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Translational Cancer Research: Balancing Prevention and Treatment to Combat Cancer Globally

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Abstract

Cancer research is drawing on the human genome project to develop new molecular-targeted treatments. This is an exciting but insufficient response to the growing, global burden of cancer, particularly as the projected increase in new cases in the coming decades is increasingly falling on developing countries. The world is not able to treat its way out of the cancer problem. However, the mechanistic insights from basic science can be harnessed to better understand cancer causes and prevention, thus underpinning a complementary public health approach to cancer control. This manuscript focuses on how new knowledge about the molecular and cellular basis of cancer, and the associated high-throughput laboratory technologies for studying those pathways, can be applied to population-based epidemiological studies, particularly in the context of large prospective cohorts with associated biobanks to provide an evidence base for cancer prevention. This integrated approach should allow a more rapid and informed translation of the research into educational and policy interventions aimed at risk reduction across a population.

The Tradition of Translational Cancer Research

Recent decades have yielded unprecedented advances in understanding the biological mechanisms underlying cancer development and progression. Translation of this knowledge to the clinic promises new treatments tailored to exploit the molecular Achilles heel of a patient's tumor (1–3). This has been described as personalized medicine, precision medicine, or, more conservatively, as stratified medicine and is popularized in the term "bench-to-bedside" research. In the cancer field, this is what is generally understood by translational cancer research. Thus, molecularly informed treatment points to marked improvements in patient outcomes. However, cancer challenges are emerging that need additional and complementary solutions.

Because of population growth, increasing life expectancies and changes in underlying cancer incidence, the annual number of cases continues to rise globally, being expected to almost double in the next 20 years (4). Currently, close to half the people living within five years of a diagnosis (13.6 million) are from the richest countries, which comprise only one sixth of the world's population (840 million) (5). Allied to this human burden is the spiraling cost of cancer therapy, which weighs ever more heavily on national budgets (6). However, the largest relative increases in new cases in the coming decades will occur in low-income countries (7), where even affordable and effective cancer treatments remain largely unavailable and demands on inadequate cancer services will only continue to grow (8). Lower income countries therefore face a "double burden" as they transition to higher numbers of cancers on top of preexisting burdens from communicable diseases and malnutrition (7).

As a consequence, there is an urgent need for a global perspective on prevention strategies to complement the emerging benefits of new treatments in high-income countries and the improved access to existing treatments in low- and middle-income countries. The shared nature of a number of risk factors for noncommunicable diseases means that benefits from prevention will stretch beyond the confines of cancer (9).

Here, we do not attempt to address specific cancer prevention and control priorities in low- and middle-income countries, which has been covered elsewhere (10,11). Rather, we focus on how the latest advances in understanding the mechanisms of carcinogenesis offer a pathway to the identification of cancer risk factors and prevention strategies, which in turn may provide the improved evidence base for more effective cancer control in low- and middle-income countries. Specifically, we suggest an opportunity for translational cancer research to be "two-way"; the same foundation and novel technologies of basic science being used to develop new treatments should be applied to study the causes of cancer and its prevention, both through the avoidance of carcinogenic exposures and through the early detection (including screening) and treatment of disease. In providing reliable information on the relationship between exposures and risk, this integrated approach should therefore facilitate and underpin the translation of research findings into a range of different interventions (eg, educational, behavioral, policy-based) aimed at risk reduction across a given population.

The promise of primary prevention is based on recognition that most cancers have a lifestyle or environmental cause, and therefore in principal more than 50% could be prevented if the specific risk factors were identified and exposures controlled effectively (12–15). Primary prevention successes exist, with declining lung cancer rates following reductions in smoking, although these improvements are mainly limited to a few high-income countries (16,17), plus the advent of vaccines against hepatitis B virus and human papillomavirus (HPV) to prevent liver and cervical cancers (18,19). However, primary prevention must be founded on identification of risk factors, and, although much progress has been made (20), for some common cancers (eg, prostate, kidney, pancreas, brain, hematological malignancies) the identity of major risk factors remains largely obscure.

The long induction time of many precancerous lesions and cancers, stretching over many years if not decades, allows early detection through screening and consequent prognostic improvements for cancers such as cervix, breast, and colorectal (21). However, this strategy of secondary prevention is frequently hampered either by the inability to detect many types of cancer at early enough stages to permit successful treatment (eg, kidney, pancreas, ovary, brain, liver) or the inability to discriminate between screen-detected lesions that would or would not have progressed to malignancy (eg, for breast and prostate); under the latter circumstances, patients may be subject to overtreatment (22,23).

There is now a remarkable opportunity to address the apparent impasse in both primary and secondary prevention by applying advances in the understanding of molecular carcinogenesis and the associated molecular tools to translational research. One must ask not whether but how the advances in basic science leading to new avenues for cancer treatment might also provide a way forward in relation to cancer causation and prevention globally (Figure 1).
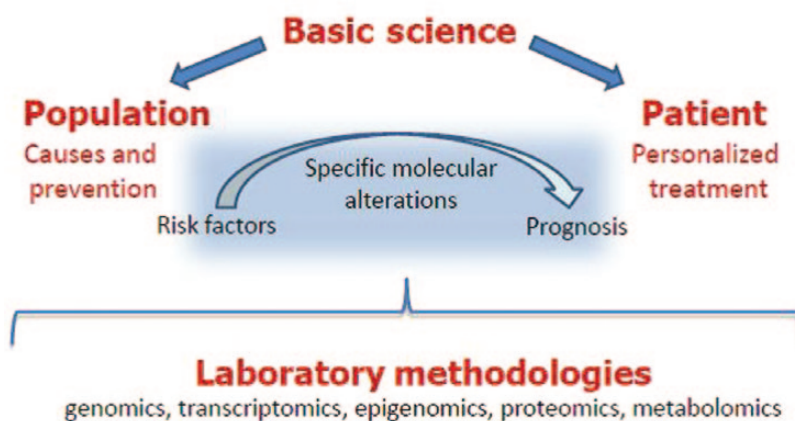

Figure 1. Two-way translational cancer research.

New Opportunities

The "omics" technologies used to probe the genome, epigenome, transcriptome, proteome, and metabolome offer opportunities to identify individual, groups, or patterns of biomarkers applicable to cancer prevention. Among the opportunities are: improved and novel approaches to exposure assessment, stratification of cancer cases by molecular subtype, elucidation of mechanistic pathways including "driver" mutations related to defined exposures, identification of molecular markers for early detection or prognosis, and use of biomarkers to evaluate the impact of interventions (24,25).

An outstanding challenge in studying etiology has been the inability to measure environmental and lifestyle exposures with the same precision or scope as for genetic analyses, leading to calls for a systematic determination of the human exposome to match the determination of the human genome (26,27). Indeed, while there have been large investments into novel technologies to define the underlying genetic causes of cancer (the human genome project and genome-wide association studies), there remains a substantial lag in investment to identify the major causes of cancer—namely environmental and lifestyle factors. Recently, new insights have been gained through application of the above-mentioned technologies. For example, Stransky et al. (28) performed whole-exome sequencing on head and neck tumors, revealing a different mutation rate and pattern in relation to HPV and smoking. Chronic low level benzene exposure was linked to different patterns of global gene expression (29) and several proof-of-principle studies used microarrays to investigate the impact of tobacco smoking on the transcriptome and epigenome (30,31). The comparison of metabolic profiles of colorectal cancer patients and matched control patients by high-resolution mass spectrometry led to the indication of unexpected risk factors for the disease that have been linked to inflammation (32). Exciting advances are also being made in the ability to characterize individual dietary exposures. For example, an initial broad-based metabolomics approach resulted in the development and validation of a new urinary biomarker for citrus fruit consumption (33). In this manner, innovations in measurement and data collection offer potential in unraveling the complex interactions between genetic and nongenetic factors.

The recognition that tumor classification requires integration of molecular characteristics for cancer treatment has its corollary in the field of etiology and prevention (34). Notably, the opportunity to subclassify tumors by their molecular profile means risk factors may be evaluated for specific molecular subgroups, offering the possibility to reveal associations cleared of the fog of heterogeneity (35,36). The potential of this strategy was demonstrated in a case-cohort study of colorectal cancer, where the risk associated with acrylamide exposure was specific to patients with mutations characteristic of acrylamide in the *K-ras* and *APC genes*; the authors noted the need for caution in interpretation of these data, particularly given the number of subgroup analyses (37). Indeed, the molecular subclassification of tumors brings its own challenges of statistical power, implying that only the largest epidemiological studies will be suited to such an approach. This approach will also need to discriminate interpatient differences in driver and possibly passenger mutations relevant to etiology from the wider inter- and intratumor genetic and epigenetic heterogeneity (38–40). Further large-scale sequencing of the cancer genome and epigenome will refine the diversity and complexity of mutational and epigenetic processes underlying carcinogenesis, as well as molecular signatures associated with exposures.

An especially important development would be the identification of preneoplastic conditions at a point when medical treatments or lifestyle changes may cure or stop disease progression. The potential to reverse epigenetic alterations provides a basis for hope (25). Such an approach would be more analogous to the effective screening approaches in cardiovascular diseases (ie, detection and medical treatment of predisposing conditions such as hypertension, hypercholesterolemia), which are far less invasive and expensive than cancer screening approaches where surgical removal of lesions is mostly required.

Cancer chemoprevention has seen modest success to date with the use of supplementation, albeit reduced risks of colon and some other cancers have been reported with nonsteroidal anti-inflammatory agents (41). It may be of interest to revisit chemoprevention by tailoring the treatment either to the genetic profile of the individual or (pre-)neoplastic lesion (42). In addition, mechanism-based biomarkers also have promise as intermediate endpoints in intervention studies, providing justification for subsequent larger, longer-term studies with clinical endpoints (43).

In each of the above areas, the application of molecular sciences and associated biomarkers permits a link from experimental models through to epidemiology, notably in establishing biological mechanisms for exposure-disease associations at the population level. Experimental data provide indications that duration of exposure and dose are important in relation to gene expression changes and indicate how "omics" technologies could be "reverse engineered" to inform primary prevention (44). In time it is likely that this "common soil" of mechanistic research will contribute to a stronger basis for hazard identification and risk assessment (45).

Tools lie idle without materials to work on. Research designs for treatment studies are feasible because of the relative ease of collecting information on patients in clinical settings. Excitingly, large prospective cohort platforms with well-characterized biospecimens provide the ideal context to study the long prediagnostic period, and recent investments in these now enable studies relevant to etiology and prevention (46,47). Recognition that early life exposures are precursors to cancer later in life points to further development of cohort platforms and innovative designs for studies over the life course (48,49).

Consortia have demonstrated a new commitment to global collaborations that deliver the large human studies needed to disentangle the biological complexity of cancer. The development and sharing of new high-throughput methods, genomic databases, bioinformatics, and biostatistical tools therefore allows advances in laboratory sciences to be applied in epidemiological studies with efficient processes to manage and interrogate enormous databases. Investigators have an increasing ability to integrate molecular data across different platforms to obtain comprehensive portraits of cancer subtypes that may reveal etiology and prevention opportunities (eg, International Cancer Genome Consortium [icgc.org], Cancer Genome Atlas Network [cancergenome.nih.gov]). Recent large-scale mutation analysis by an international collaborative team identified diverse (more than 20) mutation signatures among 30 cancer types (50). Extension of some of these approaches, particularly the establishment of prospective cohort studies, to low- and middle-income countries will provide valuable evidence for cancer prevention beyond the borders of the richer parts of the world.

Strategies to Heighten Impacts

To achieve the double benefits that could arise from translational cancer research involving both prevention and treatment, decisive action is needed at several levels.

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First, the cancer research community must seize the opportunity to apply its tremendous skills and capacity to provide the evidence base for the next generation of cancer prevention that can lead to major impacts on a global scale. A balanced and integrated approach that extends the reach and impact of the basic sciences would both complement and strengthen treatment-oriented research. In this regard, there is a requirement for the optimal use of epidemiological resources as well as further technical and methodological development to ensure the laboratory methods are suited to population studies and related biobanks to gain maximum utility (51,52).

Second, there is a need to foster interdisciplinary research. This will require capacity building by training a new generation of researchers who work in teams involving both laboratory and population sciences and who have access to the necessary tools and infrastructure. There is a need for strategic recognition of the benefits of closer working relationships forged through shared planning, research, and resources across all the relevant disciplines. The building and supporting of such teams will yield benefits at the local level, as well as through consortia at the global level, as programs develop in low- and middle-income countries.

Third, clear communication by research leaders will allow all partners and stakeholders to embrace the need for studies of causes and prevention. With prevention not being done solely in the medical care system, the broader integration that is needed will allow new stakeholders to join (eg, experts in environment, food, water, health promotion, etc.). This can overcome one of the barriers to prevention research, which is that the private sector has favored the commercialization potential of only clinical interventions, whereas innovative products and services can be envisioned that are of global reach and interest. More active involvement of the general public and public agencies will also aid in communication as more effective ways are found to detect and report the benefits of prevention research.

Fourth, building on these strategies, advocacy is needed to convince politicians, policymakers, and funding agencies to prioritize translational research into the causes and prevention of cancer on a scale not yet seen in comparison with bench-to-beside research. Champions of prevention are needed to complement the valuable and effective advocacy of cancer survivors. Molecular cancer epidemiology requires large and long-term investments in adaptation of new technologies for application to large-scale population studies, as well as prioritization of infrastructure support to cohorts, biobanks, cancer registries, and other resources. Historically, there were few funders for such work, given the lack of obvious commercial benefits, but a strategic approach can lead to huge gains in health and a broad sharing of benefits. Public and charitable funding should be directed to translational prevention research to compensate for this relative lack of market value. The longer-term benefits of prevention in reducing the economic cost of cancer will provide a large return on this investment (53), in addition to the undoubted value in terms of reducing the social and emotional burden of the disease.

Conclusion

In summary, translational cancer research stands at an exciting but critical point in time. It will not be possible to treat our way out of the cancer problem, either in aging Western societies or in poorer countries where health services are least able to serve the growing number of patients. What is needed now is a concerted effort to apply the remarkable advances in basic science to contribute to cancer prevention, with an aspiration of reducing cancer burden and the associated global inequalities in health worldwide.

Notes

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