologic sublevel in a multilevel framework for 2 reasons. First, cellular markers and processes that are measured in normal tissue, preneoplasia, or malignant tumors could serve as potential markers of exposure, disease, or prognosis. Second, tumors occur at the tissue level. Most cancers are diagnosed and staged using tissue samples or by imaging techniques that may identify lesions in a particular organ. A growing area of research is focused on the tumor microenvironment, defined by normal cells, signaling molecules, matrices, and blood vessels that surround and feed a tumor cell (49). A tumor can alter its microenvironment (as defined by cellular and genomic sublevel factors), and the microenvironment can affect how a tumor grows and spreads. Data about the role of the tumor microenvironment are rapidly becoming available via initiatives such as The Cancer Genome Atlas (TCGA; http://cancergenome.nih.gov).

Cells

The cellular sublevel is characterized by proteins, enzymes, and other biomarkers that can be detected in bodily fluids and tissues. In the context of our model, the cellular level includes the transcriptome, proteome, and metabolome, where biomarkers of exposure and disease can be measured (Fig. 2). The transcriptome includes the various forms of RNA in the cell that affect gene expression and cellular function (50–52). The proteome includes the total set of proteins expressed in a given cell at a given time (51). Examples of factors measured in the proteome include PSA and CA-125 (45, 50, 53). Complex protein interactions are referred to as the metabolome (51, 54). Therefore, even within the cellular sublevel, there is an emerging hierarchy (51). Many approaches for disease biomarker discovery focus on a single biomarker at the cellular level, despite an emerging expectation that panels of biomarker analytes will be needed to provide sufficient sensitivity and specificity for cancer screening, diagnosis, or prognosis (50, 54). Therefore, there is a shifting focus to the role of the pathway-based and statistical interactions among cellular factors, but progress in this area is limited by available, high-throughput technologies that can detect and organize the millions of proteins obtained from a given biologic sample.

Somatic genomics

The somatic genome sublevel (Figs. 1 and 2) is defined by acquired somatic genomic changes over the course of a person’s lifetime. The somatic genome level is defined by factors that can be both markers of disease and markers of exposure. Somatic genome examples include mutations, copy number variants, and epigenetic changes occurring in DNA (50, 55). Early studies of somatic genome used methods that identify potential susceptible loci a priori, but this approach used a small number of genetic markers, rarely identified robust associations between candidate genes and cancer, and most findings were not replicable in other studies (14).

Inherited genomics

The inherited genome sublevel (Figs. 1 and 2) is composed of inherited susceptibility loci that serve as markers of disease risk and outcome. Inherited genome includes hereditary cancer syndromes (56), which confer a high risk of cancer development. Inherited genome research may use family-based linkage methods to identify important inherited, high-penetration genes, such as BRCA1 and BRCA2. However, the mutations in these genes are rare in the general population (4, 14, 17), and only explain a small fraction of familial aggregation and cancer risk. GWAS have identified many dozens of cancer susceptibility loci (43, 57), most of which were not previously hypothesized to be involved in cancer susceptibility (14). Despite this success, genetic risk variants identified from GWAS, alone and in combination, explain a relatively minor proportion of disease risk, and have had limited translational value to the clinic. This has led to a focus on the identification of rare variants that may account for larger proportions of cancer genetic risk (58).

Given the limited clinical use of somatic genome and inherited genome findings focused on single disease loci and statistical interactions thereof, there has been a
renewed interest in studying epistasis, defined as genes at 2
or more loci that produce phenotype effects that are dif-
ferent than the expected effects of the individual loci (59). At
both the somatic genome and inherited genome sublevels,
gene–gene interaction studies are being conducted to ascer-
tain the independent and joint effects of risk loci on cancer
outcomes (60). These studies may use multiple cancer risk
susceptibility loci based on pathway or shared biologic
function, or be combined using statistical predictive models
independent of biologic knowledge.

Nonhierarchical effects within and across levels of
etiology
Mechanisms and example methodologies have been
proposed to build on the definition of the biologic level
and to illustrate how interactions between and among
factors at each level relates to one another, assuming a
hierarchical structure for levels of etiology (Fig. 1). Hypoth-
eses that consider the hierarchical framework of MBASIC
are readily constructed from the discussion provided
earlier. However, the effects of factors within each of these
levels need not follow a strict hierarchy. In the context of
predictive (as opposed to mechanistic) models, each level
can dynamically affect another. Thus, statistical (causal)
inferences need not be constrained in a linear hierarchical
fashion (61). Concepts in social science and genetics sup-
port this assertion. According to the social ecologic per-
spective (62, 63), human health results from the complex
interaction of personal factors (e.g., behaviors, biology,
psychology, etc.) as well as physical and social environ-
ments (e.g., geography, built environment, culture, eco-
nomics, politics, and social relationships; ref. 62). For
instance, a combination of geography, psychology, and
behavior without a clear hierarchal or biologic link could
interact (statistically) and affect disease outcomes. In
addition, changes in eating habits at the individual level
may affect social relationships at the macroenvironment
level as a person who is more conscious of their eating
habits may prefer to be around other healthy eaters; the
effect of each level on the other is not necessarily linear,
top-down, or bottom-up. In the field of genetics, pene-
trance (64) is defined by the probability of a phenotype
given genotype. Even though a person is born with a
disease genotype, lack of exposure to harmful environ-
mental factors or carcinogens may prevent the disease
from occurring. While it is likely that the disease genotype
and exposure have some biologic link, in the absence of
this knowledge, specific methodologies aimed at analy-
zing gene–environment interactions, more recently,
gene–environment interaction-wide association studies
(GEIWAS; ref. 65), can be developed to help elucidate
statistical interactions across levels. Because it is clear that
biological, social, and environmental factors interact in
some way in cancer etiology, a multilevel framework is
needed to both organize and guide traditionally separate
fields of cancer research; however, these frameworks
should also account for the dynamic nature of the disease.

Expanding MBASIC: Levels of Intervention,
Implementation, and Evaluation
MBASIC expands the use of the multilevel approach by
including levels of etiology and carcinogenesis with levels
of intervention and implementation/evaluation, all of
which can influence one another in a nonlinear manner.
Levels of intervention are characterized by primary, sec-
ondary, and tertiary prevention strategies and survivor-
ship that range from risk assessment to detection to
diagnosis and treatment (Fig. 1). Previous multilevel
studies have focused on assessing factors within the levels
of intervention (3), particularly cancer care outcomes
such as detection or screening at the individual level or practice
setting sublevel (23, 24).

The implementation/evaluation level is characterized
by changes made through the application and transla-
tion of relevant interventions (66). Implementation/
evaluation may occur through national, state, or local
policy or health care systems changes, and the impact of
interventions and implementation will ultimately be
seen in changes to the health status of a population.
The levels of implementation/evaluation are based on
the translational model of Khoury and colleagues (36,
37), which describes 5 translational phases (Fig. 1): T0/
T1 (determination of mechanisms, etiology and develop-
ment of interventional strategies); T2 (development of
evidence-based policy and practice); T3 (implement-
ing evidence-based guidelines to elicit health care sys-
tem changes); and T4 (surveillance and monitoring the
effect of changes on health outcomes in populations).
Appropriate consideration of the dissemination, imple-
mentation, and evaluation of research findings into
health systems is critical if the potential of multilevel
models is to be realized. For instance, knowledge of the
role of macroenvironmental factors (e.g., residential
location, social environment) in individuals with spe-
cific biologic characteristics and risk factor profile could
provide a resource-efficient approach to early detection
or screening for cancer.

Simultaneous consideration of multiple levels in the
MBASIC framework may impact a number of cancer
outcomes. The levels or sublevels of inference (etiology,
carcinogenesis, intervention, or implementation/
evaluation; Fig. 1) could serve as the outcome or exposure
of interest. For instance, health care system changes (e.g.,
insurance coverage) can affect individual level behavior
(e.g., participation in smoking cessation programs), which
can affect the cellular environment (e.g., carcinogen levels
and formation of DNA adducts). Therefore, interactions
within and across levels can be modeled in a variety of
ways, and extent to which the 4 levels of inference impact
the trait of interest will vary depending on the etiologic
setting. For instance, during cancer initiation, living in a
community that promotes cancer screening and having
access to primary care may play a prominent role in cancer
early detection. After cancer is diagnosed, the oncology
provider and social support may become a predominant
influence on clinical and psychosocial outcomes. Both of these scenarios may be imposed on a common biologic context (e.g., a cancer having a specific mechanistic cause), but the relevant individual and macrolevel factors may differ substantially.

MBASIC Example: Prostate Cancer

In the United States, prostate cancer is the second leading cause of cancer-related death in men (67). Prostate cancer is of public health concern because it disproportionately affects different races. African American men are more likely to be diagnosed with and die from prostate cancer than any other racial group, and this disparity is the largest observed for any cancer (68). Despite the burden of prostate cancer, particularly for African American men, little is known about the etiology and predictors of poor prognosis for the disease. At present, the only widely agreed-upon risk factors for prostate cancer are at the individual level: race, age, and family history of prostate cancer (69). Tumor and patient characteristics used to identify men with a poor prognosis include tumor stage, Gleason score or grade, and PSA level at diagnosis. However, these clinical characteristics are imperfect in their ability to determine long-term prognosis and appropriate treatment options. Thus, prostate cancer is a good example of the potential value of the MBASIC framework.

PSA screening: from the cellular level to T4 implementation

In the 1980s, studies on the cellular level showed that PSA levels could serve as markers for prostate cancer recurrence (70). The use of PSA screening for patients undergoing treatment was approved in 1986 (70–72). Despite studies in the late 1980s suggesting that PSA might not be an ideal biomarker for screening and early detection of prostate cancer (70–72), the U.S. Food and Drug Administration (FDA) also approved PSA as an early detection screening test in 1994, and PSA became one of the first FDA-approved early-detection biomarkers for cancer (70). The FDA based its approval on a large clinic study whose results suggested that men with PSA values above 4.0 mg/mL could be biopsied for cancer (73). As a result of this bench to bedside clinical translation (T1 phase), screening guidelines with often conflicting recommendations from different organizations such as the United States Preventive Services Task Force (74), the American Cancer Society (75), and the National Comprehensive Cancer Network (76), started to emerge. These guidelines affected clinical practice (T2 phase), resulting in more men being screened for and diagnosed with prostate cancer (70). The health care system was also affected by these guidelines: insurance companies, particularly the Veterans Association and Medicare, incurred large costs covering routine PSA screening (T3 phase; ref. 77). Continued research at both the population level (T4 phase) and levels of causation (cellular and individual levels) in more recent years have shown that PSA screening may not improve prostate cancer mortality rates, that early detection of prostate cancer can often lead to unnecessary treatment for some and insufficient treatment in others (70, 78, 79). As a result, researchers continue to develop enhanced PSA screening tests that are more sensitive and specific (70). Guidelines for routine PSA screening are continually being revised in the context of individual level factors. These include questioning the use of screening for men under the age of 75 years (74), focusing on screening high-risk groups (5), and recommending baseline PSA measures in men under age 50 years (58). Despite its limitations and controversies, PSA screening illustrates how cellular and individual levels of causation, resulting biomarker interventions, and health care implementation (Fig. 1) can inform one another to optimize the early detection of prostate cancer.

The PSA scenario also suggests that a comprehensive evaluation of PSA in early detection of prostate cancer may benefit from the use of MBASIC to frame the hypotheses and approaches needed to improve screening and treatment of prostate cancer. While macrolevel factors have yet to be widely used in the context of PSA screening, it is not hard to imagine that screening strategies may be optimized by having a better understanding of those men who are most likely to have unfavorable prostate cancer outcomes based on their socioeconomic situation, access to health care, or other macroenvironmental factors. The role of macroenvironmental factors in prostate cancer risk and mortality are beginning to emerge from the health disparity and PSA screening literature. Screening behaviors can be affected by economic, physical, and social characteristics of residential neighborhoods (80). Neighborhoods considered to be disadvantaged or low-income have been correlated with higher levels of pollutants, overcrowding, violence, less social cohesion, and less access to services (81). Screening practices can affect prostate cancer incidence, and low-income neighborhoods often have fewer medical facilities that are overburdened with indigent care to provide optimal screening (80). This can lead to differential screening practices by neighborhood (82) and differences in both the diagnosis and treatment of prostate cancer, particularly among Caucasian versus African American men (83, 84). Therefore, neighborhood measures could serve as a surrogate for access to care in prostate cancer and seem to be a relevant macroenvironment level measure to investigate for this cancer outcome. In the setting of an MBASIC approach, men with known biologic risk profiles may therefore benefit from targeted intervention if they also reside in defined disadvantaged neighborhoods.

This concept is further illustrated by a multilevel analysis that investigated the role of individual level characteristics and census-tract neighborhood variables and stage of prostate cancer. Consistent with data showing an association between race, stage, and socioeconomic circumstances such as living in a low income area, using geographic information systems technology, Xiao and colleagues (85) went beyond identifying factors...
associated with prostate cancer stage and suggest community education and outreach in areas with unfavorable neighborhood characteristics. In the context of MBASIC, discovery and early translation can be leveraged in a single study and can provide additional insights that would not be as readily apparent in studies focusing on a single etiologic level.

**Prostate cancer disparities: piecing together studies on biology and neighborhood**

Because of the complex etiology of prostate cancer, an understanding of prostate cancer disparities may benefit from a multilevel approach. A growing body of literature supports this hypothesis. Rundle and colleagues (86) reported that neighborhood socioeconomic status (based on median income level of a census tract) modifies the association between individual smoking status and PAH-DNA adduct levels in prostate tissue (BED). We reported an interaction between prostate cancer genetic susceptibility loci identified in GWAS and census-tract level neighborhood variables on time to PSA failure in men who had undergone radical prostatectomy (87). We identified no main effects of the genetic variants or neighborhood factors on PSA failure by themselves but found statistically significant interactions between neighborhood variables and the susceptibility loci. Specifically, genotypes at *MSMB* and *HNF1B/TCF2* predicted time to PSA failure in men from disadvantaged neighborhoods. This suggests that context-specific effects of genotype should be explored and may improve the ability to identify groups that may experience poor prostate cancer outcomes. It is important to note that these studies represent predictive models that may have implications for implementation or translation but themselves do not provide direct mechanistic conclusions. In general, these studies may motivate a continued focus on multilevel approaches and provide rationale for the use of multilevel models in cancers such as prostate cancer, where typical single disciplinary approaches provide limited insight into disease etiology.

**Charge to the Scientific Community**

We have proposed a unifying conceptual framework that allows researchers from public health, policy, oncology, health services research, behavioral science, epidemiology, and the biomedical sciences to test hypotheses of interest under a common framework. The MBASIC framework allows researchers to generate common inferences from otherwise disparate individual research findings by using a common conceptual model. As illustrated by the prostate cancer example, taking a multilevel approach can help to expedite translation of etiologic findings into translational efforts, more than would occur in studies focused on single levels of etiology alone. By providing a stronger basis for inclusion of biologic factors in a multilevel hierarchy, MBASIC bridges the gap between social science and biology to foster multidisciplinary collaboration and streamline intervention, implementation, and translation efforts. Emerging biomedical technologies enable population-based studies to include biomarker data such that the landscape of cancer research is changing and the lines between disciplines are increasingly blurring. MBASIC can serve as a road map for hypothesis generation and the development of emerging multidisciplinary teams. The MBASIC framework allows individual studies to more effectively piece together individual research findings under a common conceptual model. Knowledge gained from this integration can be used to rationalize the costs of future, large-scale, multilevel studies. Finally, MBASIC represents a framework around which transdisciplinary research (i.e., research that generates new fields of inquiry) can be built.

**Disclosure of Potential Conflicts of Interest**

No potential conflicts of interest were disclosed.

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**References**


