

Special Article

Cancer Prevention: Past, Present, and Future¹

Robert C. Young² and Christine M. Wilson

Fox Chase Cancer Center, Philadelphia, Pennsylvania 19111

Introduction

At the dawn of this new century, cancer prevention has become a new frontier for cancer research. Science and technology have evolved sufficiently to consider using our knowledge of cancer biology and genetics to identify individuals at risk and interrupt the process of malignant transformation. Identifying causes of cancer with a view toward prevention goes back generations. An early link between carcinogens in the environment and the development of cancers of the scrotum in chimney sweeps was reported in the 18th century (1). However, it was not until the mid-20th century when a series of discoveries made it possible to envision prevention and early diagnosis in more common cancers. But progress in cancer prevention is not simply a story of scientific advances. It is a story of evolution in both science and public perception, of rapidly progressing research coupled with changing societal attitudes and beliefs.

Our country was a very different place in the middle of the 20th century. It is helpful to put both medicine and society in the context of that period so that we can better understand the development of cancer prevention concepts. In 1950, the population of the United States was 149 million.³ We have since grown to 281 million, an increase of 89%.⁴ United States life expectancy rose from 68 years in 1950 to 76 in 2000.⁵ The average American salary has increased from an astonishingly low figure of \$2,992 in 1950³ to \$27,809 at the end of the century.⁶

In 1950, we were at the dawn of the nuclear age, the beginning of the Korean War. We naively thought we could protect ourselves from nuclear holocaust with primitive bomb shelters in the home. Our government with similar naiveté provided us with the construction pamphlets. There were only 48 states. Shopping malls and motels were just beginning to dot the landscape along newly constructed interstate highways. Teenagers went to drive-in movies and wore poodle skirts. Segregation was still a way of life in the South. Cancer was a

word seldom spoken publicly, and it was common practice for physicians to withhold the cancer diagnosis from patients to spare them and their family the worry and pain.

Medicine in the 1950s was on the cusp of an explosion of progress. In 1953, Watson and Crick⁷ described the DNA molecule, arguably the most significant scientific advance of the century. Jonas Salk introduced the first polio vaccine. The first successful kidney transplant was performed. The first cures for childhood leukemia using chemotherapy were achieved. And cancer emerged as a medical and scientific problem of huge dimensions, rising from the ninth leading cause of death in this country in 1900 to the second in 1950.⁵ A dominant reason for this dramatic increase was cigarette smoking, but other environmental and occupational factors as well as improved methods of diagnosis all contributed to making cancer a major focus of research and treatment efforts in the second half of the 20th century (2).

Early Progress

Several pivotal studies, all published around the midpoint of the last century, highlighted the early efforts to prevent and control some of the common cancers like lung, cervix, and breast (3). The first were the epidemiological studies by Wynder and Graham (4) and Levin, Goldstein, and Gerhardt (5) in 1950, showing a clear association between smoking and lung cancer. Although Papanicolaou and Traut first described their cytological method for detecting early cervical cancer in 1943, the publication of the *Atlas of Exfoliative Cytology* in 1954 brought widespread attention to this discovery within the medical community (3, 6). Similarly, Leborgne described the relationship between microcalcifications and breast cancer (7) in 1950. This was followed in 1956 by the development of the first dedicated mammography (8, 9) equipment. These publications were important in their own right but more importantly laid a clear foundation for future progress. However, as Peter Greenwald states, “No clear strategy existed to translate the progress being made into basic knowledge about cancer into tangible benefits, thus limiting the accomplishment of cancer prevention and control efforts” (10).

The development of a clear vision and strategy for cancer control depended to a large degree on the emergence of an infrastructure dedicated to applying cancer-related research to cancer prevention problems. The ACS,⁸ founded in 1945, soon became the leading voice for public awareness of cancer and support for cancer research in this country. The ACS made effective use of the “new television medium” to take its case to the American people. Public Service announcements, special programs, and printed materials featured the best known faces of

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² Address to which requests for reprints may be addressed, at Fox Chase Cancer Center, 7701 Burholme Avenue, Philadelphia, PA 19111. Phone: (215) 728-6900.

³ Kingwood College Library, American History 1950–1959. Internet address: www.nhmccd.cc.tx.us/.

⁴ United States Census Bureau. Internet address: www.census.gov/population.

⁵ National Center for Health Statistics. Internet address: www.cdc.gov/nchs/.

⁶ United States Census Bureau. Internet address: www.census.gov/hhes/www.income.

⁷ Watson, J. D., and Crick, F. H. C. A structure for deoxyribose nucleic acid, *Nature (Lond.)*, 171: 137, 1953.

⁸ The abbreviations used are: ACS, American Cancer Society; NCI, National Cancer Institute; NSAID, nonsteroidal anti-inflammatory drug.

the era, from President Eisenhower to Jackie Gleason to June Allyson, imploring people to recognize the “seven warning signs of cancer and fight cancer” with a check-up and a check. Or buck cancer with a buck. Although these messages might seem dated based on the knowledge of today, they did represent the first public discussion of the problem and suggested potential solutions.

The ACS strategy played a crucial role in changing the widespread perception of cancer as a sure death sentence, seldom, if ever, discussed in public or even mentioned in obituaries. The seven warning signs carried with them the message that cancer could be detected early and treated effectively. These highly visible public awareness programs were bold, for the times, in their willingness to speak openly about the disease. Slowly, as the magnitude of the cancer problem continued to grow and death rates climbed inexorably upward, public attitudes about the disease began to change. Improved cancer treatment began to produce a growing cadre of cancer survivors that contributed to both increased awareness and openness about cancer.

During the latter half of the century, the NCI also began to expand its role as the focal point for cancer research. Founded in 1937, the NCI initially focused on basic research. From 1940 to 1970, the NCI had little research activity in cancer prevention and early detection. The passage of the National Cancer Act in 1971 changed that. With the Cancer Act, Congress reaffirmed its commitment to cancer control and brought with it intensified public interest in the federal effort to advance knowledge against cancer. In 1974, the NCI created the Division of Cancer Control and Rehabilitation, which for the first time provided an infrastructure to carry out the federal mandate as well as the resources to develop an effective cancer prevention and control strategy. The Division of Cancer Prevention and Control followed in 1983 (10). It focused on human intervention and defined a scientific logic for cancer control that paralleled the efforts being made in basic research. Peter Greenwald describes this process very well in his book *Cancer Control and Prevention*, noting that “a key feature that has emerged from this approach has been the adoption of prevention and chemoprevention clinical trials as the ‘gold standard’ of evidence. The application of the scientific approach to prevention research has brought a level of rigor and quality control to these trials that was not previously possible” (10).

By the early 1980s, the necessary ingredients were in place to accelerate cancer prevention research (10). Public attitudes had evolved, making cancer a major focus of awareness and interest; the organizational infrastructure was in place, and the science of cancer prevention was developing rapidly. In 1981, Doll and Peto (11) published their landmark study on avoidable risk of cancer. They estimated that roughly 30% of cancer deaths were related to smoking, 35% related to diet, and an additional 35% to other environmental and occupational causes. That article provided the framework for understanding the concept of environmental risk and focused attention on the major contributing factors of smoking and diet.

A review of the progress made in cancer prevention and control in the last half of the 20th century reveals both important successes and some intriguing failures. Solid progress in early diagnosis has been made with progressively better, faster, and

cheaper mammography. Cervical cancer smears have made a dramatic contribution to the progressive decline in cervical cancer mortality in this country. Colonoscopy, although less extensively used at present, may turn out to be the most powerful of the three with both diagnostic and therapeutic benefits possible with the same procedure. The gargantuan efforts made to persuade the public to stop smoking have borne fruit, reducing the percentage of smokers in this country from 42% in 1965 to 23% in 1999 (12). That figure, although encouraging in a general sense, still leaves open perplexing questions as to why individuals, and especially children, who are so well informed about the dangers of smoking continue to take up the habit and risk addiction. It also obscures the less successful smoking-cessation efforts that have taken place in lower income and minority communities. The mixture of success and failure of our smoking cessation programs to date illustrates the complexity of the problem, the need for messages targeted to specific populations, and the difficult challenge of behavioral modification in general.

Other cancer prevention developments provide important proofs-of-principle. The development of the hepatitis B vaccine and its impact in lowering the morbidity and mortality from primary liver cancer, especially in Asia, is a remarkable example of primary prevention and a fascinating model for research. It is a story that brings together elements of basic and clinical research, epidemiology, and virology, that range from the study of institutionalized Down’s syndrome children to the vast populations of Africa and Asia. It begins with Baruch Blumberg’s discovery of an odd antigen associated with a high rate of leukemia and ends with the successful development of the first vaccine known to prevent a human cancer (13). A 1997 study demonstrated that children in Taiwan who were vaccinated against hepatitis B virus had far lower rates of primary hepatocellular carcinoma, a highly prevalent disease in many areas of Asia and Africa (14).

The term “chemoprevention” was first used by Michael Sporn in 1976 in his paper on vitamin A and retinoids and their effect in retarding chemical carcinogenesis (15). However, major proof-of-principle came in 1998 with the completion of the tamoxifen breast cancer prevention trial (16). But much work had actually preceded this study. Almost unrecognized at the time was the fact that over 130,000 subjects had already participated in more than 70 randomized chemoprevention trials (17). None, however, attracted the public and professional attention of the tamoxifen trial or illustrated the myriad of challenges involved in conducting large-scale, highly visible prevention trials. This study was based on knowledge obtained from clinical trials using tamoxifen as therapy for established disease. In earlier studies, perceptive investigators had noticed a decrease in the frequency of breast cancer in the contralateral breast of patients with diagnosed disease (18). The use of tamoxifen to prevent breast cancer in high-risk women was a solid advance both conceptually and therapeutically, demonstrating that a drug could reduce the development of breast cancer in high-risk women by approximately 40%. This was the first trial of its kind to use public awareness campaigns to recruit healthy subjects for a large-scale study.

Receiving less public attention, but nevertheless highly important, were the chemoprevention effects seen in premalignant

nant lesions of the head and neck and of the colon (19–21). The retinoid 13cRA has been shown to be an effective treatment for premalignant oral lesions, although the toxicity of this drug is high, and the patients frequently develop lesions once treatment is discontinued (19). That said, these studies do provide a rationale and a pharmacological basis for next-generation trials using less toxic retinoids.

NSAIDs are to premalignant precursors of gastrointestinal cancer what retinoids are to premalignant lesions of the head and neck. Numerous trials support the concept that NSAIDs are active in preventing recurrent colon polyps (21). The FDA has now approved use of one, celecoxib, a cyclooxygenase (COX)-2 inhibitor, to reduce the numbers of polyps in individuals with familial adenomatous polyposis (22). These and related studies are providing critical new data on the role of NSAIDs in inhibiting colon carcinogenesis and in identifying new molecular targets for new chemoprevention agents.

Prostate cancer has also been a target for prevention studies. The SELECT trial testing the effect of selenium or vitamin E as potential prevention agents in prostate cancer opened in July 2001 (23). SELECT, a follow-up to the ongoing Prostate Cancer Prevention Trial (24), is expected to be the largest cancer prevention trial ever conducted, ultimately using a 2×2 factorial design to assess the effectiveness of selenium and vitamin E in 32,400 men.

But the road to successful chemoprevention has not always been smooth. As in all aspects of medicine, progress comes in fits and starts. Cancer prevention is no exception. Many of the failures seem counter-intuitive and are viewed by many pessimistically. Vitamin E and β -carotene not only did not help to prevent lung cancer in heavy male smokers but also may, in fact, have promoted it (25). Nor did 13cRA and 4-HPR reverse bronchial metaplasia in chronic smokers (26, 27). Neither low-fat diets (28) nor supplemental wheat bran (29) help to reduce the numbers of recurrent colorectal adenomas. The use of sunscreens has had disappointing results in preventing the development of malignant melanoma (30). These noteworthy failures provide ample arguments for those skeptical of prevention to question the wisdom of a prevention focus in the same way as the positive trials mentioned earlier excite the optimism of the prevention believers. The truth, as is often the case, is somewhere in-between.

Failure is rarely synonymous with lack of progress. There are many reasons why any particular intervention trial may have failed, and thoughtful review will hopefully provide useful lessons for the future. It is possible that some of these trials, although seemingly well designed, suffered from simple flaws. They may have involved the wrong dosages, schedules, duration, or study populations. The epidemiology on which they were based may have incorrectly linked effect to cause. Given the complexity of the human organism, it is useful to reflect that carcinogenesis occurs over decades, whereas prevention trials last only a few years. The development of melanoma, for example, may be associated with very early damage, which is not altered by using sunscreens later in life. We may also have made the reasonable, but perhaps flawed assumption, that purified synthetic agents used in trials are the real active principles in natural substances found in dietary fruits, vegetables, and fiber. These natural substances may combine or interact *in vivo*

in ways that we do not fully understand at present. Finally, progress in medicine is rarely, if ever, smooth and is usually characterized by an uneven pace, often with unpredictable results, and admixtures of success and failures. Why should we expect that cancer prevention would be different?

The Future

However uncertain our past progress in prevention, the future is still harder to predict. Nevertheless, several factors are certain to transform medicine and science in the next century, and cancer prevention and control with them. The rate of medical and scientific progress has accelerated, and that pace is certain to continue. It is certain that cancer prevention will be a significant focus of research and intervention during the next decades, propelled by the realization that we will be able to identify, very specifically, individual susceptibility to particular cancers and the molecular targets that can alter or stop the process of carcinogenesis.

Public and governmental activism toward medical research is here to stay and likely will increase. Through the Internet and other electronic resources, the public now has access to unprecedented, unlimited amounts of information in whatever degree of complexity they wish. The challenge will be to sort out the useful from the specious (31). Led by the successful activism in breast cancer and AIDS, patients now expect not just to be full participants in research trials but also to mold the direction of the research effort itself. The baby boomers staring old age and mortality in the face are using their political acumen and clout to push for medical progress in the diseases that threaten them most, cancer among them.

Another transforming change in this next century is the explosion of knowledge about human genes and the biological processes they regulate. In genetics and genomics, it is likely that researchers and clinicians will have some very potent tools to develop the cancer prevention weapons of the 21st century. This information will allow us to develop novel new diagnostics based on the reading of error messages inherent in cancers. It will allow us in a matter of hours to define an individual's susceptibility to particular cancers. It will allow us to use pharmacogenetics to solve the perplexing problem of why certain people respond to treatment and others do not. The result will be the ability to do disease-risk profiling and to tailor interventions to match individual needs. The fields of pharmacology and genetics are partnering to develop chemoprevention agents designed to affect molecular targets linked to specific premalignant or predisposing conditions. The ultimate role of gene therapy will be to use knowledge of the genome to reengineer the genetic predisposition to disease.

Cancer causation is not only the result of genetic predisposition and environmental exposures to carcinogens but is also influenced by the ability of the body to rid itself of carcinogenic insults. Individual cancer risk is clearly influenced by an individual's capacity to detoxify carcinogens. Molecular and biochemical studies, for example, suggest that oltipraz affords cellular protection by inducing the expression of a battery of Phase II detoxification enzymes (32). Oltipraz is a synthetic dithiolthione that is similar to a naturally occurring substance found in cruciferous vegetables, a food group long thought to

have some protective effect against cancer. Oltipraz was originally used as an antischistosomal agent. In studies designed to define the basis for its antiparasitic activity, it was observed that oltipraz seemed to increase cellular protection. Subsequent works had documented its value as a radioprotector and an antiviral and chemopreventive agent. Oltipraz appears to have broad applicability in protecting numerous organs against a variety of carcinogens. In preclinical studies, it has been demonstrated (32) that oltipraz can inhibit tumor formation in animal models and elevate detoxification enzyme expression in humans as well as mice. This is true in tumors affecting the colon, liver, lung, trachea, lymphatic system, breast, skin, pancreas, and bladder. The broad range of activity and ease of administration of this substance make it one of the most intriguing and exciting potential chemoprevention agents under development.

A third major force to alter medicine in the 21st century will be the information and computer revolution. In 1965 Gordon Moore, the cofounder of Intel, observed that the capacity of transistors on integrated circuit chips had doubled every 18 months since 1959. The implications of “Moore’s Law” are nothing short of astonishing. It suggests that by 2010, your home computer will have the capacity of current supercomputers. By 2020, your home computers will have the computing power equal to all of the Silicon Valley. By 2030, your laptop may have the computing power of the human brain (33). Although Moore’s Law will not hold indefinitely, it will still transform society, and medicine with it.

Most computer experts now feel that we will have the capacity to store and retrieve all medical information on everyone. Your hemoglobin at birth, a Pap smear from 1958, and every screening X-ray you ever had. Retrievable—easily and quickly. The extraordinary capacity of computers will allow worldwide dissemination of necessary medical records instantaneously. A colonoscopy can be done in California with a second opinion performed by reviewing all of the videos the next afternoon in London. A perplexing Pap smear performed in Singapore can be reviewed hours later by pathologists in Milan and Berlin.

With the power of computers, Internet cooperative groups for worldwide clinical prevention trials become feasible. Patients anywhere in the world can be evaluated for eligibility through an Internet-based study form, and the appropriate experimental drugs can be sent the same day to the physician much like Amazon.com sends you books.

Powerful computing will also revolutionize medical diagnostics (34). Miniaturized diagnostics will explore the colon without colonoscopy. Intravascular, freely mobile microrobots may allow constant monitoring of critical body functions, allowing dramatically altered ways of managing a patient’s health at home. Wristwatch devices will be available for biomonitoring; massive amounts of self-help information will be provided to patients through computers; and health coach software will be provided to assist patients interested in behavioral modification. This revolution will allow meaningful electronic house calls faster, cheaper, and more productively than those carried out two generations ago.

Telemedicine will allow the remote delivery of medical care to far-flung regions of the world where access and expertise

is not easily available (35). Video conferencing with physicians, patients, and patient support groups will be increasingly common and of great benefit to those homebound.

Although advocacy, demographics, genetics, and informatics seem destined to change the cancer prevention environment in the next century, it would be foolish to suggest that we can predict everything that will impact on cancer prevention over the next several decades or even years. “Wild cards” are likely to unexpectedly appear that alter our thinking and our opportunities. Indeed wild cards may be the norm, not the exception. Even the forces that we are sure will play a central role may end up impacting in completely unanticipated ways. We can be certain that medical records will become increasingly electronic, integrated and accessible to both doctors and patients, and that they will include in-depth profiles of an individual’s risk of disease.

For centuries, physicians have relied on the hand-written medical record. It is poorly organized, difficult to follow, hard to decipher, and bulky. Despite these limitations, it is a unique combination of medical information, a thoughtful analysis of medical problems and the synthesis of a strategy for rendering care. Its utility and complexity has allowed the written medical record to persist long into the computer age. However, the 21st century will likely see voice-recognition computing, electronic data transfer, and multimedia communications become perfected and widely available. Imagine the impact of an electronic medical record that could be transferred with the click of a mouse to anywhere where care was being delivered.

All doctors lament the increasing pressures on their time. But large amounts of each clinical encounter are consumed with information transfer and not medical care. Imagine a clinic day in which all pertinent information had been gathered before the patient arrived, all questions answerable in advance had been answered, and the only physician responsibility was to dispense care, or if care was not feasible, then solace.

We may see combinatorial chemistry, the computerized design of chemical compounds based on three-dimensional structure, lead to the accelerated development of chemoprevention agents, and their utility defined more rapidly through large-scale internet-enhanced clinical trials. Although the human genome project is an important advance, we all recognize that it is proteins not DNA that are the final messengers that bring cellular action. Their study, known as proteomics (36) will be a huge engine for change during the next century. We can be confident that DNA vaccines aimed at specific molecular targets will emerge with increasing rapidity as the sciences of genetics and molecular biology surge forward.

Medicine can also expect to have some strange partners in this brave new world (34). Corporations are demonstrating the enormous power of media not just to entertain and inform, but also to participate actively in changing behavior. It is inevitable that as electronic media, telephone, TV, movies, and Internet-service purchasing fuse into one seamlessly integrated system, there will be a resounding impact on medicine. We all wish that patients did not smoke, drink, eat too much, and exercise too little—but they do. Doctors are not very good at behavioral modification nor do they have time to spend in the present environment even if they were good at it. It is likely that corporations like Disney and MTV, both masters of behavior

modification of our children, could do a better job with healthy behavioral changes. Finally, comprehensive Internet systems like WebMD, focused on the needs of doctors, hospitals, and patients, may facilitate the work of all three.

Media, like medicine, can be tailored to identify and meet individual needs (34). Driven by a market economy, it is likely that patients will increasingly become consumers of medical services, scheduling and purchasing their procedures in an "e-bay"-like model. As we all know, there is great maldistribution of medical resources. Lines form waiting for access to procedures in one medical setting, while across town the waiting room is empty. How about E-Bay Medicine that uses computers to match supply and demand? This could find you an open mammography slot at 9 am tomorrow morning. One could list available time slots for appointments, say for a colonoscopy, on an interactive web site and have patients choose the time and place to receive these services.

The ultimate wild card may be in the development of nanotechnology.⁹ A nanometer is a billionth of a meter, the equivalent of three to four atoms wide. Whereas such a measure is almost conceptually impossible to imagine, it is now possible to construct molecular motors that allow for molecular manufacturing and repair on an atom-to-atom basis. We are still grappling with the complexity and moral considerations involved in intrauterine fetal surgery, while we stand at the brink of an era in which we might be able to change the molecular structure of individual genes and cells. Consider the possibilities of a nanosurgeon who could manipulate a few atoms to modify genetic predisposition, construct an intracellular repair kit, or implant an artificial immune system custom-designed to fight a specific disease or condition. Although this seems beyond comprehension, in the 1950s, Richard Feynman, the Nobel-prize-winning physicist, suggested that there were no laws of physics that would prevent such intercellular mechanics.¹⁰

In summary, there are a number of safe predictions that can be made regarding the future of cancer prevention. Public and governmental interest and activism will continue to increase. Political advocacy on medical and health-related issues is now a fixture in our society and can only become more sophisticated, better funded, and better fueled by the endless amount of information now available to the public. Disease prevention will be a major focus of medical-political efforts. The informatics revolution will allow for the rapid development of cancer prevention models, self-help risk reduction programs, and the completion of large-scale prevention trials.

Genetics and genomics will continue to power scientific advances. They will provide the tools for identifying populations and individuals at high risk for a wide spectrum of diseases, including cancer. Advances in cancer-screening technology focused on these high-risk populations will increase the speed and accuracy of early diagnosis and result in a more efficient and cost-effective system for applying screening interventions. From there, it is not difficult to envision an accelerated

chemoprevention drug-development program based on specific molecular targets. It is happening now. It is also likely that we will better define the interaction of environmental and host factors as well as the mechanisms by which chemopreventive agents function in human beings.

The history of cancer prevention is short. The future brims with promise. For all that has been, and is to be, the most solid, indisputable truth about this rapidly emerging field is that there will be surprises. It is the unimagined advances of the next 50 years, the things that we do not now have the tools or vision to foresee, that will likely make more profound changes than anything that has been discussed here.

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