Behavioral Oncology and the War on Cancer: Partnering with Biomedicine

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Abstract
The call for interdisciplinary research in the war on cancer has escalated over the past several years. Behavioral science has played a key role in cancer control, and several exciting opportunities exist and will develop with the ongoing significant advances made in biomedical science. The current article briefly reviews the maturity of behavioral science in the areas of prevention, early detection, and survivorship and how the partnership of behavioral and biomedical science can effectively impact cancer incidence, morbidity, and mortality.

Introduction
According to the American Cancer Society, there were over 1.4 million new cancer cases and 550,000 cancer deaths in 2008 (1). In a global population exceeding 6 billion in the year 2002, there were approximately 10.9 million new cancer cases, 6.7 million cancer deaths, and 22.4 million persons surviving from cancer diagnosed in the previous 5 years (2). In 2020, it is expected that the world's population will increase to 7.5 billion, with 15 million new cancer cases and 12 million cancer deaths. Since 1970, the number of cancer survivors has increased four-fold, with cancer survivors representing roughly 3.5% of the U.S. population and 5-year survival rates increasing into the 60% range. This raises issues related to long-term and late effects of cancer treatment and the realization that cancer survivors represent 16% of all new primary cancers (3).

Over the past decade, increased attention has focused on the role of behavioral science in the war against cancer, from prevention to survivorship. The National Cancer Institute (NCI) created the Division of Cancer Control and Population Sciences, and, within this Division, a formal Behavioral Research Program. The American Cancer Society created an intramural research program, the Behavioral Research Center, in addition to increasing attention to extramural funding of behavioral research. The AACR initiated a Task Force on Behavioral Science in 2004 to attempt to integrate behavioral science into the biomedical cancer research agenda. The American Association of Cancer Research initiated a Behavioral Research Program, in addition to increasing attention to extramural funding of behavioral research. The NCI's Translational Research Working Group was created to ''feature vigorous interactions across its research areas and facilitate collaborations between laboratory, behavioral, epidemiologic, and clinical scientists." In sum, the field of behavioral oncology has come of age, and behavioral researchers are eager to increase collaborations with the biomedical cancer research community.

In this Perspectives article, we share with our medical colleagues the promise of behavioral science in the areas of prevention, early detection, and survivorship, focusing on "translational" research, defined by the NCI's Translational Research Working Group as research that "transforms scientific discoveries arising from laboratory, clinical, or population studies into clinical applications to reduce cancer incidence, morbidity, and mortality" (4).

Behavioral Oncology across the Cancer Continuum
To best illustrate the current range of work and promise of behavioral science in translational research related to cancer, this article includes examples moving across the cancer continuum from prevention to early detection to cancer survivorship (4). In addition, there is ongoing behavioral research in areas with the potential to cut across the cancer continuum, and these are noted in the final section of the article.

Prevention
Tobacco use is the single greatest preventable cause of cancer mortality in the United States. Despite this, approximately one in four Americans are current smokers, and these rates are as high as one in two in the developing world. Behavioral science research has made important contributions to our understanding of the biobehavioral basis of nicotine dependence, has accelerated progress in the development of preventive and therapeutic interventions, and has generated an important evidence base for policy changes related to tobacco products and policies worldwide (5).

Evidence from animal models has identified adolescence as a critical period for susceptibility to the addictive effects of tobacco via the effects of nicotine on brain circuits, which regulate attention, affect, and executive cognitive function (6). Social researchers have long recognized the role of social norms on increased adolescent risk-taking behaviors from multiple behavioral science perspectives (7). The most effective programs to prevent smoking initiation in youth are those combining health communication strategies to alter normative beliefs and enhance perceptions of harm with behavioral treatments to enhance social and personal competence in resisting peer influences (8). These efforts are being extended to special populations of youth with medical and psychiatric comorbidities who may have increased susceptibility to tobacco use (9).

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Important advances are also being made in the treatment of tobacco use. More refined characterization of the positive and negative reinforcing effects of smoking (10) and the validation of preclinical and human models to screen promising medications (11) have greatly facilitated treatment development efforts. Studies have also identified genetic factors in smoking persistence as well as psychological factors that mediate treatment efficacy (12). Development of efficacious therapeutic approaches for special populations is still urgently needed (13, 14).

One clear example of how basic and behavioral scientists can engage might involve parallel investigation of behavioral phenotypes related to nicotine dependence in rodents and humans that harbor a protective or risk allele for dependence (15). Rodent studies can provide an important complement to the human research for characterizing the neurobiological basis of behavioral phenotypes beyond what can be accomplished by studying humans only, whereas the human component can clarify the clinical significance of the preclinical research findings.

This trajectory of bidirectional research involving animal models→human treatment illustrates bench-to-bedside translational work, and the NIH multiple Principal Investigator mechanism can be used to support such exciting integrative proposals in this research domain and others in cancer prevention.

Behavioral scientists working jointly with policy researchers have developed the critical science base for reducing tobacco harm through aggressive policy legislation. For example, interdisciplinary research has led to the validation of novel biomarkers of tobacco harm, which are being applied to the study of new potentially reduced exposure tobacco products (16, 17). Such efforts are being expanded to the international level to combat increased international marketing efforts of U.S. tobacco companies (18).

As we extend translational research to include "community" applications, recent work on social networking provides fertile ground for intervention (19). Findings indicate that smoking behavior does indeed spread through close and distant social ties and groups of interconnected people stop smoking in concert. Such work has significant implications for clinical and public health interventions to reduce and prevent smoking.

This area of tobacco research shows the potential of collaboration with the history of the Transdisciplinary Tobacco Use Research Centers (20). This P50 mechanism, cofunded by the NCI and National Institute on Drug Abuse in 1999, has supported transdisciplinary groups of scientists across fields of epidemiology, behavioral science, molecular biology, genetics, neuroscience, and marketing, among others. These centers have been extremely productive in moving research forward from biobehavioral research to community interventions (12).

Maintenance of a healthy weight throughout life is now considered one of the most important ways to protect against cancer (21). The prevalence of overweight and obesity in the United States and globally has increased markedly in the past decade (21, 22), and excess weight is also associated with the development of other major chronic conditions, including diabetes and heart disease (23). The major behavioral contributors to overweight and obesity are excess food consumption and inadequate physical activity (23). Diet, physical activity, and weight are important both to cancer etiology and survival and prevention of recurrence (see below under Cancer Survivorship). Behavioral science research has long been critical to advances in understanding how to promote healthy eating and activity for primary prevention and cancer survivorship (24).

The Women's Health Initiative (WHI) Dietary Modification Trial, the largest ever randomized trial of dietary changes hypothesized to prevent cancer, was substantially informed by state-of-the-science behavior change strategies, resulting in impressive sustained diets that were low in fat and high in fruits, vegetables, and grains (25). Although the WHI low-fat dietary pattern intervention did not reduce the risk of invasive breast cancer (26) or colorectal cancer in postmenopausal women (27), ovarian cancer risk was lower in the intervention than in the comparison group (28). The findings of the WHI leave open many questions, including the effect of combined diet and physical activity on cancer prevention; such issues will require the involvement of behavioral researchers as future investigations unfold.

Growing evidence suggests that the problem of obesity is powerfully influenced by social and built environment factors, such as the availability and price of healthful food (29–31). Disparities in the availability of healthful, affordable foods with lower access in minority, poor, and rural communities have been increasingly well documented (31, 32). Physical activity is also influenced by the neighborhood environment. Research on neighborhood walkability suggests that people are more physically active when they live in neighborhoods with higher residential density, a mixture of land uses, recreational facilities, connected streets, and enjoyable scenery (33, 34). Public health policy solutions are being proposed and enacted (31), among them the introduction of calorie labeling in chain restaurants in several large cities in the United States. These strategies will require timely evaluation beginning with behavioral science and ultimately linking with health outcomes research and biomedical outcomes.

A developing area of collaboration involves the development and use of preventive or therapeutic cancer vaccines. Currently, the human papillomavirus vaccine is available for the prevention of cervical cancer, and continuing attention to knowledge of the vaccine and assessment of barriers to uptake is needed to significantly reduce the incidence of cervical cancer. There is some early indication that the general population is aware of the vaccine, but a much smaller percentage is aware of its benefits (35). Moreover, differential access to health information may contribute to use or nonuse of the vaccine and ongoing cervical cancer disparities. In addition, issues such as patient-health care provider trust may play a role in vaccine uptake as well (36).

**Cancer Screening**

The U.S. Preventive Services Task Force recommends regular breast cancer screening by mammography, cervical cancer screening by PAP test, and colorectal cancer screening by fecal occult blood test, flexible sigmoidoscopy, colonoscopy, or double-contrast barium enemas (37–40). Although over 15,000 lives could be saved each year if all eligible Americans received appropriate screening, only 78% of women ages ≥18 years reported PAP tests within the previous 3 years and <70% of women ages ≥40 years reported mammograms within the previous 2 years (37–40). The data for colon cancer screening are even more discouraging (38, 40). Screening behaviors face the additional challenge of repetition at recommended intervals. The recent increased interest in risk perception in cancer (41) links advances in screening technology with needed behavior change. There is evidence that although not all individuals realize their colon cancer risk (42), there seems to be an association between risk perception and screening behavior (43). Thus, ongoing work to determine how risk
is best presented and how risk is processed by patients in medical situations will hopefully maximize screening adherence and the use of developing technologies (virtual colonoscopy) to detect cancer in its early stages. Such work is arguably even more critical in individuals without a family history who may feel at low risk and dismiss the need for cancer screening.

Thus, screening tests have been developed and are effective in saving lives, if such tests are recommended by health care providers and adhered to by the public. In this case, the role for behavioral science partnering with biomedicine to change the behavior of health care providers and the public to increase cancer screening behaviors is clear and can save lives or extend survival.

In addition to the need for behavior change in cancer screening on a population level, part of the promise of the recent genetic revolution has involved the possible public health effect of the receipt of genetic risk information. One motivation of offering mutation testing to individuals or offering testing for other types of biomarkers is to stratify risk levels so that more aggressive prevention and surveillance methods can be instituted early and targeted specifically to these populations. The ultimate goal is to increase cost-effectiveness of medical care by providing health care resources to those who stand to benefit most from these efforts.

Furthermore, the discovery of low-penetrant genes that may combine to increase risk or combine with environmental risk factors such as diet to increase risk for cancer is anticipated to contribute to improved cancer risk stratification and risk reduction. Most cancers arise from small contributions of many different genes, which may work in combination with one another or with environmental factors (e.g., diet) or behavioral practices (e.g., smoking; ref. 44). Some aspects of genetic risk assessment (e.g., BRCA1/BRCA2 testing) are being routinely integrated into health care; however, other aspects (single nucleotide polymorphisms and gene-environment risk factor testing) are not yet part of routine health care but are expected to become a common practice. Thus, the possible effect of the provision of genetic risk information on prevention and surveillance practices may be great. Behavioral science is central to translational research in this area.

Before incorporating these tests into routine clinical practice, it will be important to understand the degree to which genetic risk information alters cancer screening and surveillance practices. Indeed, as has been pointed out in previous discussions of the effect of genetic risk information on behavioral change (45), this information can both increase and decrease the likelihood of desired health behavior change. For example, a negative BRCA1/BRCA2 test result can provide false reassurance, lower perceptions of risk, and thereby reduce the likelihood that the individual will pursue recommended mammography.

The largest empirical literature exists on the effect of mutation testing for widely penetrant genes, such as BRCA1/BRCA2, CDKN2A/p16, and mismatch repair genes associated with Lynch syndrome on cancer screening practices, including colonoscopy, transvaginal ultrasonography, endometrial sampling, breast self-examination, and mammography/magnetic resonance imaging screening. These studies have suggested that genetic testing results in more appropriate screening and surveillance practices after disclosure (46–49). That is, carriers increase their use of screening and noncarriers reduce their frequency of engagement in screening to fall into line with recommendations. The findings are quite consistent, suggesting that mutation testing has a significant effect on screening and surveillance. Recent evidence suggests that there may be some international variation in these effects, at least among BRCA1/BRCA2 carriers (50).

To date, there have been no studies evaluating the effect of biomarker or genetic polymorphism feedback provided with or without environmental risk information on cancer screening and surveillance practices. As the significance of these biomarkers and polymorphisms becomes better understood, it will be important to evaluate their effect on health behavior. One example of this type of study has recently been published by Myers and colleagues (51) who examined the effect of MTHFR gene and dietary folate feedback on perceptions of colorectal cancer risk. Participant knowledge about genetic and environmental risk assessment and colorectal cancer screening, and perceived social support for colorectal cancer screening, increased significantly from baseline.

Cancer Survivorship

Cancer survivorship research encompasses a large portion of the cancer control continuum, ranging from diagnosis through end-of-life care (52). A critical area for translational research in cancer survivorship involves treatment decision making (53, 54). Patients and survivors are often presented options with regard to treatment and follow-up care plans. These options can be associated with different risk for acute side effects, late and long-term effects, and disease recurrence and long-term survival. Consequently, risk communication and comprehension, often under conditions of high uncertainty and distress, are critical elements of the decision-making process. Risk information can be presented in different ways, patients have preferences for different methods of presentation (55), and the method of presentation may affect subsequent decisions (56, 57). Although a large amount of literature has examined decision making and risk communication outside of the health domain (58, 59), it is relatively recently that the relevance of this research to the oncology setting has been recognized. Efforts are under way to translate what is known about decision making and risk communication into clinical applications that can foster optimal decision making and greater decision satisfaction in cancer patients and survivors (53, 60).

Another essential component of survivorship care is intervention to prevent recurrent cancers and late effects or to minimize mortality and morbidity associated with these outcomes (52). Cancer diagnosis and treatment are associated with a host of physical and psychological morbidities. Identification of variables linked to the risk for these morbidities has been a significant research focus. Both genetic and treatment-related variables have recently come under scrutiny. For example, recent work has noted an increased risk for psychological symptoms with taxane-based chemotherapies, increasingly used for the adjuvant treatment of early and locally advanced breast cancer (61). Patients may have not only more significant emotional distress during treatment but slower psychological recovery after treatment, with recovery taking an average of 2 years after treatment. Additionally, the apolipoprotein E (APOE) gene, as well as other genetic polymorphisms, has been linked to risk for cognitive impairment in cancer survivors treated with cytotoxic chemotherapy (62). Although these findings have not been translated into clinical applications to reduce risk for cognitive morbidity in cancer survivors, their translational potential is evident. Chemotherapy treatment protocols could be modified to account for APOE gene status, or cognitive rehabilitation strategies (63) could be targeted toward...
APOE gene carriers to minimize cognitive morbidity. Similarly, recent research suggesting genetic risk factors for depression and stress vulnerability in the general population (64) may have high translation potential in the cancer survivorship setting. Identification of genes potentially linked to psychological morbidity in cancer survivors can potentially increase efficient use of scarce clinical resources and suggest what types of interventions might be most successful with specific individuals.

Finally, minimization of recurrence risk is a paramount concern of survivorship care. Observational research with cancer survivors has suggested a link between risk for recurrence and/or survival and weight gain and/or obesity (65, 66), physical activity (67), diet (66, 68, 69), and smoking (70, 71). These observational data have led to efforts to develop behavioral interventions to promote dietary change (72, 73), increased physical activity (72, 74), and smoking cessation (75, 76) in cancer survivors.

Cross-Cutting Research Areas

There are several research areas with key collaborative potential that cut across the cancer continuum. Enrollment for clinical trials has been a long-standing challenge in prevention, early detection, and treatment, with estimates noting only 5% of patients with cancer participating in clinical trials (77). Surprisingly, there are few data available on the effect of cancer care environments and protocol characteristics on clinical trial participation (77). In addition, comprehensive reviews (78) of recruiting underrepresented populations to cancer trials note numerous weaknesses in publications to date, including representativeness, reliability, and validity of data collection methods, potential for bias, and data analysis problems. A focus on developing and testing models such as the Accrual to Clinical Trials framework among underrepresented populations holds much promise (79), as do behavior change strategies that may affect provider- and patient-related and programmatic factors. Collaborative work in this critical area to advance clinical care may not only affect accrual but also decrease accrual time, lighten staff workload, and decrease overall resource use dedicated to patient accrual across clinical trials.

One developing area of possible collaborative interest is the area of pharmacogenetics or, more broadly, personalized medicine. As reliable molecular signatures are discovered and pharmacogenetic-based therapeutics are translated to applications, we need more information on the knowledge and acceptance of such approaches by patients. Very preliminary work suggests that patients are receptive to the idea of targeted therapeutics but have concerns about privacy, accuracy of test results, and payment issues (80). It is also unclear whether patients might be more willing to pay to apply such approaches for certain diseases (chronic versus acute conditions, those conferring high risk of mortality or morbidity, etc.). As personalized medicine is more deeply incorporated into health care, patient needs, knowledge, and risk perceptions will be critical to assess to achieve high acceptance of these more tailored approaches.

Finally, related to the above examples and others across the cancer continuum, health informatics research is key in making progress in all stages of the cancer continuum and translating findings from the laboratory to eventual clinical application. This is an area where successful ongoing collaboration already exists with the work of the NCI Centers of Excellence in Cancer Communication Research (CECCR; ref. 81). The CECCR Initiative, funded in 2003 and refunded in 2008, focuses on interdisciplinary efforts to “translate theory and programs into practice” and includes projects on smoking cessation, increasing nutritional intake, and developing formats for presenting risk information and statistical information. Other work focuses on how to present genetic information that may be best understood by the lay public. These projects move from prevention through survivorship and relate to the issues of clinical trial participation and personalized medicine noted above. At issue is how best to take biomedical discoveries and prevention and treatment options and present them in ways best understood by the intended audiences.

One key issue is how basic scientists and clinicians can identify and engage with behavioral scientists to realize the potential described in this article. Perhaps the most efficient route is to access the NCI-funded Cancer Centers programs.6 With 65 funded Centers, 40 of these are designated Comprehensive Centers and necessarily have programs including behavioral science (the other 25 funded Centers may or may not have this area as a key component). These programs may have different formal titles but focus on cancer prevention and population sciences linking with basic and clinical sciences. Other ways of linking with behavioral scientists is at the institutional level with departments of behavioral science, such as psychology or psychiatry, or schools of nursing or public health. Finally, many professional organizations that include basic scientists and clinicians (American Society of Clinical Oncology, AACR, and ASPO) include a substantial number of behavioral scientists accessible through task forces or special interest groups. An additional option is to access one of the cooperative groups in oncology, such as the Eastern Cooperative Oncology Group or the Southwest Oncology Group, although such groups may have more of a specific focus on quality of life issues as they relate to clinical trials. Finally, there are stand-alone behavioral science organizations with cancer special interest groups (Society of Behavioral Medicine) or Divisions devoted to health psychology (Division 38 of the American Psychological Association). Once contact is made, typically “outreach” from a basic scientist or clinician is greeted warmly by behavioral scientists, with a high likelihood of engagement. The potential for enriching behavioral research with basic or clinical scientists is appreciated and well received.

Biomedical science has clearly made significant advances in the war on cancer over the past several decades. Behavioral science has done likewise, moving from broad, descriptive studies of psychological distress in cancer patients (82) to more refined descriptive work and targeted interventions, guided by medical and technological advances in the prevention, early detection, and treatment of cancer. The current emphasis on translational and interdisciplinary research will hopefully enhance the productive partnership of behavioral science with biomedical science as together we work on reducing cancer incidence, morbidity, and mortality.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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