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Perspectives on Cancer in Japan and the United States[1]

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The challenge of cancer research can be summarized in the mortality statistics published by Aoki *et al.*[1)] Some of the important cancer mortality trends are shown in Figures 1–16.[2] Both the USA and Japan are sharing in the worldwide decline in deaths due to gastric cancer (Figs. 15 and 16), that is most probably a result of improved food storage, diminished salt intake, and perhaps better access to citrus fruits and allium vegetables. Yet, in many arenas, cancer incidence and mortality are increasing, and cancer is now the leading cause of death in Japan. We must all work together to eradicate the death and suffering from cancer, to cure cancer once it starts, and ultimately to prevent cancer. To this end, implementation of initiatives that promote continued development of sophisticated molecular technologies and clinical application of those technologies to the prevention, diagnosis and treatment of cancer is a surpassingly high priority. But at the same time, we must all have sound and straightforward public health policies.[2–4)] The recent comprehensive ten-year strategy for cancer control in Japan is a very important national project in this regard.

Epidemiologic studies tell us that at least 30–50 percent of cancer is directly related to smoking, diet and environmental factors. For example, exposure to some materials such as asbestos, carcinogenic polyhydrocarbons or radon gas, increases the risk of lung cancer, but both primary smoking and second-hand smoking are surpassingly important risk factors. Treatment studies indicate that significant gains in survival are possible and have already been achieved in some cancers based on early detection and intervention, with promise from new drugs and other modalities (including genetic engineering) for still other cancers. Prevention strategies have the potential to achieve a substantial reduction in cancer mortality (through smoking reduction, diet, national environmental measures, chemoprevention and vaccine development). This reduction, if fully realized, would result in hundreds of thousands of lives saved per year in the United States and Japan. And a large number can be saved just by applying what we already know. The lung cancer death rates (see Figs. 5 and 6) are especially disturbing since they are clearly linked to tobacco use, and therefore preventable for the most part. Cigarette consumption and smoking prevalence are very high in Japan, and tragically the lung cancer death rate in Japan can be expected to catch up with the death rate in the USA in the not-too-distant future.

Molecular Medicine

A growing understanding of the molecular interactions that determine both normal physiology and pathology is forming the basis for rational, targeted therapy and prevention strategies aimed at eradication of diseases, in particular the many diverse cancers that impair both the length and quality of life.[2)] As an example, the ability to define and modulate specific components of the cell signalling process (by which growth factors mediate their growth-controlling effects from the extracellular environment through their interactions with specific cell membrane-based receptors to the nucleus) is becoming critical to many therapeutic disciplines, including gene-directed therapies and antibody-based approaches. The paradigm of molecular medicine to date is the growing appplication of gene transfection technology to the treatment and, in the future, perhaps the prevention of cancer and immunodeficiency states. The ability to alter specifically the profile of gene expression of cells by replacing lost or defective genes or inserting genes that confer new cellular function is a triumph of our commitment to basic research, showing much promise in its earliest clinical applications. And yet, we must avoid unrealistic expectations about how rapidly such advances can reduce the incidence and mortality of common cancers.

Cancer Vaccines

Vaccines offer opportunities for primary disease prevention, prevention of disease recurrence or the occurrence of a new second disease episode, and treatment of active disease. The idea of a vaccine to prevent cancer has been only a dream for many years, but recent progress in basic biomedical research has now made the goal of a vaccine approach to cancer treatment and preven-

[1] This article is a summary of my lectures delivered on February 12, 1993 in Tokyo, and on February 15, 1993 in Osaka, which were supported by the lectureship program of the 10-Year Strategy for Cancer Control.

[2] Figures 1–16 are based on World Health Organization mortality data. Such data are supplied by the cooperating countries, and are based on death certificates. Of course, procedures for handling death certification may vary between and within countries, and, therefore, the data should be viewed as giving results indicative of the order of magnitude and direction of trends in mortality for comparative purposes only.

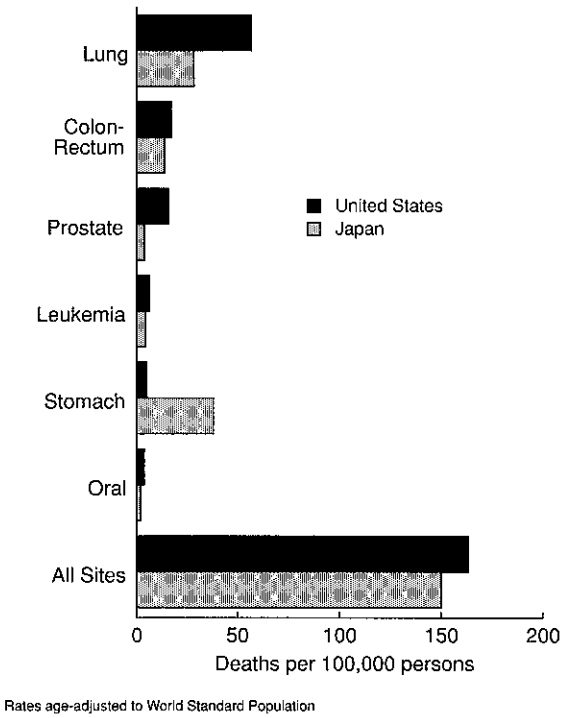


Fig. 1. Cancer mortality rates: Japan vs. United States, 1986–88: males.

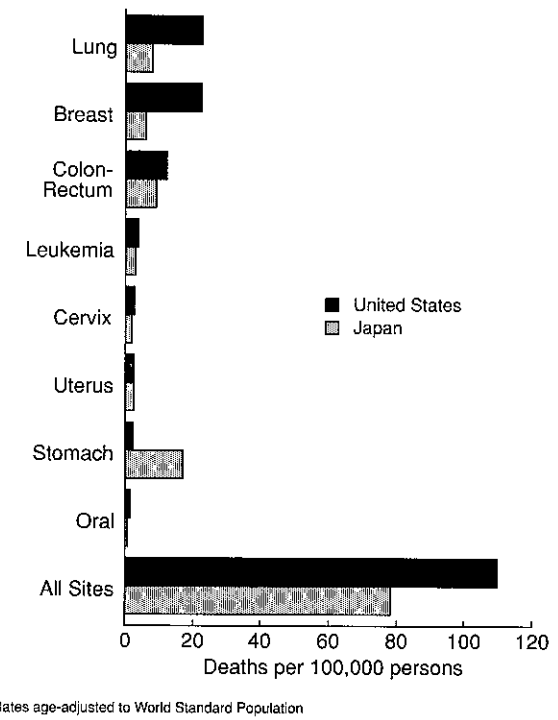


Fig. 2. Cancer mortality rates: Japan vs. United States, 1986–88: females.

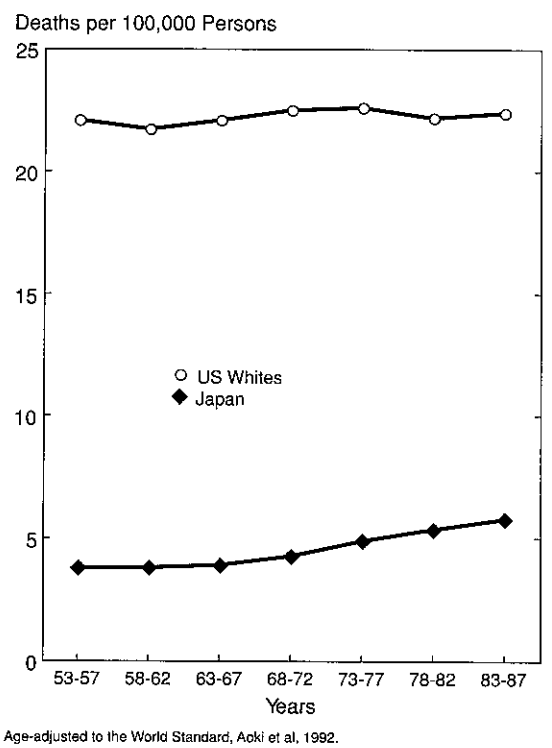


Fig. 3. Cancer mortality rates: breast cancer, females.

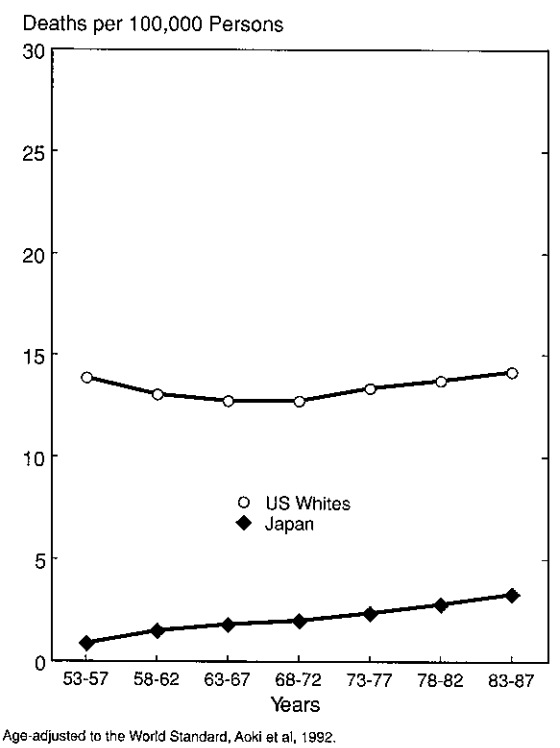
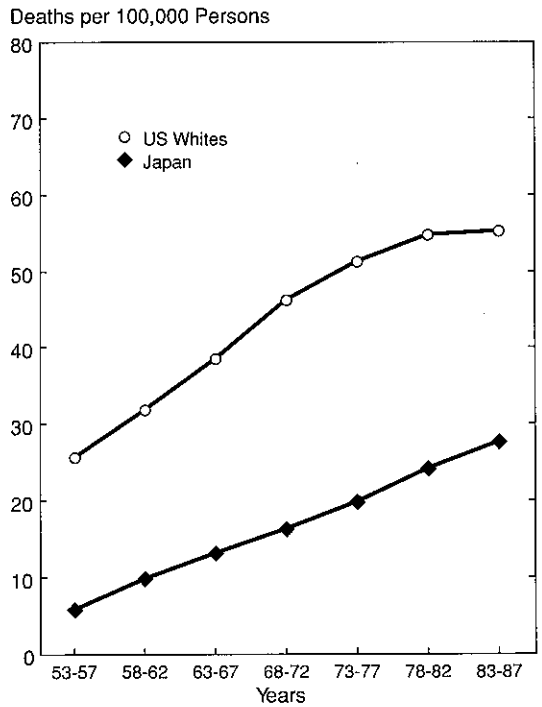
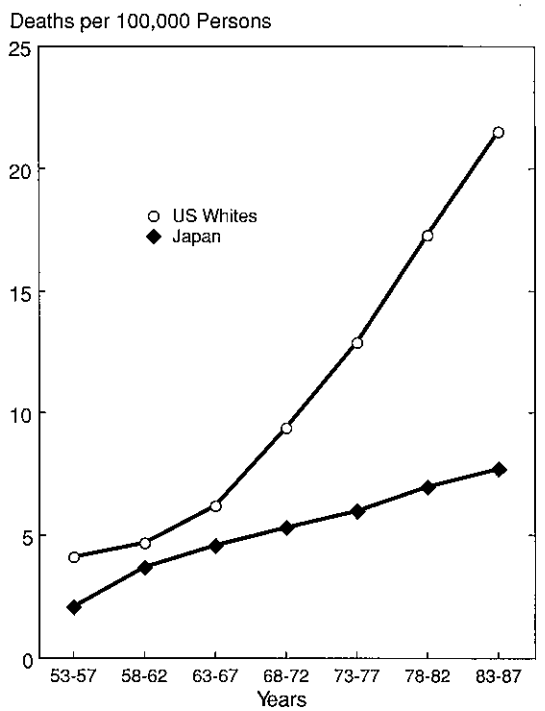


Fig. 4. Cancer mortality rates: prostate cancer.



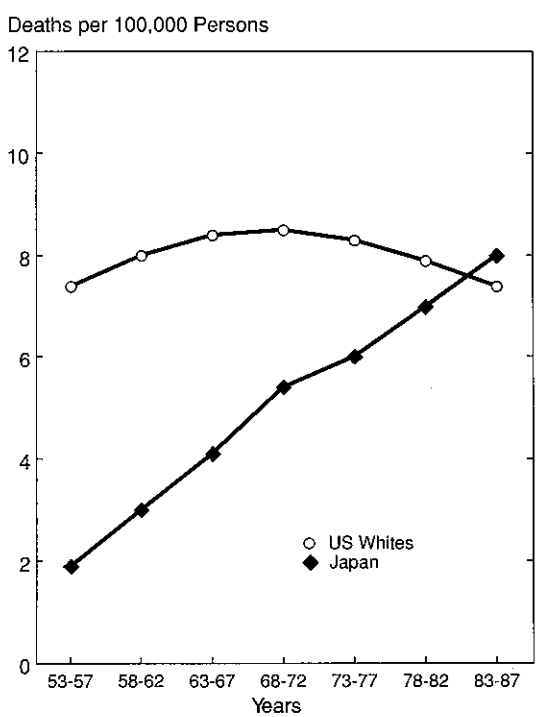
Age-adjusted to the World Standard, Aoki et al, 1992.

Fig. 5. Cancer mortality rates: lung cancer, males.



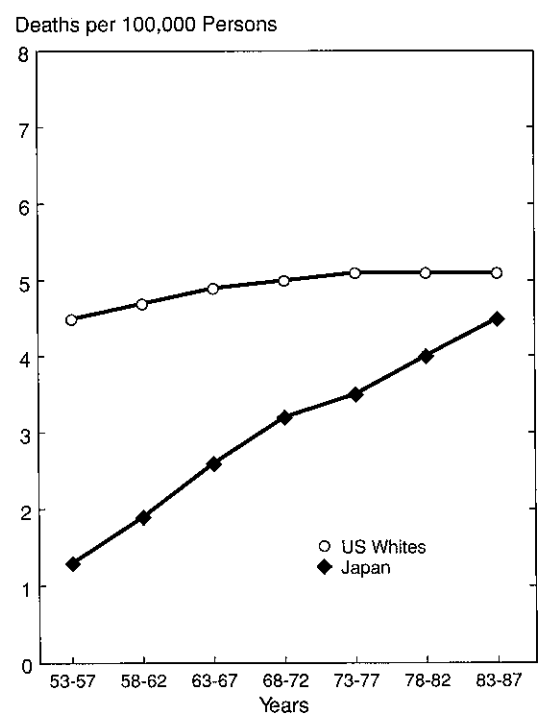
Age-adjusted to the World Standard, Aoki et al, 1992.

Fig. 6. Cancer mortality rates: lung cancer, females.



Age-adjusted to the World Standard, Aoki et al, 1992.

Fig. 7. Cancer mortality rates: pancreatic cancer, males.



Age-adjusted to the World Standard, Aoki et al, 1992.

Fig. 8. Cancer mortality rates: pancreatic cancer, females.

tion realistic. Current progress and future directions for cancer vaccine development reflect the growing understanding of virus and tumor cell immunobiology and, in particular, the expansion of genetic engineering technology and its application to gene therapy.[5,6]

Viruses are important causes or facilitators of cancer. Thus, Epstein-Barr virus, hepatitis B and C viruses, human T-cell leukemia virus, and human papilloma viruses are examples of biologic carcinogens found in the environment (in the broadest sense of that term). The molecular dissection of specific viral structures (in particular, the identification of new immunogenic subcomponents or viral "oncoproteins," as in the case of human papillomaviruses) and the biochemical consequences of virus-host interactions are being combined with classical techniques for vaccine development to create novel antiviral vaccines. Innovative approaches to vaccine development for non-viral malignancies are fusing gene therapy and immunomodulatory mechanisms to augment the antigenicity of specific determinants. One such vaccine construct combines genes encoding weak antigens with highly antigenic recombinant vectors such as vaccinia. Using this approach and related approaches, we should soon be able to construct experimental vaccines targeted against specific oncogenes or suppressor genes associated with certain common cancers.

The intracellular transfection of genes for interleukins or other growth factors which, in turn, enhance the cell surface expression of major histocompatibility complex antigens and thus generate specific cytotoxic T lymphocytes is yet another creative fusion of the principles of immunomodulation with genetic engineering technology.

The Scientific Foundations of Cancer Prevention

The ability to prevent the emergence and perpetuation of cancer is becoming an increasingly realistic goal as we gain a deepening understanding of the molecular interactions that determine normal cellular behavior or, when disturbed, lead to aberrant development.[7] Prevention efforts must not await basic research in the future, and can start with an empirical, public health orientation. Once again, smoking cessation must be the highest priority. Sensible dietary principles based on reducing fat and increasing fiber, relying heavily on fresh fruits and vegetables, are also priorities.

Environmental and occupational exposures to carcinogens contribute to cancer risk in both Japan and the USA. This kind of research is made more urgent by certain trends, some of which we cannot explain. For example, why is the death rate from pancreatic cancer climbing dramatically in Japan (see Figs. 7 and 8)? Smoking may be partially responsible, but is there an unknown environmental factor? A cross-cutting discipline, molecular epidemiology, integrates the study of specific gene sequences and alterations in those sequences with the environmental triggers that may lead to net cellular dysregulation. Molecular epidemiology measures both the biologically effective dose of a carcinogen at the level of the host genome and the host's cancer susceptibility on the basis of multiple factors such as metabolic activation of carcinogens, DNA repair mechanisms, endogenous mutation rates and inheritance of mutated tumor suppressor genes and/or oncogenes. Molecular epidemiology is perhaps best exemplified through studies of the tumor suppressor gene *p53*. Losses, deletions and/or mutations of the *p53* gene in somatic cells are among the most common genetic abnormalities detected in a wide variety of epithelial and lymphohematopoietic cancers — breast, lung, colon, bladder and UV light-induced skin cancers, aflatoxin- and/or hepatitis B virus-induced hepatocellular cancers, and B-cell lymphomas and leukemias. In addition, study of the rare familial Li-Fraumeni syndrome has pinpointed an inherited mutation of *p53* as the responsible factor for multiple diverse tumors, including a striking incidence of breast and bone cancers, that occur in patients with this devastating predisposition to cancer.

New concepts regarding the inheritance of gene expression will have a major impact on the determination of cancer predisposition. The accurate dissection of an individual's propensity to develop certain malignancies — i.e., the inherited susceptibility to carcinogenic effects of a particular exogenous agent — is confounded by the non-Mendelian inheritance of some genes, known as genomic imprinting. The recent recognition of genomic imprinting in humans has astonishing implications. This process, where differential gene expression is determined by the parental origin of the particular gene in question, might operate in the overall determination of individual cancer risk.[8-10] Indeed, genomic imprinting probably contributes to the net phenotypic expression of various diseases, for example, the Prader-Willi vs. Angelman syndromes, where the clinical constellation is dependent on the source of chromosome 15q13 deletion, paternal vs. maternal, respectively.

Genomic imprinting may also influence the expression of certain cancer-prone syndromes such as the Beckwith-Wiedemann syndrome (a classic example of uniparental disomy, where duplication of the paternally derived chromosome 11p15.5 may lead to overexpression of insulin-like growth factor-2), Wilm's tumor, neurofibromatosis, glomus tumors, osteosarcoma and perhaps retinoblastoma (both related to structural and/or functional loss or mutation of the retinoblastoma gene). Certain translocations show specific, non-random maternal and paternal origins of the involved chromosomal segments. Specifically, the Philadelphia chromosome that typifies chronic myelogenous leukemia is formed from the translocation

and recombination of the *abl* oncogene on chromosome 9q34 and the breakpoint cluster region (*bcr*) gene on chromosome 22q11. Recent elegant studies demonstrate that the 9q34 segment containing *abl* is paternally derived, while the 22q11 segment containing *bcr* is maternally derived. It is conceivable that certain epigenetic factors — steroid hormones (in particular, estrogens and androgens), other growth factors (inflammatory interleukins) or dietary factors (e.g. folate, oxidants, free radicals) — could modulate the DNA methylation state of either the maternally or paternally derived allele. Such changes in DNA methylation could result in changes in gene transcription that, in turn, might alter the balance of expression of parentally imprinted genes.

Prevention research encompasses the full spectrum of cancer research, from basic molecular and biochemical investigation to clinical trials and large population-based studies. Even though the possibilities of altering the genetic make-up or blocking its consequences are just being explored, there is progress in identifying and preventing transforming events. The burgeoning field of chemoprevention — namely, the prevention of cancer through the development of pharmacologic, nutritional and endocrinologic interventions that inhibit or delay the process of carcinogenesis — is evolving from a concept to a testable clinical practicality for several commonly occurring cancers. To date, one successful approach is based upon the biochemistry and pharmacodynamics of vitamins and other micronutrients, especially the retinoid family of vitamin A derivatives. Another investigative strategy, now being tested in or considered for landmark clinical trials, uses hormonal suppressive agents to prevent the emergence and progression of hormonally responsive malignancies, namely tamoxifen and finasteride (Proscar) to prevent the emergence of breast and prostate cancers, respectively. Critical areas of emphasis are the identification and evaluation of new active compounds with unique mechanisms of action, and the initiation of new prevention clinical trials. In addition, biochemical markers of altered gene expression are being developed to measure emergence or reversal of early transforming events.

Special opportunities for making progress in the science of cancer prevention have been made possible by the pre-eminant research team lead by Sugimura and colleagues.[11-13] We now know that pyrolyzed amino acids and cooked protein-containing foods, notably red meat, can contain heterocyclic aromatic amines (HAA). Several of these compounds are mutagenic in certain systems, and they are carcinogenic in experimental studies. They may also be a risk factor in humans. Certain comparatively simple steps (e.g., avoiding excessively cooked beef, utilizing microwave cooking methods, increased consumption of fish, poultry, and vegetables) may reduce exposure to HAA formation and risk.[14]

Cancer surveillance is a critical component of the National Cancer Institute's cancer prevention and control program. The tracking and analysis of trends in cancer incidence, mortality and survival rates are pivotal to the development of new activities, the stimulation of new research and the monitoring of program effects. The Surveillance, Epidemiology and End Results (SEER) Program monitors the cancer burden on the population of the United States through the measurement of cancer incidence, mortality, and survival and the assessment of individual and societal factors that mediate these cancer measures both directly and indirectly. The ultimate purpose of cancer surveillance is to guide future programmatic decisions of the National Cancer Program based on the net shift in cancer incidence and mortality, brought about through improvements in early detection, therapy and ultimately prevention, that reflect progress or, in counterpoint, continuing challenge and need for additional attention. To this end, the surveillance effort includes the development of information and statistical analysis systems, such as population-based registries and national probability surveys and conduct of a broad series of studies focused on specific cancer control indicators. It may be important for SEER programs to grow and blossom in Japan.

Tumor Detection, Diagnosis and Prognosis

Short of disease prevention, the ability to eradicate cancer often depends upon the early detection of that cancer at a time when the total tumor burden is small and localized and before the accumulation of genetic abnormalities conferring tumor invasiveness and/or drug refractoriness. In addition, the detection of genotypic or phenotypic tumor cell determinants that portend aggressive or drug-refractory behavior may identify patients at greatest risk for cancer recurrence and may further identify those individuals who might benefit from intensive therapeutic approaches, especially in the adjuvant setting. Molecular technologies such as allelotyping and the polymerase chain reaction (PCR) are lowering the threshhold for such detection, conferring the ability to uncover genetic alterations in extremely small numbers of cells and at a particularly early stage of carcinogenesis (i.e., "premalignant" genetic changes that predispose to malignant transformation) or to detect small amounts of residual tumor cells despite the appearance of complete remission. Detecting such minimal residual disease will help to define those patients who need further therapies to achieve cure or who are developing resistance to current treatment regimens and may thus need alternative approaches.

Certain early detection, screening, and intervention

efforts may need to receive special attention. Cancer of the large bowel is one such area (Figs. 9–14). Many epidemiologists quite correctly prefer to report colon and rectal cancers together (see Figs. 11 and 12). Recognizing that there may be certain errors of diagnosis as to specific sites and possible time-trend inconsistencies, it is still perhaps worth looking at colon and rectal cancers separately for a moment. When we do so, certain potentially disturbing trends emerge. Has the "Westernization" of Japanese traditional diets had a deleterious effect? What explains the dramatic rectal cancer trends? Should there be better public and medical education and screening programs? Are follow-up interventions adequate? Clearly, the declining rectal cancer death rate in the USA and the reciprocal increased death rate in Japan (Figs. 13 and 14) require further explanations.

Cancer Therapy

The definition of critical molecular lesions and the dissection of the mechanisms by which those lesions derail normal cellular development is being increasingly applied to the design of therapeutic interventions.[3] The rational design of drugs on the basis of structure and/or function of specific molecular targets is becoming a dominant theme in cancer therapy. Innovative combinations of multiple modalities, in particular those centering around radiation therapy are under preclinical development and clinical testing for several disparate cancers. New cytotoxic and biologic agents with unique mechanisms of action — the natural product-based drugs such as taxol and the camptothecins in particular — exert antitumor activities by targeting unique molecular pathways and tumor cell "survival" mechanisms. Genetically engineered humanized monoclonal antibody-radioisotope conjugates or targeted toxins are directed toward tumor cell surface components, while other approaches — inhibition of signalling pathways through abrogation of tyrosine kinase activity, blockade of the post-translational modification processes known as isoprenylation and farnesylation (critical to *ras*-encoded G protein function and to intracellular sterol synthesis) or, alternatively, initiation of programmed cell death (apoptosis) — are constructed on the basis of intracellular biochemical pathways.

As surgery, radiation, chemotherapy and/or biomodulatory interventions are optimized and are able to extend survival, both physical and psychosocial issues of quality of life, rehabilitation and organ preservation gain increasing importance and are thus becoming a focus of all clinical investigations. Examples of treatment advances which improve the long-term well-being of cancer patients include limb-sparing surgery for bone and soft tissue sarcomas, procedures to preserve speech and swallowing function in cancers of the head and neck, breast conservation approaches and surgical techniques to maintain sexual function and urinary continence in management of localized prostate cancer.

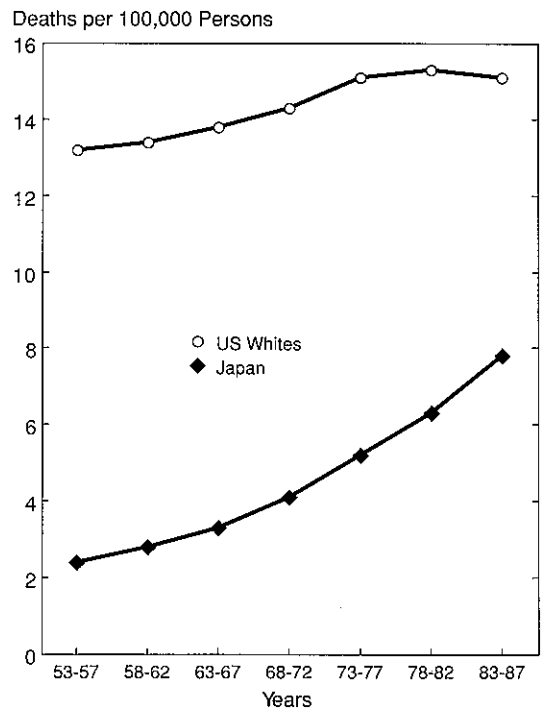
Women's Health Issues

Cancer remains the second leading overall cause of death among women in the United States, with over 150,000 women expected to succumb to cancers of the lung, breast, colon, and reproductive tract (uterus, ovary, cervix) annually. Approximately 250,000 women will die from all cancers this year, in particular lung cancer, which has surpassed breast cancer as the leading cause of cancer death in women since 1989 in the USA. Still, breast cancer is the most frequent major tumor in American women, responsible for about 32 percent of all cancers in women with an estimated 180,000 new diagnoses (for a lifetime risk of occurrence of 1 in every 8 women) and 46,000 deaths per year. For women in their early 40's breast cancer is the number one cause of death from any cause. While there are some differences, cancer is certainly a major problem in Japanese women as well. In Japan, breast cancer mortality is still low, but starting to climb.

There has been great progress toward the goal of eradicating death and suffering from breast cancer in terms of developing and implementing rationally designed prevention clinical trials for breast cancer. The precedent-setting Breast Cancer Prevention Trial in the USA, using tamoxifen as primary chemoprevention for certain high-risk premenopausal and postmenopausal women, and the Women's Health Trial testing the role of dietary fat reduction in preventing breast cancer (and other diseases) are the vanguard of prevention strategies targeting breast (and perhaps other) cancers in women. Other areas of continuing progress are the result of efforts aimed at the accessibility and delivery of state-of-the-art health care to underserved women; the clinical development, procurement and availability of promising new therapies such as taxol and autologous bone marrow transplantation; the design, construction and clinical development of breast or ovarian cancer vaccines directed toward tumor-associated antigens and a human papillomavirus (HPV) vaccine for cervical cancer; and the establishment of Specialized Programs of Research Excellence (SPOREs) focused on breast and lung cancers (and, perhaps in the future, on ovarian and colorectal cancers) for the purpose of rapid translation of basic research discoveries into clinical investigation and treatment advances.

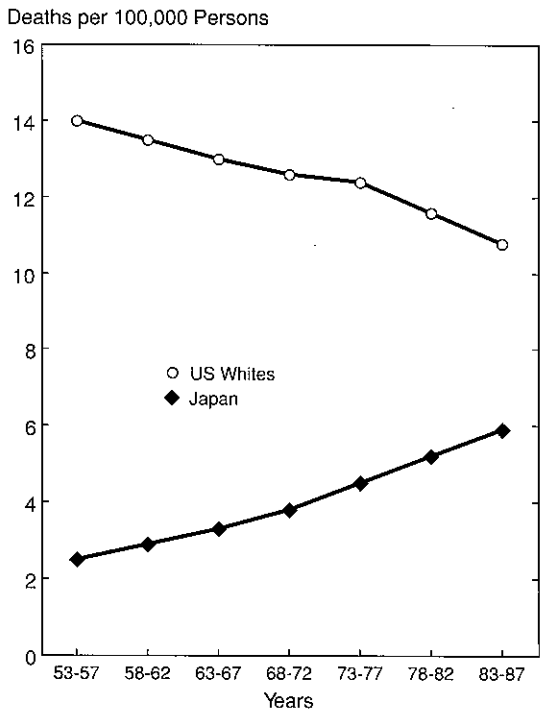
Unfinished Business

The final measures of progress against cancer are incidence and death rate. When the U.S. National Cancer Act was passed in 1971, surgery was the primary treat-



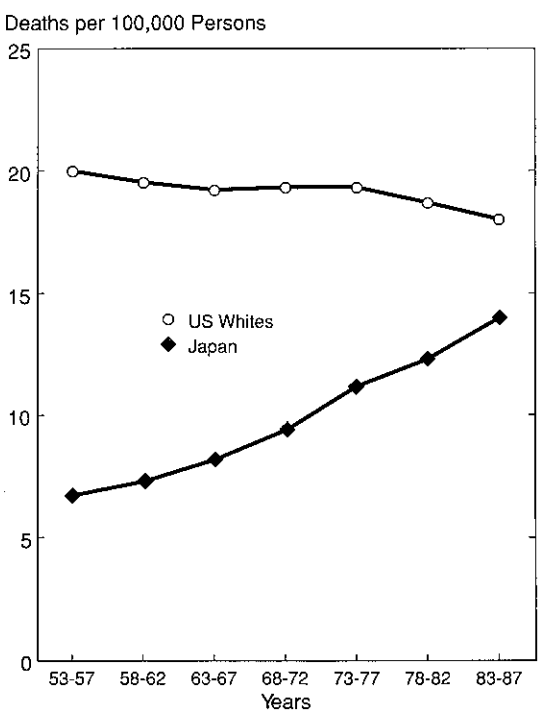
Age-adjusted to the World Standard, Aoki et al, 1992.

Fig. 9. Cancer mortality rates: colon cancer, males.



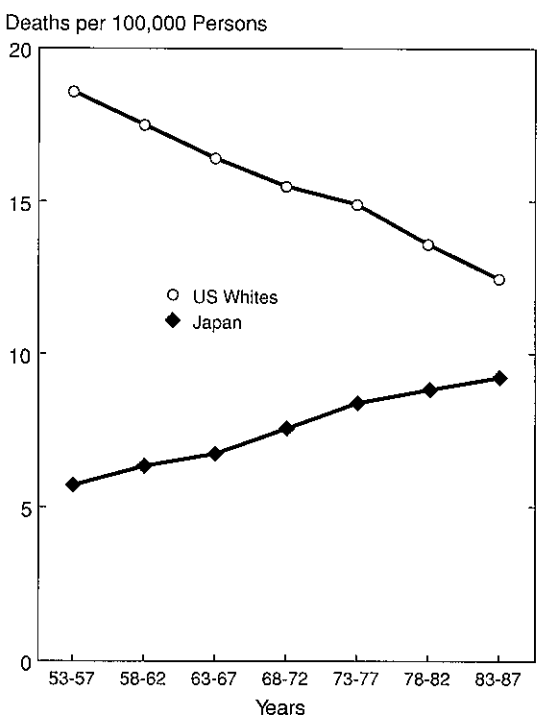
Age-adjusted to the World Standard, Aoki et al, 1992.

Fig. 10. Cancer mortality rates: colon cancer, females.



Age-adjusted to the World Standard, Aoki et al, 1992.

Fig. 11. Cancer mortality rates: colorectal cancer, males.



Age-adjusted to the World Standard, Aoki et al, 1992.

Fig. 12. Cancer mortality rates: colorectal cancer, females.

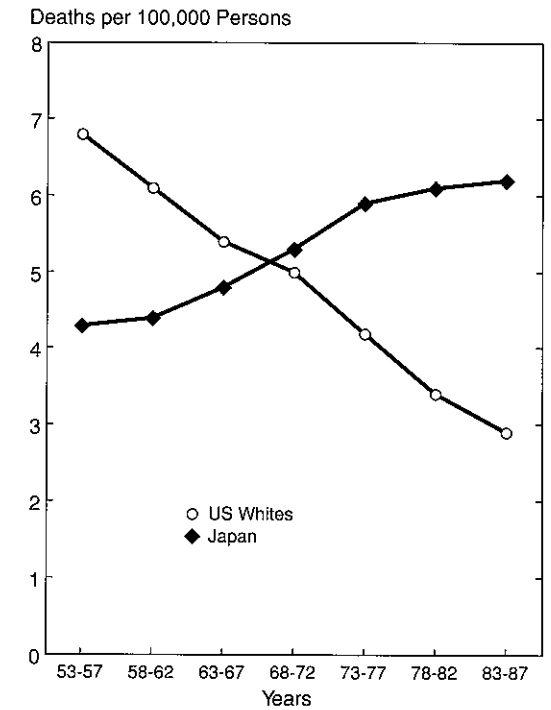


Fig. 13. Cancer mortality rates: rectal cancer, males.

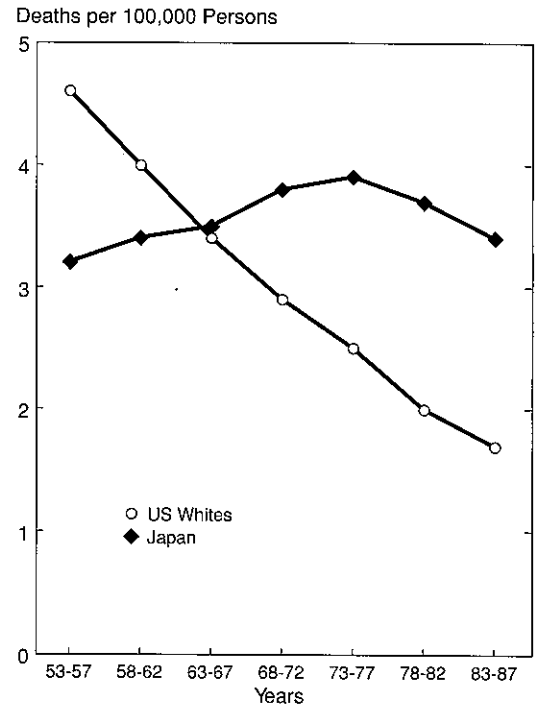


Fig. 14. Cancer mortality rates: rectal cancer, females.

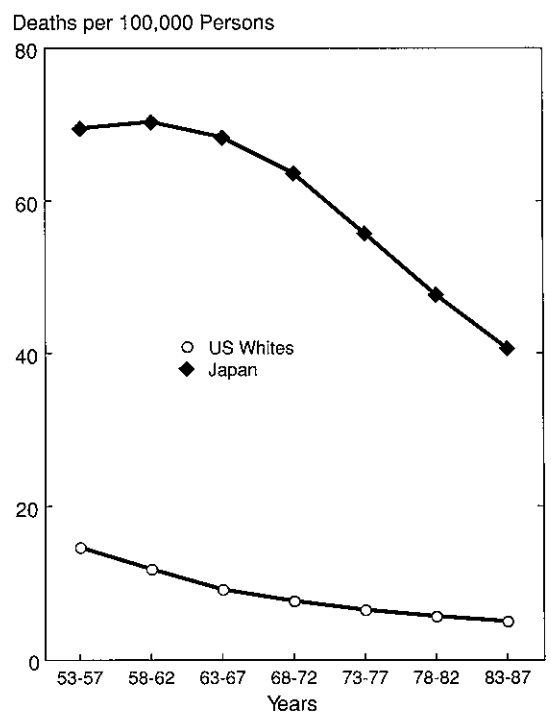


Fig. 15. Cancer mortality rates: stomach cancer, males.

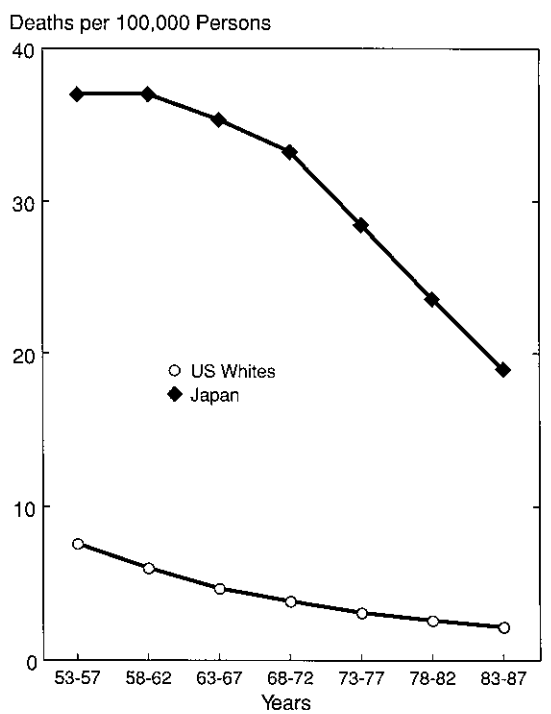


Fig. 16. Cancer mortality rates: stomach cancer, females.

ment for cancer; radiotherapy was being developed and chemotherapy was in its infancy. Strategies were just being developed to allow for more intensive therapy, such as the use of empiric combinations of antibiotics and the availability of supportive platelet transfusions. The concept of "curability" was for most cancers so bold as to be almost unthinkable. Since then, major progress has been made in reducing deaths from childhood cancers — a reduction of 38 percent since 1973 in the USA, with almost two-thirds of children with cancer surviving to the five year "cure" landmark and beyond. The astonishing progress against Hodgkin's disease, for which there has been a 55 percent reduction in death rate, or against testicular cancer, for which there has been a 64 percent reduction, is well-recognized. But there has been progress against several of the more common adult malignancies, as well, mainly for individuals under the age of 65. For example, in this age group, the death rate in the USA for colon cancer has fallen by approximately 18 percent, for ovarian cancer by about 26 percent (in fact, for women under 50, there is a 43 percent decrease), for cervical cancer by over 40 percent, and for bladder cancer by about one-third. For white women under the age of 50 with breast cancer in the USA, mortality has decreased by 12.5 percent. We clearly cannot be satisfied with this, but at the same time, we need to acknowledge that first steps in reducing the toll of this terrible disease have been made. The decrease in gastric cancer is gratifying, but we must not overlook the many challenges (Figs. 1–16) that we must still confront both in the USA and Japan.

Many of the recent therapeutic innovations offer patients an improved quality of life as well as a chance for longer life. With breast cancer, for instance, treatment has advanced toward earlier and more accurate diagnosis, less invasive surgery, breast reconstruction and increased survival. For osteosarcomas, colorectal cancers and bladder cancers, we are more adept at avoiding radical organ removal or functional impairment and preserving organs that define an individual's autonomy and independence. For cancer of the larynx, we can more frequently preserve function and save the ability to speak, a gift of immeasurable value.

Despite rewarding progress and promise in these and other areas, we still have much unfinished business and many urgent challenges. While there are some cancers and some groups of people for whom the progress against cancer is significant, there are increased cancer mortality rates in the older population (those over age 65), in minorities, and among the impoverished — the underserved — who do not have access to the advancing technologies that will change the impact of cancer on both the length and the quality of life. In many situations around the world, poverty is a kind of carcinogen. For example, cancer incidence rates are about 10 percent higher and mortality rates are 30 percent higher for African-Americans than for white Americans. For certain cancers, the discrepancies are even more pointed. Such discrepancies are exemplified by the urologic cancers, which exert a great burden of death and suffering on a large proportion of the population. The three predominant urologic cancers — prostate, kidney and bladder — are expected to occur in over 200,000 people per year in the USA with roughly 80 percent of those affected being men. In particular, prostate cancer now accounts for over 132,000 new cases of cancer in men in the USA, more than lung cancer, and is second only to lung cancer as the leading cause of cancer deaths in men. Prostate cancer is expected to cause about 35,000 deaths in the USA annually. The death rate from prostate cancer in African-Americans is tragically high, more than twice the death toll in whites. The prostate cancer death rate is low in Japan, but there are disturbing signs that this may be changing (Fig. 4).

The greater burden imposed by cancer on African-Americans extends to other malignancies, as well. African-Americans have three times the death rate from esophageal cancer or cervical cancer as compared with whites. While the mortality rates for leukemia and cancers of the breast, larynx, pancreas, colon and rectum have been steadily decreasing for whites (particularly those under the age of 65), they have been increasing for African-Americans. Indeed, the 12.5 percent decrease in mortality for younger white women stands in contradistinction to the 5.3 percent increase in mortality seen for premenopausal African-American women and, most disturbingly, to a 22 percent increase in breast cancer-related mortality in postmenopausal African-American women in the past 16 years or so.

Lung cancer is a special problem of overwhelming proportions. It is common, increasing, and quite lethal. A reduction in smoking initiation rates is important, but as Yamaguchi and co-workers point out, its impact alone against lung cancer mortality is seen only slowly.[15] Smoking cessation and the interruption of smoking initiation are both crucial goals everywhere. At least for now, we must confront the reality that no therapy now available or even in a planning stage can be realistically expected to reduce the death rate from lung cancer anywhere on a national or international level. In sum, the discovery, translation and optimal implementation of knowledge is a lengthy process, and one which requires objective scrutiny and validation at each way station. Our new technologies are beginning to unravel ancient mysteries surrounding the processes that define growth and differentiation at the most fundamental level. It is ironic that we now stand on the threshhold of using sophisticated science to end the devastation caused by cancer, yet we have so much unfinished business. In the

USA, long-term gains will only be realized through an investment in the training and education of the people, especially the young scientists with fresh perspectives, who will generate new ideas. The same general considerations apply to Japan. To ensure progress toward these goals, we must be able to expand the bidirectional flow of information between basic and clinical investigations already in motion for several malignancies and ensure that the resulting progress toward cancer cure and prevention is available for all in need. And both nations must be prepared to commit the resources needed to do the job.

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