

Hypothesis/Commentary

Cancer Epidemiology in the 21st Century

Provocative Questions in Cancer Epidemiology in a Time of Scientific Innovation and Budgetary Constraints

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Abstract

In a time of scientific and technological developments and budgetary constraints, the National Cancer Institute's (NCI) Provocative Questions Project offers a novel funding mechanism for cancer epidemiologists. We reviewed the purposes underlying the Provocative Questions Project, present information on the contributions of epidemiologic research to the current Provocative Questions portfolio, and outline opportunities that the cancer epidemiology community might capitalize on to advance a research agenda that spans a translational continuum from scientific discoveries to population health impact. *Cancer Epidemiol Biomarkers Prev*; 22(4); 496–500. ©2013 AACR.

In 2010, Harold Varmus began his stewardship as the director of the National Cancer Institute (NCI) with a key initiative called the Provocative Questions Project. The primary purpose of the Provocative Questions Project is to invigorate and "engage a diverse range of scientists in a challenging intellectual exercise to define and then solve the major unsolved or neglected problems in oncology" (1). The initiative builds on a rich history of scientific discoveries and comes at a time of great scientific and technological advances in fields like genomics and related disciplines. The NCI's Provocative Questions Project differs from larger global initiatives that tend to set overarching goals (e.g., the United Nations' Millennium Development Goals) or post challenges (e.g., Gates Foundation's Grand Challenges in Global Health; ref. 1). Instead, this NCI initiative identifies and funds the search for answers to specific scientific questions, reflecting the belief that addressing specific and intractable problems can inspire the most outstanding work in science.

Toward this effort to identify important but unanswered scientific questions, the NCI launched the Provocative Questions Project website (2) and gathered questions from the cancer research community. Concurrently, in a series of workshops across the country,

an assembled group of scientific leaders deliberated on potential questions and selected 24 Provocative Questions questions to provide the basis of the Provocative Question's Funding Opportunity Announcements (FOA; ref. 3) in October 2011. As noted on the website, these questions do not represent the scope of NCI's priorities in cancer research, but serve to probe and challenge cancer researchers to deliberate about problems in key areas of cancer research that are significant but have been neglected.

Contemporaneous with the introduction of the Provocative Questions Project, an independent undercurrent of thought-provoking publications appeared. These publications simultaneously call for a reexamination of priorities and strategic approaches across different health-related disciplines, as the conduct of scientific research (and thinking) must adapt quickly to an evolving technological, demographic, and budgetary landscape. For example, in their essay on 21st century public health, Lang and Rayner lamented the need to revamp the practice of public health and alter the public's misconception of the field by reminding the audience of the inter-relationship between health and societal progress (4). Furthermore, they advocated for the embracement of ecological public health as essential to progress instead of its abandonment or neglect in times of economic hardships (4). Coincidentally, epidemiology, a discipline at the heart of public health, is undergoing a similar rethinking. The field, opined Michael Lauer, Director of the Division of Cardiovascular Sciences of the National Heart, Lung, and Blood Institute, is in need of a "creative transformation" to include refocused scientific questions, incorporation of technologies, centralized governance, cross-discipline collaboration, and clinical trials embedded in registries (5). In tandem, the Epidemiology and Genomics Research Program (EGRP) at NCI led a strategic planning "longitudinal" meeting, *Trends in 21st Century Epidemiology*:

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From *Scientific Discoveries to Population Health Impact* in December 2012 to invigorate 21st century epidemiologists (6, 7). From the NCI's workshop, several recommendations emerged for the epidemiology community to consider. These recommendations, published elsewhere in this special edition (see Khoury and colleagues 2013), include (i) extending the reach of epidemiology beyond discovery and etiologic research to include interdisciplinary/multilevel evaluation, implementation, and outcomes research; (ii) transforming the practice of epidemiology by moving towards more access and sharing of protocols, data, metadata, and specimens to foster collaboration, to ensure reproducibility and replication, and accelerate translation; (iii) expanding cohort studies to collect exposure, clinical and other information across the life course and examining multiple health-related endpoints; (iv) developing and validating reliable methods and technologies to quantify exposures and outcomes on a massive scale, and to assess concomitantly the role of multiple factors in complex diseases; (v) integrating "big data" science into the practice of epidemiology; (vi) expanding knowledge integration to drive research, policy and practice; (vii) transforming training of 21st century epidemiologists to address interdisciplinary and translational research; and (viii) optimizing the use of resources and infrastructure for epidemiologic studies. Echoing across these intellectual discourses is a concerted exhortation for adaptation of changes (e.g., disruptive technologies) and optimizing resources to evolve constructively and ensure relevance and continued contribution to society.

The current fiscal constraints for funding scientific research, however, dampens enthusiasm for the translation of these ideas into actions as budgetary constraints act as a major disincentive for expanding or extending research. Nevertheless, a resource-scarce environment necessitates greater resourcefulness and innovation. Although receiving less attention, the Provocative Questions Project's second purpose is to experiment with an innovative funding mechanism that permits investigators to "propose intriguing questions in cancer research that need attention but would usually find it difficult to get" (1). In the initial FOAs, \$17 million were dedicated to fund awarded Provocative Questions proposals. The NCI received approximately 750 applications in response to the Provocative Question's Request For Applications (RFA). In reaction to this overwhelming response from the scientific community, the fiscal year 2012 budget dedicated to funding Provocative Questions projects increased to \$22 million.

While the Provocative Questions Project does not focus on particular scientific disciplines, Dr. Varmus and the NCI leadership recognized the contributions of epidemiology in cancer. In a 2011 town hall meeting (8), Dr. Varmus stated, "I expect to see a pretty dramatic revolution in epidemiology... defining cancers by genetic subsets. I expect to see molecular tools brought more forcefully into the realm of cancer diagnosis... talking

about ways to discriminate among early lesions and precancerous lesions that may have malignant potential". Examination of the Provocative Questions applications received in response to the initial RFAs revealed that there was an underrepresentation of applications submitted that were epidemiologic in nature. For the purpose of this commentary, we broadly defined epidemiologic research as research conducted on human populations to understand determinants of cancer occurrence and outcomes. Of the total 748 applications, only 40 (5%) of the applications were from population scientists and referred to the NCI's Division of Cancer Control and Population Sciences (DCCPS), Fig. 1. These statistics are grossly lower than the typical number of applications received by NCI and referred to DCCPS annually. For example in fiscal year 2012, NCI received 10,448 competing applications for funding, and approximately 14% ($N = 1,509$) were related to population sciences and referred to DCCPS. This suggests that cancer epidemiologists might not have fully capitalized on this new funding mechanism and opportunity.

The success rate for funding of epidemiology-related Provocative Questions proposals was slightly higher comparatively to the proportion of applications. The NCI awarded 57 applicants whose research individually sought to answer one of the 24 provocative questions. Population sciences research represented 9% ($N = 5$) of the 57 awarded applications (Fig. 1). The majority of the Provocative Questions applications referred to DCCPS were responding to 3 Provocative Questions questions: (i) How does obesity contribute to cancer risk? (PQ-1); (ii) what environmental factors change the risk of various cancers when people move from one geographic region to

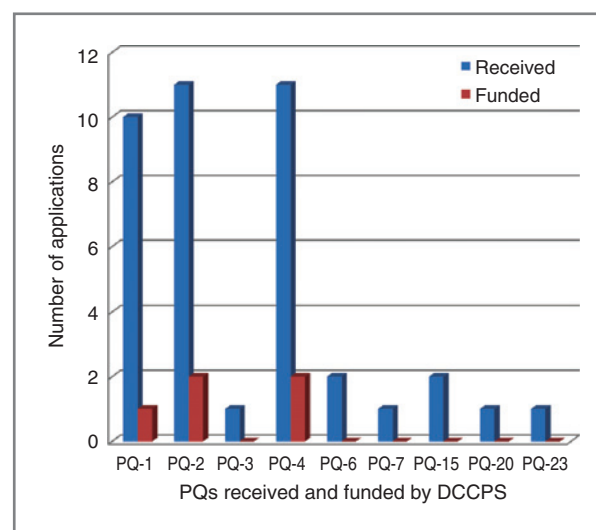


Figure 1. Applications received from the initial announcement of the Provocative Questions (PQs) Project that were referred to and funded by the NCI, Division on Cancer Control and Population Sciences (DCCPS). The Provocative Questions from the initial announcement can be found at: <http://provocativequestions.nci.nih.gov/rfa-archive>.

Table 1. List of current 24 provocative questions by group and thematic focus

Provocative questions (PQ) group	Focus	Questions
Group A (RFA-CA-12-015 and RFA-CA-12-016)*	Cancer prevention and risk	<ul style="list-style-type: none"> • PQA1: What is the molecular mechanism by which a drug (such as aspirin or metformin) that is chronically used for other indications protects against cancer incidence and mortality? • PQA2: How does obesity contribute to cancer risk? • PQA3: How do cognitive processes such as memory and executive function interact with emotional or habitual processes to influence lifestyle behaviors and decisions, and can we use this knowledge to design strategies to change behaviors that increase cancer risk? • PQA4: As modern measurement technologies improve, are there better ways to objectively ascertain exposure to cancer risk? • PQA5: How does the level, type or duration of physical activity influence cancer risk and prognosis? • PQA6: How does susceptibility of exposure to cancer risk factors change during development?
Group B (RFA-CA-12-017 and RFA-CA-12-018)*	Mechanisms of tumor development or recurrence	<ul style="list-style-type: none"> • PQB1: Why do second, independent cancers occur at higher rates in patients who have survived a primary cancer than in a cancer-naïve population? • PQB2: As we improve methods to identify epigenetic changes that occur during tumor development, can we develop approaches to discriminate between "driver" and "passenger" epigenetic events? • PQB3: What molecular and cellular events determine whether the immune response to the earliest stages of malignant transformation leads to immune elimination or tumor promotion? • PQB4: What mechanisms of aging, beyond the accumulation of mutations, promote or protect against cancer development? • PQB5: How does the order in which mutations or epigenetic changes occur alter cancer phenotypes or affect the efficacy of targeted therapies? • PQB6: Given the difficulty of studying metastasis, can we develop new approaches, such as engineered tissue grafts, to investigate the biology of tumor spread?
Group C (RFA-CA-12-019 and RFA-CA-12-020)*	Tumor detection, diagnosis, and prognosis	<ul style="list-style-type: none"> • PQC1: Can we determine why some tumors evolve to aggressive malignancy after years of indolence? • PQC2: How can the physical properties of tumors, such as the cell's electrical, optical or mechanical properties, be used to provide earlier or more reliable cancer detection, diagnosis, prognosis, or monitoring of drug response or tumor recurrence? • PQC3: Are there definable properties of pre-malignant or other non-invasive lesions that predict the likelihood of progression to metastatic disease? • PQC4: How do we determine the significance of finding cells from a primary tumor at another site and what methods can be developed to make this diagnosis clinically useful? • PQC5: Can tumors be detected when they are two to three orders of magnitude smaller than those currently detected with <i>in vivo</i> imaging modalities? • PQC6: What molecular events establish tumor dormancy after treatment and what leads to recurrence?

(Continued on the following page)

Table 1. List of current 24 provocative questions by group and thematic focus (Cont'd)

Provocative questions (PQ) group	Focus	Questions
Group D (RFA-CA-12-021 and RFA-CA-12-022)*	Cancer therapy and outcomes	<ul style="list-style-type: none"> • PQD1: How does the selective pressure imposed by the use of different types and doses of targeted therapies modify the evolution of drug resistance? • PQD2: What molecular properties make some cancers curable with conventional chemotherapy? • PQD3: What underlying causal events - e.g., genetic, epigenetic, biologic, behavioral, or environmental - allow certain individuals to survive beyond the expected limits of otherwise highly lethal cancers? • PQD4: What properties of cells in a pre-malignant or pre-invasive field - sometimes described as the result of a cancer field effect - can be used to design treatments for a tumor that has emerged from this field or to block the appearance of future tumors? • PQD5: Since current methods to predict the efficacy or toxicity of new drug candidates in humans are often inaccurate, can we develop new methods to test potential therapeutic agents that yield better predictions of response? • PQD6: What mechanisms initiate cachexia in cancer patients, and can we target them to extend lifespan and quality of life for cancer patients?

NOTE: This grouping does not reflect any priority of PQs for review or funding purposes. Supporting information relating to the 24 PQs can be found at: <http://provocativequestions.nci.nih.gov/rfa>. *Letter of Intent in response to PQ's RFAs due on May 20, 2013.

another? (PQ-2); and (iii) Why don't more people alter behaviors known to increase the risk of cancers? (PQ-4). Successful Provocative Questions epidemiology-related proposals reflected this distribution (Fig. 1).

Some of the remaining 21 Provocative Questions posed could have leveraged epidemiologic methods; unfortunately, these received very few applications from population scientists. Several reasons may explain the lackluster number of Provocative Questions applications from the cancer epidemiology community. Population-based research is costly and it is conceivable that the original funding allocated for the Provocative Questions Project may have deterred some epidemiologists from applying. However, as mentioned earlier, the NCI leadership devoted more funding to the initial round to fund additional meritorious Provocative Questions proposals.

Another reason for the lower number of epidemiologic applications may be that the 24 provocative questions originally identified may have been viewed as skewed heavily towards basic science and thus leaving a narrow opportunity for applications that uses epidemiologic concepts and methods to answer the questions. The reach and application of epidemiology should not be narrowed by this misperception. Epidemiology is circular by nature—findings can inform bench science which informs epidemiology and further downstream can influence translation of findings into policy and guidelines. As a central infrastructure, epidemiologic concepts and methods can be leveraged to address some of the basic science questions such as those in the Provocative Questions. Extend-

ing the boundaries of epidemiology as recommended by the NCI Workshop (see Khoury and colleagues 2013) requires creativity, provocativeness, resourcefulness, and collaboration across disciplines. Proposals to integrate basic or clinical studies within the framework of traditional epidemiologic studies, for example, could be submitted. Alternatively, epidemiologists can modify or adapt the current Provocative Questions to develop proposals with a more population approach or gauge the programmatic interests based on the questions to generate new research ideas. These proposals can be submitted under the omnibus investigator-initiated FOAs (9). Finally, the Provocative Questions Project is a dynamic initiative in which provocative questions are continually being developed.

Over the past year, NCI updated the original set of 24 Provocative Questions. The revised 24 Provocative Questions are categorized into 4 groups (group A–D) based on Provocative Questions theme (Table 1). For example, group A consists of 6 questions related to cancer prevention and risk while the questions of Group D relate to cancer therapy and outcomes. Cancer epidemiologists should think more broadly across the translational research continuum when reviewing the revised set of Provocative Questions as well as their research objectives. Collaborations between basic, clinical, and population scientists, for example, can extend the boundaries of traditional epidemiology to help unravel the answers to some of the Provocative Questions. Illustratively, the answer or answers to PQD3 "What underlying causal

events, for example genetic, epigenetic, biologic, behavioral, or environmental, allow certain individuals to survive beyond the expected limits of otherwise highly lethal cancers?" may benefit from such a trans/multidisciplinary collaboration. New approaches like integrative epidemiology, as advocated by Spitz and colleagues (10) can be applied to explore the mechanistic underpinnings of epidemiologic observations in cancer risk and outcomes.

For the current Provocative Questions process, NCI has issued 8 FOAs, using the RO1 ($N = 4$) and R21 ($N = 4$) funding mechanisms (11). The scientific scope of the application must correspond to one and only one Provocative Question in the group (Table 1). The next deadline for response to RFAs relating to the Provocative Questions Project is in May 2013. We encourage epidemiologists to collaborate with their basic science and clinical colleagues to take full advantage of this funding mechanism. Development of provocative questions for 2014 is underway, which may include new population science questions. Investigators should stay alert for subsequent Provocative Questions announcements.

Cancer epidemiology is at the cusp of a paradigm shift and several "drivers" have been influencing the field in the near decades (7). The drivers include: (i) collaboration and team science; (ii) methods and technologies; (iii) multilevel analyses and interventions; and (iv) knowledge

integration from basic, clinical, and population sciences (7). The Provocative Questions Project is one vehicle to enable the incorporation of these drivers into cancer epidemiologic research and part of a collective and fluid movement towards a transformation in health research. The provocativeness lies not only in the scientific questions, but also in the resourcefulness of the investigators to seize funding opportunities and to think in creative and transformative ways to get to answers that can have an impact on reducing the burden of cancer in populations.

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No potential conflicts of interest were disclosed.

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

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