

# Sixty Years of *CA: A Cancer Journal for Clinicians*

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## Abstract

The first issue of *CA: A Cancer Journal for Clinicians* was published in November of 1950. On the 60th anniversary of that date, we briefly review several seminal contributions to oncology and cancer control published in our journal during its first decade. *CA Cancer J Clin* 2010;60:345-350. ©2010 American Cancer Society, Inc.

## Happy 60th Birthday *CA!*

We suspect that most of you have, by now, noticed the American Cancer Society (ACS)'s birthday-themed media campaign that began a little over a year ago. The point of that message is to memorably and concisely invite others to join us in working toward “a world with less cancer and more birthdays,” and to summarize our strategy for accomplishing that goal—helping people “stay well” (prevention and early detection), “get well” (support and information for people facing cancer), “fight back” (advocacy), and “find cures” (research).

This article, however, refers to a more literal birthday—the 60th anniversary of the first issue of *CA: A Cancer Journal for Clinicians*. Although some scientific and medical journals are far older, *CA* is among the most venerable of oncology and cancer control journals.

Nearly all of the content in our journal is focused on current standards of care and on research likely to impact those standards in the near future. There is still so far to go toward the ACS's mission of “eliminating cancer as a major health problem” that time for retrospection is a luxury, especially for a journal with as few pages as *CA*. Nonetheless, we feel that after 60 years, it is reasonable to allocate a few pages to a brief look at where we have been.

Members of this editorial board therefore set aside several hours for perusing content from the first decade of *CA* (still known at that time as *CA: A Bulletin of Cancer Progress*). It is impossible for us to summarize a decade of articles in a few pages, so we will briefly discuss only a few articles that represent each of 4 themes: prevention, early detection, treatment, and clinician-patient communication. For each theme, we have paired several articles from *CA*'s first decade (1950-1959) and the most recent decade (2000-2009, 50 years later).

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**DISCLOSURES:** Dr. Patricia Ganz reports that her husband serves as the Chief Scientific Officer for Intrinsic Life Sciences, and they retain stock in Intrinsic Life Sciences. Dr. Peter Johnstone serves as President/CEO of the Midwest Proton Radiotherapy Institute. Dr. Martin Mahoney serves as a consultant for Merck; he has received research funding from Pfizer, and serves as a member of the speaker's bureau for Merck, Novartis, Pfizer and Sanofi Aventis. Dr. William Oh has served as a consultant for BIND Biosciences, Inc.; Genentech; and Centocor Ortho Biotech, Inc. Dr. Andrew Vickers serves as consultant for Theradex and for GlaxoSmithKline. Dr. Otis Brawley serves as an unpaid medical consultant to GlaxoSmithKline, Sanofi-Aventis, and CNN. The authors report no other conflicts of interest.

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The selection of just a few articles to review herein from the quite extensive list of *CA* articles with genuine historical importance was a difficult task, and we salute all of the authors and their articles that were so critical to the fight against cancer but which we were not able to summarize in these pages.

## Prevention: Lung Cancer Epidemiology and Tobacco Control

Tobacco use was, and still remains, the single greatest cause of cancer deaths, and so it is difficult to appreciate the level of evidence required for this to become accepted. Adverse health effects from smoking had been hypothesized much earlier, but it required extensive scientific evidence that began to accumulate during the 1950s to remove any reasonable doubt that smoking caused lung cancer in men.

Fortuitously, the evidence emerged in parallel on both sides of the Atlantic. In 1951, the ACS epidemiologists Hammond and Horn began planning the first large prospective epidemiological study of smoking in the United States, coincident with the initiation of the British Doctor's Study by Doll and Hill in England.

In a 1952 *CA* article, Hammond and Horn<sup>1</sup> noted the limitations of retrospective case-control studies in establishing the hazards of smoking. Two years later, citing preliminary evidence from what came to be known as the Hammond-Horn study, Hammond predicted that "...it may turn out that cigarette smoking not only greatly increases the probability of developing lung cancer but also markedly increases the death rate from other causes." Hammond also anticipated the difficulty of changing smoking behavior: "...it is by no means easy for heavy smokers to give up the habit or even to cut their consumption down to a moderate level. Furthermore, it is amazing to see how little effect danger sometimes has as a deterrent to people doing what they want to do..."<sup>2</sup>

Powerful economic and political forces sought to further confuse the issue, as illustrated in the March/April 1958 issue of *CA*, devoted entirely to lung cancer epidemiology. This featured a summary of results from the Hammond-Horn study, which found lung cancer death rates of 3.4 per 100,000 man-years in never smokers compared with 157.1 in current smokers of at least one pack of cigarettes daily.<sup>3</sup> It quoted Dr. Leroy Burney, then the Surgeon General of the United States, saying "...the Public Health Service

feels the weight of the evidence is increasingly pointing in one direction: that excessive smoking is one of the causative factors in lung cancer."<sup>4</sup> In the same issue, a tobacco industry representative dismissed the evidence, saying "For at least four years there have been repeated, sensational and fear-arousing statements and resultant headlines on the theoretical lethal nature of tobacco smoke...the statistical evidence in support of the cigarette theory has not been accepted as proof of generalized conclusions about smoking by several distinguished statisticians..."<sup>5</sup> Rutstein then rebutted the tobacco industry argument, saying "Lung cancer is a serious disease which causes much suffering and cuts down people in the prime of life. Should not public health authorities immediately recommend the obvious remedy suggested by sound epidemiologic observation and confirmatory laboratory evidence? If not, why not?"<sup>6</sup>

The following year, Davies wrote "The American Cancer Society considers the facts adequate and concludes that CIGARETTE SMOKING IS THE MAJOR CAUSATIVE FACTOR IN LUNG CANCER. This disease offers a greater opportunity for cancer prevention than any other type of cancer. The discoveries of the last decade in lung cancer research represent a breakthrough in the truest sense."<sup>7</sup>

Cokkinides et al<sup>8</sup> reported that the prevalence of cigarette smoking among persons in the United States age 18 years and older for the year 2008 was 20.5%, representing an approximate halving of the 42% smoking rate observed in 1965. This accomplishment is the result of a large and diverse body of basic science, clinical, and public health research and the application of evidence-based interventions. Much has been learned about the pharmacology and psychology of nicotine addiction, leading to effective use of behavioral interventions, nicotine replacement, and non-nicotine medications in smoking cessation.<sup>9,10</sup> There has also been tremendous progress in developing public health and policy interventions such as health education, excise taxes, cessation support services, legislation to reduce youth access to tobacco products, and clean indoor air legislation.<sup>8,11-14</sup>

Despite this substantial progress, economic and political factors remain, as Hammond predicted, a substantial barrier to eliminating the leading cause of death from cancer worldwide, and the global burden of deaths from cancer and other diseases related to smoking continues to rise.

Not all population segments have benefitted equally from tobacco control interventions; individuals with lower income and less education are more likely to initiate tobacco use during adolescence and less likely to quit successfully. There is evidence that the tobacco industry targets low-income and minority communities to influence smoking-uptake patterns. Tobacco control organizations are now seeking to reduce disparities in tobacco use and its health consequences by developing and implementing initiatives for these populations.<sup>8</sup>

Although a review of cancer risk factors is beyond the scope of this editorial, it is notable that the epidemiologic strategies used during the 1950s to recognize tobacco as a carcinogen have been very successfully applied to identify many other risk factors for cancer and other chronic diseases and to demonstrate that socioeconomic gradients exist in exposure to other risk factors. Moreover, comprehensive tobacco control strategies can serve as a model for addressing many other risk factors.<sup>15</sup>

### Early Detection: The Papanicolaou Test

With a few notable exceptions, early cancer detection during the 1950s referred largely to prompt recognition of signs and symptoms. During that period, ACS public education regarding early detection stressed awareness of the “7 warning signs of cancer.” This approach was the best available at the time, and there is little doubt that it permitted curative local therapy in some cases, and in others may have extended survival. Unfortunately, few cancers recognized by blood-tinged sputum or changes in bowel habits were curable with therapies of that era.

It was during this decade that the Papanicolaou (Pap) test was vigorously promoted and widely accepted, and *CA* featured 4 articles by George N. Papanicolaou between 1952 and 1957,<sup>16-19</sup> as well as additional articles by other cytologists, gynecologists, and other clinicians. In a 1952 review, Papanicolaou explained that “In reviewing the present status of exfoliative cytology it appears that its greatest contribution to science and to humanity is that it has furnished us with the means of detecting cancer in its incipiency. Thus, we are provided not only with the chance of attacking cancer while it still may be amenable to treatment but also with the material for the study of its earlier developmental stages. Such material is now

amply supplied by the large number of carcinomas in situ of the cervix, which are uncovered by the generalized use of this method. The thorough study of this material will lead us to the formulation of more exact criteria for early neoplastic change supplementing the well-established criteria based on the more advanced stages.”<sup>16</sup> Five years later, Papanicolaou predicted the profound impact of his method on cervical cancer mortality: “Looking into the future, one may find great encouragement in the warm-hearted support and endorsement given to cytologic research by the Public Health Service and the American Cancer Society. Their farsightedness in sponsoring mass screening projects and their unrelenting efforts to arouse public interest and to expedite education and training in this special field hold great promise that at least one form of cancer, that of the uterine cervix, may eventually be controlled and its death potential substantially reduced, if not fully eradicated. This, if accomplished, will be the realization of a dream, which only a few years ago would have had to be regarded as a Utopia.”<sup>19</sup>

It has been estimated that perfect adherence to cervical cytology screening every 1 to 3 years can reduce the incidence of invasive cervical cancer by more than 90%, but that because of incomplete adherence, the actual reduction in cervical cancer mortality after the introduction of cervical cytology screening in several North American and European populations has varied from 20% to 60%.<sup>20</sup> The Pap test remains among the current ACS recommendations for the early detection of cancer. The most recent ACS guideline update, in 2002, added testing for human papillomavirus (HPV) DNA as a screening option in combination with cervical cytology among women aged older than 30 years, and a 2007 ACS prevention guideline discussed HPV vaccination for cervical cancer prevention.<sup>21,22</sup>

Although we possess the technology to virtually eliminate death from cervical cancer, consistent implementation of evidence-based screening remains only a dream in many low-resource nations and a work in progress even for North America and Europe. Within the United States alone, substantial variation is observed in Pap test use among population segments, and the most powerful predictors of whether an American woman receives age-appropriate cervical cancer screening are educational level and health care insurance coverage.<sup>23</sup>

The Utopian cancer screening test, with near-perfect sensitivity and specificity, that can be performed with minimal morbidity and cost, and that permits curative treatment for asymptomatic lesions, still eludes us in 2010. Several current guideline-recommended tests, albeit imperfect, have not closely approached their lifesaving potential because of insufficient, uneven, and imperfect utilization.<sup>23</sup>

In a 1953 commentary, Hammond noted that cancer screening had not yet been proved to reduce cancer mortality. He further suggested that some neoplasms reach an incurable stage before they are detectable by current screening tests, that others will remain curable even after reaching a size that is obvious without screening, and that the most relevant subset is comprised of asymptomatic lesions detectable by screening that are still curable.<sup>24</sup> Hammond's comments foreshadowed much of the current controversy concerning overdiagnosis by screening of indolent cancers that would remain clinically insignificant, as well as the increasingly sophisticated epidemiological methods now used to develop evidence-based screening guidelines.<sup>23</sup>

## Treatment: Chemotherapy

Several important *CA* articles published during the 1950s reviewed the contemporary standards of care in surgical oncology and radiation oncology and the value of these modalities in the palliation and cure of cancer. In retrospect, however, perhaps the 2 most interesting *CA* articles on cancer treatment from that decade were juxtaposed in the September/October 1955 issue. One article, by Karnofsky, reviewed the current status of cancer chemotherapy, and the second, by Hamilton, discussed the relevance of DNA to medical oncology.<sup>25,26</sup>

We hope and expect that cancer drugs in use 50 years from now will be far more effective and safer than today's cytotoxic chemotherapy. However, this modality has contributed greatly to the survival of millions of patients during the past half century, and its role in oncology is likely to continue for the foreseeable future. In 1955, Karnofsky wrote that "Since the beneficial results of chemotherapy are thus only partial and temporary, with resistance ultimately appearing, it is hoped that a combination of several chemotherapeutic agents may produce a longer therapeutic response or actually cure the disease."<sup>25</sup>

Hamilton explained that "Our increasing knowledge of nucleic acids has been a major factor in dissipating the pessimism that has long shrouded the search for cancer-controlling chemicals. The nucleic acids have thus not only removed a long standing psychological barrier but also have provided an important practical basis for cancer chemotherapy... The natural sciences are essentially empirical and the science that underlies cancer chemotherapy is no exception. Thus aminopterin and amethoptenin, antagonists of folic acids, were found to be useful palliative agents in the treatment of acute leukemia in children before any knowledge of the intimate mechanism of their chemotherapeutic effect had been achieved." Anticipating the future of cancer biology and pharmacology, Hamilton suggested that "Just as the chemical formulation of the building blocks of DNA has permitted the design of antagonists for these building blocks, so it is reasonable to expect that this new knowledge of the arrangement in space of the building blocks of DNA and the impressive possibilities for determining the site of DNA specificity will provide a new target for 'rational cancer chemotherapy.'"<sup>26</sup> Thus began the gradual transition of cancer pharmacology from empirical endeavors such as screening natural products for in vitro cytotoxicity to the design of drugs based on an intimate understanding of molecular anatomy and physiology. Although today we tend to exclude cytotoxic drugs from the category of targeted therapies, one could reasonably view the breakthroughs in nucleic acid chemistry and biology of the 1950s as key events in early targeted therapies. Following this line of reasoning, the difference between targeted therapies of the 1950s and those of the current decade is that the former were mostly aimed at pathways of nucleic acid metabolism and gene structure whereas the latter generally target pathways that regulate cell proliferation and survival.

It seems notable in retrospect that initial clinical studies of cytotoxic chemotherapy did not produce any cures and provided rather brief responses, but the combination of basic and clinical research over several decades incrementally improved the efficacy, controlled the toxicity, and refined the indications for this modality. Some forms of cancer (such as Hodgkin disease, germ cell cancer of the testis, acute lymphoid leukemia, and some types of non-Hodgkin lymphoma) are now frequently cured by cytotoxic chemotherapy alone; other forms are occasionally curable;

and, for many others, cytotoxic chemotherapy makes a substantial contribution (often in combination with other modalities) to curative therapy, extending survival, and palliating symptoms.<sup>27</sup> The current diversity of pharmacologic approaches targeting membrane-bound receptor kinases, intracellular signaling kinases, epigenetic abnormalities, protein dynamics, and tumor vasculature and microenvironment and the rational precision of their design are impressive products of decades of basic research.<sup>28</sup> With few exceptions, these agents have not yet yielded the cures that preclinical studies led us to hope for. Only time, patience, and perseverance will reveal whether today's new classes of drugs follow a similar trajectory as clinicians learn to optimally combine them with one another and with other modalities.

### Clinician-Patient Communication: Prognostic Disclosure

Given the poor prognosis associated with a cancer diagnosis during the 1950s, the attention to end-of-life care in *CA* articles during that decade is not surprising. What does seem remarkable, particularly when viewed in the context of current ethical views, is that the wisdom of diagnostic and prognostic disclosure was frequently debated in *CA*, and that authors often recommended against disclosure. In the January/February 1953 issue, Spencer and Laszlo focused on treatment options for patients with advanced cancer but also addressed the following question: "Should the patient be told his diagnosis and prognosis? This is a very controversial topic and no fixed answer is applicable to all patients. However, it seems that the physician and responsible members of the family can bear the burden of the diagnosis and prognosis better than the patient. The fear associated with this disease in the minds of the public is sometimes so great that acute depressions and suicidal attempts have followed the disclosure of such information. Furthermore, there seems no apparent advantage to the patient in burdening him with this knowledge. If the symptoms are explained to him in terms other than cancer and a concise plan of management is offered, difficulties are rarely encountered."<sup>29</sup>

In considering this topic, it is difficult for us to avoid what historians call the bias of presentism ("an attitude toward the past dominated by present-day attitudes and experiences"<sup>30</sup>). Another article in the same

issue of *CA*, by Finesinger et al,<sup>31</sup> described a series of interviews with 72 oncology patients, revealing rather shocking attitudes and beliefs about cancer. They reported that "These feelings of guilt—it is my fault that I have cancer; I must have done something wrong—occurred in every one of our patients. Many patients react to cancer as they would to venereal disease—"It is foul,' 'I am ashamed to have it,' 'I am ashamed to talk about it.'" Denial was a common behavioral defense mechanism: "...the behavior in at least two thirds of the cases showed clear evidence of avoiding facing their problem realistically..." and "A few (five patients) actually denied that they had a cancer, attributing their symptoms to other causes. Many others (twenty-six) denied the gravity of their situation by displaying an unnatural lack of concern..." They considered the views of this 56-year-old woman with inoperable breast cancer to be representative: "It's not like heart trouble because it is such a dirty disease—so unclean—repellent. In the end there is an odor—often there is deformity. People fear contagion. They don't like to be with cancer patients. You can not know how awful it is. In the past when I had known people had cancer, I always felt so badly for them. Heart disease is not unclean. People don't object to being with these people. It's all my fault too. I must have done something to deserve all this." They conclude with the following advice: "How much of the truth should we tell? From the strict operational point of view the answer would be all that is necessary to achieve the goal of therapy. In some patients more information is necessary than in others. We have found this operational rule useful in many difficult problems. Our job is not to make psychiatrists, psychologists, pathologists, or surgeons of our patients. It is to supply them with enough practical information to help them use the best available therapy with the minimal personal disturbance. We need not tell the whole truth but whatever we say should be truthful."<sup>31</sup>

During the past 5 to 6 decades, our attitudes toward physician-patient communication and prognostic disclosure have changed as dramatically as, and perhaps as a result of, the concomitant progress in understanding, detecting, and treating cancer. Delivering appropriate information and delivering information appropriately are now recognized as essential skills for oncology care professionals. The importance of this skill in optimizing patient choices regarding treatment, and especially so regarding end-of-life care, as

well as reducing distress among patients and their families has been emphasized in several recent *CA* reviews.<sup>32-35</sup> Studies have demonstrated that frameworks such as SPIKES (Setting, Perception, Invitation, Knowledge, Empathy, and Strategize) and NURSE (Naming, Understanding, Respecting, Supporting, and Exploring) can facilitate prognostic disclosure and responding to patients' reactions to that information, and that training in these and other techniques can improve communication effectiveness and reduce provider burnout.<sup>32-33</sup>

## Conclusions

We have undertaken this brief historical activity in part as a celebration of our journal's longstanding role in providing valuable information about cancer to clinicians. In so doing, however, we have been profoundly touched by this reminder of the courage, determination, and inspiration with which patients, clinicians, and scientists confronted the bleak reality of cancer during the 1950s. Public health without tobacco control or medical oncology before recognition of the double helix seems shockingly primitive by today's standards. It is our prediction and our sincere hope that future retrospection will reach the same conclusions regarding cancer control and clinical oncology practices of this decade, and that information in this journal will continue to assist clinical and public health professionals, as it has for the past 60 years, in diminishing and eventually eliminating the burden of cancer on individuals and society. ■

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