# The War on Cancer
## *A Progress Report for Skeptics*

*Although there has been some progress in the war on cancer initiated by President Nixon in 1971, the gains have been limited.*

REYNOLD SPECTOR

In 1971, President Nixon and Congress declared war on cancer. Since then, the federal government has spent well over $105 billion on the effort (Kolata 2009b). What have we gained from that huge investment? David Nathan, a well-known professor and administrator, maintains in his book *The Cancer Treatment Revolution* (2007) that we have made substantial progress. However, he greatly overestimates the potential of the newer so-called "smart drugs." Researchers Psyrri and De Vita (2008) also claim important progress. However, they cherry-pick the cancers with which there has been some progress and do not discuss the failures. Moreover, they only discuss the last decade rather than a more balanced view of 1950 or 1975 to the present.

On the other hand, Gina Kolata pointed out in *The New York Times* that the cancer death rate, adjusted for the size and age of the population, has decreased by only 5 percent since 1950 (Kolata 2009a). She argues that there has been very little overall progress in the war on cancer.

In this article, I will focus on adult cancer, since child cancer makes up less than 1 percent of all cancer diagnosed. I will then place the facts in proper perspective after an overview of the epidemiology, diagnosis, and treatment (especially with smart drugs) of adult cancer in the United States.

## The Cancer Facts

Figure 1 shows the ten biggest killers in the United States in 2006. Cancer (23 percent) has almost caught up with heart disease. Figure 2 shows the death rates from cancer in men and women (adjusted for the size and age of the population) since 1975; the cancer death rates have declined in men but not in women. The decline in men is largely due to fewer lung cancer deaths in men due to less smoking (see figure 3). However, there were about 200,000 more deaths from cancer in 2006 than 1975 because of the substantial increase in the U.S. population.

These summary statistics show that the war on cancer has not gone well. This is in marked contrast to death rates from stroke and cardiovascular disease (adjusted for the age and size of the population), which have fallen by 74 percent and 64 percent, respectively, from 1950 through 2006; and by 60 percent and 52 percent, respectively, from 1975 through 2006 (Kolata 2009a). These excellent results against stroke and heart disease are mainly due to improvements in drug therapy, especially the control of high blood pressure to prevent stroke and the use of statins, aspirin, beta blockers, calcium channel blockers, and ACE inhibitors (now all generic) to prevent and treat heart disease. Cancer therapy is clearly decades behind. However, these data conceal a great deal of useful information and do not provide guidance on how to make progress against cancer.

**Table 1**

Critical Terms Defined in the Text

1) Cancer—three kinds: local, regional, distant (metastatic)
2) Carcinoma (cancer) in situ—e.g., ductal carcinoma of the breast (DCIS)
3) Slow cancers—e.g., prostate, breast
4) Cancer treatments: surgery, chemotherapy, radiation therapy
5) Partial response
6) Complete response
7) Cure
8) Median survival, one/five-year survival

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**U.S. Mortality, 2006**

| Rank | Cause of Death | No. of Deaths | % of All Deaths |
|---|---|---|---|
| 1. | Heart Diseases | 631,636 | 26.0 |
| **2.** | **Cancer** | **559,888** | **23.1** |
| 3. | Cerebrovascular Diseases | 137,119 | 5.7 |
| 4. | Chronic Lower Respiratory Diseases | 124,583 | 5.1 |
| 5. | Accidents (unintentional injuries) | 121,599 | 5.0 |
| 6. | Diabetes Mellitus | 72,449 | 3.0 |
| 7. | Alzheimer Disease | 72,432 | 3.0 |
| 8. | Influenza & Pneumonia | 56,326 | 2.3 |
| 9. | Nephritis* | 45,344 | 1.9 |
| 10. | Septicemia | 34,234 | 1.4 |

*Includes nephrotic syndrome and nephrosis

Sources: U.S. Mortality Data 2006, National Health and Statistics, Centers for Disease Control and Prevention, 2009

Figure 1

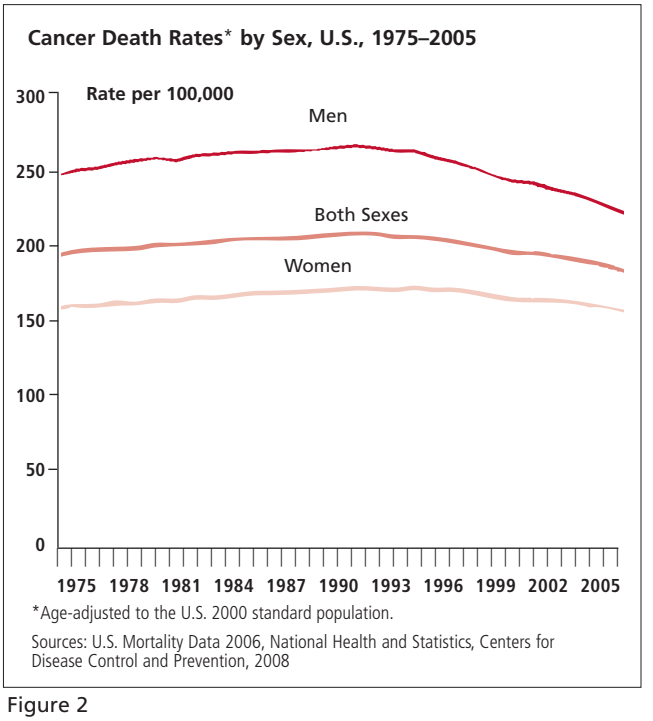


Figure 2

## Methodological Issues

To understand the issues, we must describe a few statistical traps and define our terms (see table 1). For example, there are several types of detection bias. First, if one discovers a malignant tumor very early and starts therapy immediately, even if the therapy is worthless, it will appear that the patient lives longer than a second patient (with an identical tumor) treated with another worthless drug if the cancer in the second patient was detected later. Second, detection bias can also occur with small tumors, especially of the breast and prostate, that would not harm the patient if left untreated but can lead to unnecessary and sometimes mutilating therapy. Another type is publication bias, whereby positive studies (especially those funded by the pharmaceutical industry) tend to be published while negative studies do not.

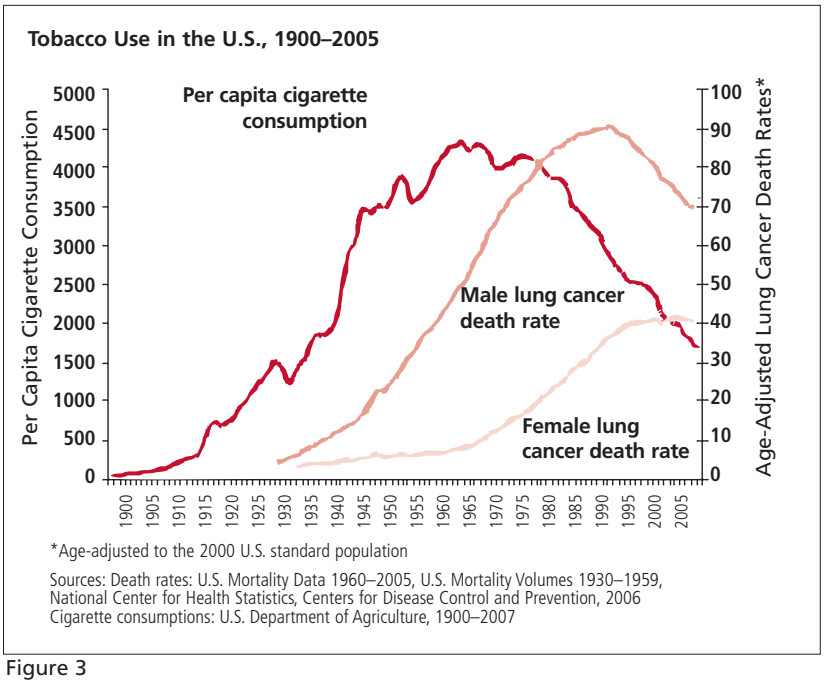

Figure 3

What is cancer? Cancer is a large group of diseases characterized by the uncontrolled growth and spread of abnormal cells locally, regionally, and/or distantly (metastatically) (American Cancer Society 2009). A carcinoma (cancer) in situ is a small cancer that has not invaded the local tissue. Some cancers grow very slowly, and the patient may survive for ten years or more with minimal treatment. Other cancers (e.g., lung and pancreas) grow quickly and, even today, kill more than half of the patients in less than one year (see table 2) (American Cancer Society 2009). The therapy for cancer is generally surgery, if possible, and/or chemotherapy and/or radiation therapy. Chemotherapy aims to kill the cancer cells, but most chemotherapeutic drugs are nonspecific and also kill sensitive normal cells, especially in the intestine and bone marrow. Radiation therapy is also nonspecific. In chemotherapy and radiation therapy, a partial response is defined as shrinkage of the tumor in each

**Table 2**

Common Cancers

Current Death and Survival Statistics (American Cancer Society 2009)

| Cancer Origin | Percent of Cancer Deaths | One-Year Survival (%) | Five-Year Survival (%) |
|---|---|---|---|
| Lung | 28 | 41 | 15 |
| Colon/Rectum | 9 | 83 | 64 |
| Breast | 8 | >95 | 89 |
| Pancreas | 6 | 24 | 5 |
| Prostate | 5 | * | * |
| Leukemia | 4 | ** | 51 |
| Lymphoma | 4 | 82 | 68 |
| Liver | 3 | † | <10 |
| Other | 33 | †† | †† |

*Survival statistics for prostate cancer are very misleading since they include many treated cancers that would not have harmed (or killed) the patient (see text).
**Leukemia is a heterogenous group of diseases. The five-year survival figure is an average of all types.
†Liver cancer is a rapidly fatal disease in which treatment is ineffective.
††Other cancers are so heterogenous that the reader should consult the American Cancer Society (2009) for specific data.

**Table 3**

Examples of Probable or Definite Causes of Cancer (American Cancer Society 2009)

1) External Factors
   a) Tobacco
   b) Chemicals (e.g., asbestos, benzene, alcohol)
   c) Radiation
   d) Infections, organisms (e.g., hepatitis B, papilloma virus, *Helicobacter*)
   e) Hormone replacement therapy with estrogen

2) Internal Factors
   a) Genetic mutations
      1) inherited
      2) acquired
   b) Hormones (e.g., estrogen)
   c) Immune disorders (e.g., AIDS)
   d) Epigenetic changes
   e) Obesity

dimension by 50 percent; a complete response means no detectable tumor, but this does not necessarily mean a "cure." Many complete responses are only transitory. Median survival is the length of time in which one-half of the patients in a cohort die.

## What Do We Know about Cancer?

The "causes" of cancer are shown in table 3 (American Cancer Society 2009), though there is still much we don't know. For example, we do not know exactly how smoking causes cancer; in most cases, we do not know how "acquired" mutations cause cancer. In some cancers, there are more than five hundred identifiable genetic abnormalities—no one knows which one(s), if any, is "causative" (Downing 2009). The importance of epigenetic changes is currently speculative. It is quite possible that there is a completely unknown causal mechanism in many cancers.

The diagnosis of cancer today is relatively straightforward with imaging techniques (x-ray, CAT, MRI, PET) and biopsies that are subjected to routine histology, electron microscopy, and immunological techniques.

## Cancer Therapy

To have a reasonable discussion of cancer therapy, we need to agree on the objectives of therapy (Fojo and Grady 2009), as shown in table 4. Everyone agrees that meaningful prolongation of life, preferably complete surgical removal of the tumor and cure, is a high priority. The treatment should also improve the quality of life. But, as is well known, many chemotherapeutic and radiation regimens cause mild to devastating—even fatal—side effects. Nathan (2007) compares conventional chemotherapy to "carpet-bombing," an extreme but realistic metaphor. Finally, the results of a cost-benefit analysis must be reasonable (Fojo and Grady 2009). (In some cases, justifiably and importantly, chemotherapy and/or radiation and/or other drugs are used as palliative measures exclusively to counter symptoms from the disease [e.g., pleural effusions in the chest cavity or bone pain] or from the treatments [e.g., vomiting, mucositis, low white blood counts, heart failure, nerve damage, diarrhea, and/or inflammation of the bladder]). In the final analysis, what counts are the criteria in table 4. Partial or even complete remissions, unless they prolong life and/or improve the overall quality of life at a reasonable cost, are scientifically interesting but of little use to the patient.

**Table 4**

Criteria for Utility of Cancer Therapy
(Fojo and Grady 2009)

1) Meaningful prolongation of life or cure (mortality)

2) Improvement of quality of life (symptoms)

3) Value of treatment (compared to cost)

**Table 5**

Bevacizumab (Avastin)—Utility

| Cancer | Evidence for Prolongation of life; time* |
|---|---|
| Bowel/ Rectum | Yes, four months (median survival) with other drugs |
| Lung | No + |
| Breast | No |
| Kidney | No |
| Glioblastoma (Brain) | No |

*Compared to randomized control (if available)
+"No" means a lack of a statistically significant prolongation

Currently there are a few metastatic cancers that can sometimes be cured with chemotherapy and/or radiation therapy, but unfortunately these cures make up a very small percentage of the whole cancer problem. These cancers include testicular cancer, choriocarcinoma, Hodgkin's and non-Hodgkin's lymphoma, leukemia, and rare cases of breast and ovarian cancer. A few cancers can be made into chronic diseases that require daily treatment, e.g., chronic myelogenous leukemia.

Returning to table 2, lung cancer, the most common cancer, is a devastating disease; if the surgeon cannot totally remove it, the diagnosis is grim. In fact, about 60 percent of lung cancer patients are dead within one year of diagnosis with the best available therapy, and only 15 percent survive five years.

There has been some progress in the death rate from colorectal cancer (figures 4 and 5), especially in women. This is mainly due to earlier diagnosis and surgical therapy.

Cancer of the breast is often a slow cancer and has a five- to ten-year median survival rate with just surgical therapy. As can be seen in figure 5, there has been a modest decline in death rates from breast cancer since 1975. It is worth noting that currently, if the breast cancer is metastatic, five-year survival is only 27 percent (American Cancer Society 2009). However, breast cancer presents a serious dilemma. Early detection of invasive breast cancer by screening is good; however, about 62,000 cases of ductal carcinoma in situ (DCIS) are also discovered every year (American Cancer Society 2009). In greater than 50 percent of these women, especially older women, these lesions will not progress and do not need treatment. However, it is difficult to predict who will not need therapy, so the American Cancer Society (2009) recommends all patients with DCIS undergo therapy—generally breast surgery. Thus, more than thirty thousand patents annually are unnecessarily treated (Evans et al. 2009). We need to figure out which DCIS are harmless in order to avoid unnecessary treatment. On balance, I feel that breast cancer screening has a small but positive net benefit (Esserman et al. 2009).

Pancreatic cancer is devastating (see table 2 and figures 4 and 5), and little progress has been made against it since 1975. Pancreatic cancer is very challenging because the tumors are surrounded by dense fibrous connective tissue with few blood vessels (Olson and Hanahan 2009). Because of this, it is difficult to deliver drugs to pancreatic tumors. Moreover, this explains in part why chemotherapy is so ineffective for pan-

creatic cancer (see table 2). Better animal models are needed.

Prostate cancer mortality has declined slightly since 1975 with an unexplained increase in the mid-1990s (see figure 4). But prostate cancer therapy also presents a serious quandary. At autopsy, approximately 30 percent (or more) of men have cancer foci in their prostate glands, yet only 1 to 2 percent of men die of prostate cancer. Thus less than 10 percent of prostate cancer patients require treatment. This presents a serious dilemma: whom should the physician treat? Moreover, recently, two large studies of prostate cancer screening with prostate specific antigen (PSA) have seriously questioned the utility of screening. In one study, the investigators had to screen over a thousand men before they saved one life. This led to about fifty "false positive" patients who often underwent surgery and/or radiation therapy unnecessarily (Schröder et al. 2009). The second study, conducted in the United States, was negative (Andriole et al. 2009), i.e., no lives were saved due to the screening, but many of the screening-positive patients with prostate cancer were treated. Welch and Albertson (2009) and Brawley (2009) estimate that more than a million men in the U.S. have been unnecessarily treated for prostate cancer between 1986 and 2005, due to over-diagnostic PSA screening tests. In the end, screening for prostate cancer will not be useful until methods are developed to determine which prostate cancers detected by screening will harm the patient (Welch and Albertson 2009; Brawley 2009). Many men—especially elderly ones—with a histological diagnosis of prostate cancer elect "watchful waiting" with no therapy, a rational strategy (Esserman et al. 2009).

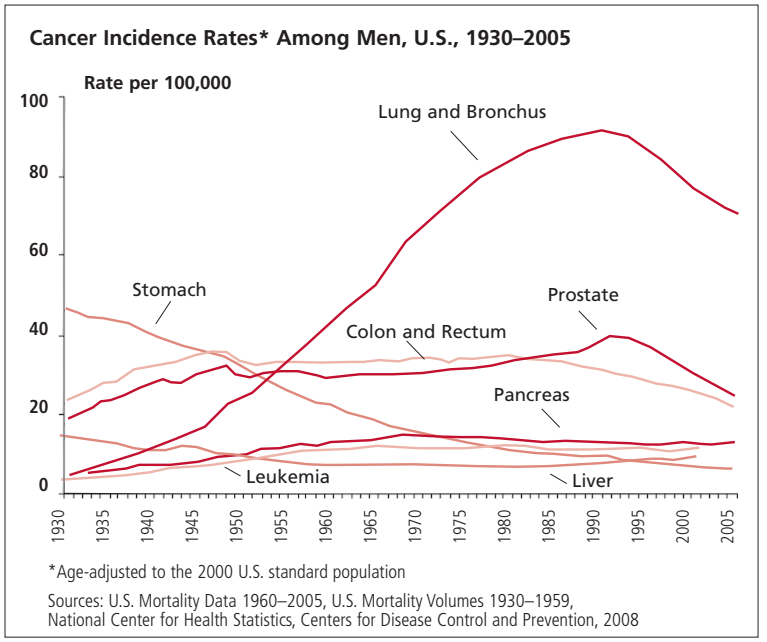


Figure 4

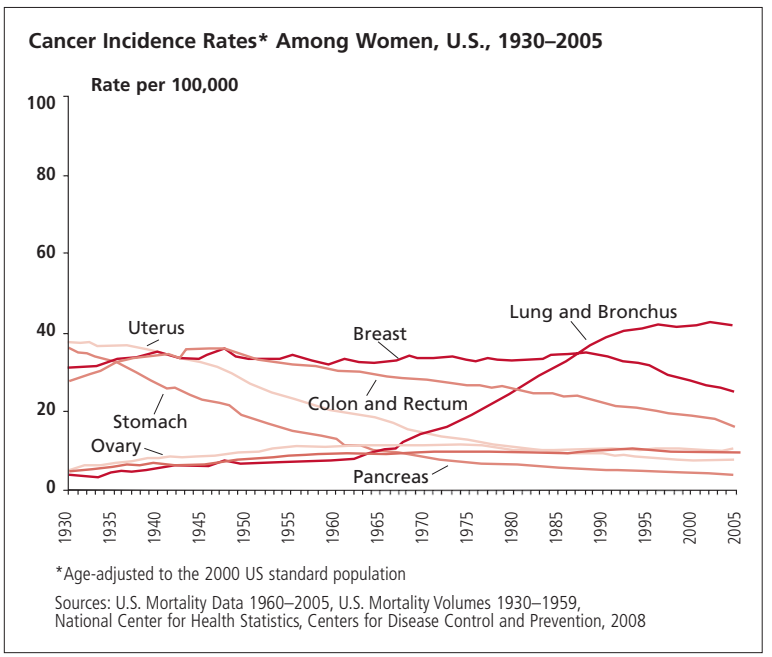


Figure 5

There are many other things we do not understand about cancer—even on a phenomenological level. For example, in the United States, the incidence and death rates from cancer of the stomach have fallen dramatically since 1930 (see figures 4 and 5). The reason for this is unknown but may be due to changes in food preservation; it is not due to treatment.

## Smart Drugs

David Nathan (2007) extols the virtues and potential of the new "smart drugs." Smart drugs are defined as drugs that focus on a particular vulnerability of the cancer; they are not generalized but rather specific toxins. But the *Journal of the American Medical Association* (Health Agencies Update 2009) reports that 90 percent of the drugs or biologics approved by the FDA in the past four years for cancer (many of them smart drugs) cost more than $20,000 for twelve weeks of therapy, and many offer a survival benefit of only two months or less (Fojo and Grady 2009). Let us take bevacizumab (Avastin), the ninth largest selling drug in America ($4.8 billion in 2008), costing about $8,000 per month per patient (Keim 2008). Bevacizumab, a putative smart drug, is an intravenous man-made antibody that blocks the action of vascular endothelial growth factor (VEFG). It sometimes works because tumors (and normal tissues) release VEFG to facilitate small blood vessel in-growth into the tumor. These small blood vessels "nourish" the tumor (or normal tissue). The idea is to "starve" the growing tumor with once or twice monthly intravenous injections of bevacizumab.

The FDA has approved bevacizumab for the cancers listed in table 5 (Physicians Desk Reference

[PDR] 2009; Health Agencies Update 2009). Since the median survival of colorectal cancer is eighteen months, bevacizumab therapy would cost about $144,000 (in such a patient) for four months prolongation of survival (Keim 2008). In the other cancers in table 4, there is no prolongation of survival. Moreover, bevacizumab can have terrible side effects, including gastrointestinal perforations, serious bleeding, severe hypertension, clot formation, and delayed wound healing (PDR 2009). By the criteria in table 4, bevacizumab is at best a marginal drug. It only slightly prolongs life, demonstrable only in colorectal cancer, has serious side effects, and is very expensive.

Bevacizumab is frequently cited as an example of the so-called newer smart drugs. But by interfering with small blood vessel growth throughout the body, it is a nonspecific toxin—and hence has serious side effects. It is not so different from the older non-specific chemotherapy.

The use of bevacizumab and similar drugs raises another issue. According to Gina Kolata, 60 to 80 percent of oncologists' revenue comes from infusion of anti-cancer drugs in their offices. Many believe that such economic incentives are the reason for the substantial overuse of expensive chemotherapeutic drugs (Kolata 2009c). However, it is very difficult to document the extent of the overuse of cancer chemotherapy. Does it make sense to employ such expensive drugs that do not prolong life (see table 5) and have such serious side effects (Fojo and Grady 2009)? Moreover, although VEGF and bevacizumab are interesting science, there has been gross exaggeration of bevacizumab's clinical utility in the press (see tables 4 and 5).

So why does the U.S. Food and Drug Administration (FDA) approve bevacizumab (and other drugs) that do not improve longevity and/or the quality of life (see table 5)? The answer is that bevacizumab coupled with other drugs can cause partial remissions, "stabilization" of the cancer, or "lack of progression" for several months. However, this often does not lead to prolongation of life in most of the cancers in table 5. Moreover, many patients pay a heavy price in terms of side effects and cost. It is also worth noting that several European national regulatory authorities do not accept the utility of some of these smart drugs and do not license them for sale in their countries. In agreement with the Europeans, scientists at the U.S. National Cancer Institute are urging the oncology community, regulators, and the public to set limits on the use and pricing of such marginal drugs (Fojo and Grady 2009). They view the current situation as unsustainable.

**Table 6**

Why Has the War on Cancer Failed?

1) We don't understand the cause/pathogenesis in most cases of cancer—smoking is an obvious phenomenological exception.
2) Most treatments (except surgery) are nonspecific cell killers and not "smart" (Nathan 2007).
3) Clinical trials and the grant system don't foster innovation—need reform (Kolata 2009c).
4) Screening for useful drugs against cancer cells has not worked.
5) Animal models of cancer are often inadequate—e.g., pancreatic cancer as described in this article (Olson and Hanahan 2009).
6) Unproductive "fads" in research come and go.

**Table 7**

The Way Forward

1) Prevention (cancer prevented)
   a. Stop smoking (lung; others) (see figure 3)
   b. Minimize hormone replacement therapy (breast)
   c. Vaccines
      1) Hepatitis B (liver)
      2) Papilloma virus (cervical, anal, penis)
   d. Eliminate *Helicobacter* with antibiotics (stomach)
   e. Prevent contracting AIDS (sarcoma)
   f. Chemoprophylaxis
      3) finasteride (prostate)
      4) tamoxifen (high risk breast)
   g. Decrease alcohol (liver, esophagus)
   h. Decrease obesity (many types)
2) Screening for
   a. Cervical cancer
   b. Colorectal cancer
   c. Breast cancer
3) More knowledge of cancers' causes and better animal models
4) Better drugs—once appropriate targets identified

## Why Has the War on Cancer Failed?

As documented above, unlike the successes against heart disease and stroke, the war on cancer, after almost forty years, must be deemed a failure with a few notable exceptions (Watson 2009). Why? Is it because cancer is an incredibly tough problem, or are there other explanations? In table 6, I have listed six reasons for the failure, although there is little doubt that effective, safe therapy of the various cancers is a difficult problem.

## Where Should We Go from Here?

In my view the principal problem is that we just do not understand the causes of most cancers. We don't even know if the problem is genetic or epigenetic or something totally unknown. In theory, problems 2 through 6 in table 6 are all correctable with political and scientific will and more knowledge. Even though we know cancer of the lung is caused by cigarette smoking, we do not know the mechanism, and (except for surgery) we do not know how to meaningfully intervene (see table 2). The pharmaceutical industry cannot

make real progress until we understand the mechanisms and molecular causes of cancer so that industrial, academic, and governmental scientists have rational targets for intervention. We will make no progress if there are five hundred or more genetic abnormalities in a single cancer cell. Where would one begin?

## What Should We Do Now?

We can still do a lot even today (see table 7). Smoking and hormone replacement therapy are a cause of lung and breast cancer, respectively, and should be stopped or minimized. For hepatitis B (which causes over 50 percent of liver cancer) (Chang et al. 2009) and papilloma virus (which causes almost all cervical cancer and some anal and mouth cancers), we can vaccinate with vaccines that are essentially 100 percent effective. *Helicobacter* (the probable cause of some stomach cancer) can be easily eliminated with antibiotics. Prophylactic finasteride and tamoxifen (both generic) can decrease prostate and breast cancer, respectively (in high risk patients). We must also decrease alcohol intake (liver and esophageal cancer) and obesity. Obesity is associated with increased cancer risk but the mechanism, if causal, is obscure (Dobson 2009).

**The pharmaceutical industry cannot make real progress until we understand the mechanisms and molecular causes of cancer so that industrial, academic, and governmental scientists have rational targets for intervention.**

We can screen for cervical, colorectal, and breast cancer, although the value of breast cancer screening is not clear (due to overdiagnosis), as I discussed above (Singer 2009). However, in my view, the benefit of breast cancer screening slightly outweighs the harm. For example, if DCIS treatment could be rationalized and provided only to those who need it, breast cancer screening would then be unarguably useful. All attempts to screen for lung cancer, even in smokers, have so far been futile (Infante et al. 2009).

If all these recommendations were followed, we could cut cancer deaths in half. Moreover, with better mechanistic understanding of cancer, we could make truly "smart" drugs, as has been done in recent years for atherosclerosis (heart attacks), hypertension (strokes), gastrointestinal diseases (ulcers), and AIDS—with truly remarkable results. Let us hope cancer is next. □


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