

Conquering Cancer in Our Lifetime: New Diagnostic and Therapeutic Trends

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Cancer has now surpassed cardiovascular disease as the number 1 killer of both men and women (1). Approximately 1 of 3 of us will develop cancer during our lifetime. Despite the war on cancer declared more than 40 years ago by President Richard Nixon, the battle has not yet been won, despite a substantial investment in resources. The US National Cancer Institute has an annual budget of approximately \$5 billion and since 1971 has spent >\$90 billion on the science, treatment, and prevention of cancer (2). The pharmaceutical industry has invested several times that sum in developing anticancer drugs and antibodies. Small-molecule inhibitors such as imatinib have changed the natural history of chronic myelogenous leukemia and gastrointestinal stromal tumor. Antibodies that include rituximab and trastuzumab have improved overall and long-term survival for patients with lymphoma and breast cancer, but many new targeted agents approved by the US Food and Drug Administration have extended progression-free survival times by only a few months. Of greater concern is that only 1 in 20 new oncologic agents entering clinical trials proves to be sufficiently safe and effective to achieve approval. Progress has been slow and sometimes inefficient.

Some scientists have claimed that the cancer incidence and mortality rates have not changed over the last 15 years. The fact is, however, that the overall cancer mortality rate has declined significantly in the US since 1990, despite the aging of the population. For example, the incidence for the major killer, lung



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cancer, began to decline in the early 1980s, owing to the antismoking campaigns, and the overall 5-year mortality rate decreased by 1.6% by 2010. The 5-year mortality rate has decreased by 3% for colorectal cancer, 2.2% for breast cancer, 3.3% for prostate cancer, and 1.3% for leukemia. For some other cancers, however, the 5-year mortality rate has actually increased, by 0.6% for pancreatic cancer and by 2.2% for liver cancer.

Are we winning or losing the war against cancer? There is no question that clinical outcomes for patients with some hematologic cancers have changed dramatically for the better, whereas the results are far more modest for many solid tumors. Focusing only on median 5-year survival, however, may ignore the substantial improvement in survival for subsets of patients treated with erlotinib or crizotinib for lung cancers that bear the appropriate genotypic changes in the epidermal growth factor receptor or anaplastic lymphoma kinase. Over the last decade, our understanding of cancer at the cellular and molecular levels has continued to increase exponentially, not only by identifying



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many new targets for diagnosis and therapy but also by documenting the extraordinary heterogeneity within and between different cancers. Given this heterogeneity, not only is it clear that we must write different prescriptions for patients with the same histotype of cancer, but it is also apparent that single drugs or modalities are not likely to cure individual patients.

Despite the disappointing projections for cancer incidence, which is expected to increase dramatically, especially in developing nations (3), it is also true that cancer is now amenable to much more scrutiny than ever because of powerful genomic, proteomic, metabolomic, and epigenomic technologies. Multinational projects, such as the International Human Cancer Consortium (4) and the Cancer Genome Atlas, along with genomewide association studies and a myriad of fundamental biological studies on pathways that are activated or deactivated in cancer, are giving us unprecedented opportunities to continue fighting this disease and developing incremental improvements in cancer patients' survival prospects and quality of life. We are now witnessing the publication of entire cancer genomes (not just one, but hundreds) of patients with various cancer types, part of our effort to understand the genetic basis of cancer. Although novel actionable mutations have not been found at all disease sites [e.g., the recently published ovarian cancer genome (5)], studies of copy number abnormalities have identified amplified targets for which multiple drugs are already available. Mutational analysis of clinical material is now possible for hundreds of genes. Matching patients who have cancers with activating mutations in the phosphoinositide 3-kinase (PI3 kinase) signaling pathway to phase I protocols testing PI3 kinase inhibitors has improved response rates and survival (6). Within the next few years, advances in next-generation sequencing promise to provide affordable whole-genome data for each patient's cancer.

Genomics is not the only weapon we currently have against cancer, however. Cancer proteomics, epigenomics, metabolomics, and glycomics are being exploited intensely to identify novel biomarkers for early detection, a cornerstone of effective management. Our understanding of metabolism is being reinvented after key enzymes in energy-generating pathways were found to be frequently mutated in some cancers (7). The cancer stem cell hypothesis provides clues and opportunities for both new diagnostics and therapeutics (8). Major new findings are providing a better understanding of the development of drug resistance (9), one of the most frustrating of clinical problems, whereby originally highly promising therapies ultimately fail. This new knowledge could lead to the reversal of drug resistance and to prolongation of drug efficacy (9). A better understanding of the mechanisms of metastasis and the tumor microenvironment should help

in identifying relevant therapeutic targets and in developing new, more effective drugs (10). The field of cancer prevention, probably the best way to combat cancer, is making important strides as new chemopreventing drugs, vaccines, and diets with anticancer properties are identified (3). Let us not forget that approximately 20% of all cancers are linked to a preventable cause, obesity (11).

In the past, well-intentioned attempts to accelerate progress have proved premature. In 2003, for example, the director of the National Cancer Institute set the ambitious goal of halving the suffering and death from cancer by 2015. Given the advances in our understanding of cancer over the last decade and the availability of new and transforming technologies, we believe that now is an appropriate time to reassess the opportunities for translating our new knowledge to improve outcomes for cancer patients by identifying those subsets of cancer for which prevention, early detection, and multimodal targeted therapy will affect patient outcomes substantially over the next decade. An important requirement for this translation will be further development of diagnostic biomarkers and imaging probes that inform critical clinical decisions.

The fight against cancer has proved much more difficult than anticipated, and the suffering caused by this disease continues to be a major health problem. We hope that the diverse articles presented in this special cancer issue of *Clinical Chemistry* will provide a state-of-the-art snapshot of where we are now and where the hot battlefields will be over the next 10 years. Obviously, we cannot cover every topic, and some debates, such as the cancer stem cell hypothesis, are likely to continue for years to come (12). Genomic, proteomic, metabolomic, epigenomic, and other omics covered in this issue will provide more details on cancer initiation and progression. Other topics covered consider such important issues as biomarker failures, the cancer microenvironment, circulating cancer cells, and microRNAs. Finally, we have not forgotten to include memoirs from the discoverers of important and clinically used biomarkers, such as prostate-specific antigen, cancer antigens CA125 and CA19-9, and carcinoembryonic antigen. We should remain optimistic, however, because despite the hurdles, slow—but real—progress has already been made; thus, the prospects for new progress in diagnostics and therapeutics for this devastating disease appear better than ever.

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