Testimony

Before the

Special Committee on Aging

United States Senate

Statement of
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Wednesday, May 7, 2014

Mr. Chairman, Senator Collins, and others:

I am pleased to appear today on behalf of the National Cancer Institute to discuss the relationship of cancer to aging.

It is an opportune moment for this discussion. Thanks in large part to improvements in health care, life expectancy has been extended at unprecedented rates, both in our country and around the world. The number of people over age 65 is growing especially rapidly in countries like the United States that experienced sharp increases in birth rates shortly after World War II, nearly 70 years ago. Furthermore, significant progress is being made in cancer research, with a much deeper understanding of the nature of this complex set of diseases and with improvements in the way we prevent, diagnose, and treat many kinds of cancers. Hence, there is both a need and an opportunity to address more effectively the problems presented by cancers in the elderly.

Because most types of cancer—but not all—are commonly diagnosed in older age groups, the number of people with cancer is rising, and will continue to rise, here and globally. This chart (the only one I will show) displays both the current and anticipated future distribution of new cases of cancer, grouped by age range, in the United States. As you can see, the absolute number of cases will rise from about 1.7 million today to about 2.5 million by 2040. The majority of new cases already occurs in three age groups—65 to 74, 75 to 84, and 85 or greater. The proportions will increase in all three groups over the next thirty years, assuming that current patterns are maintained, with little change in the younger groups. Of course, we aspire to change those patterns with more effective means to prevent cancers. But the pace of such change is inherently slow, in part because cancers develop over many years, not days or months.

As the elderly population grows and our ability to treat cancer improves, we are also observing greater numbers of people, especially among the older age groups, who are survivors of cancer. Cancer survivors are people who have had a cancer diagnosed at anytime in the past, whether or not they remain under treatment or have evidence of cancer currently. At present, there are over 13 million cancer survivors in the United States, up from about three million in the early 1970s, and the number is expected to rise to about 18 million by 2020. More than half of these people are over 65 years of age, and that older group will experience the major increase in numbers.

During the next several minutes, I will summarize what we know about the biological basis of the relationship of cancer to aging; what can now be done to prevent, detect, and treat cancer more effectively, especially among the elderly; and how the NCI and its research community plan to expand our knowledge of the relationship of cancer to aging, in hopes of reducing the burden of cancer among those at advanced ages.

In considering all of these topics, it is important to keep in mind the special vulnerabilities of older individuals—including, in particular, co-existing medical conditions (referred to as "co-morbidities") that can shorten life independently of the effects of cancer and can complicate delivery of cancer therapies.

The relationship of cancer and aging

Overall, cancers are diseases caused by accumulated changes, mostly mutations, in a cell's genome. Since those changes accumulate with age, the incidence of cancers also increases as people age. Further, the number of cases in each country rises as life expectancy increases, even without any increase in the incidence (or rate of occurrence). This is a large part of the reason why cancers, as well as other non-communicable diseases, have recently become major causes of morbidity and mortality in the developing world, where overall life expectancy is rising rapidly.

To distinguish between changes in the age distribution of a population and changes in our ability to prevent and treat cancers, it is important to monitor progress against cancer by reporting rates of incidence and mortality, adjusted for changes in length of life, not simply by counting the numbers of cases. Furthermore, the relationship of cancer to age is not simple: not all cancer types show an increased incidence with increased age.

Recall that there are many types of cancer, and these types arise in different kinds of cells and in different organs. Moreover, we now know that these different cancers generally carry different constellations of changes in DNA. This means that the incidence of each cancer type is influenced by the numbers of cells at risk of becoming cancerous in each organ at different ages. The risk of developing cancers of different types is also affected by the degree of exposure to environmental agents that cause mutations; by gene variations inherited from one's parents; by the function of the immune system, which itself appears to weaken as we age; and by the availability of methods that prevent cancers or detect abnormal cells before they become fully malignant.

In view of these varied factors, it is not surprising that types of cancer vary with regard to the time of onset. Most dramatically, some cancers—like retinoblastomas, some leukemias and lymphomas, and some brain and bone cancers—are largely confined to children, adolescents, and young adults. In contrast, the median age of onset of most of the common cancers is between

the ages of 61 and 72, consistent with the more general conclusion (reflected in the chart) that over half of all cancers are diagnosed in older age groups. There is one further complication: while most findings argue for increasing rates of cancer with increasing age, the age-adjusted rate (or incidence) of many cancers appears to fall at highly advanced ages.[1]

I will say more in a few minutes about some of these perplexing—and potentially informative—relationships between age and cancer incidence. But I want to conclude this segment of my testimony by reminding you of the dominant facts and their implications. First, the U.S. population is rapidly aging. The numbers of people over the ages of 65, 75, and 85 will all increase markedly over the next three decades, with nearly a doubling of the number over 65 and nearly a tripling of those over 85. Second, even now over half of all cancers are diagnosed in people over the age of 65, so age must be viewed as a major risk factor for cancer, along with use of tobacco, excessive exposure to other carcinogenic agents, and inheritance of certain genetic variations. Thus the number of cancer cases is likely to rise significantly over the next few decades in this country and around the world.

Preventing cancer as people age: risk assessment, screening, early diagnosis

For people of any age, the first line of defense against cancers and their damaging consequences is prevention. Prevention encompasses at least four strategies: the methods (behavioral change or vaccines) that avoid cancer-causing agents or conditions, like tobacco use, obesity, or infection with certain viruses; an assessment of inherited genetic risk; the screening procedures that detect abnormal cells before they develop into life-threatening cancers; and the long-term use of drugs, as proposed for aspirin, that reduce the incidence of certain cancers.

Some of these have attributes that are particularly relevant to today's discussion of cancer in older populations. I want to mention three of these: tobacco cessation, screening methods, and aspirin use.

(1) It is widely known that use of tobacco, especially cigarette smoking, is the major avoidable risk factor for several types of cancer, especially lung cancers. Nevertheless, the health benefits of stopping tobacco use in middle age are underappreciated, and the benefits of stopping at more advanced ages have been inadequately studied. A recent review by Jha and Peto (New England Journal of Medicine 370:60, 2014) points out that even long-term smokers can relatively quickly regain several years of life-expectancy lost by active smoking when they stop at age 50. However, not enough information is available about elderly people who have recently stopped smoking to know how significant the benefits would be at higher ages.

(2) Screening tests have been developed for several common types of cancer—such as breast, skin, cervical, prostate, and colorectal cancers—but the use of those tests has often been controversial because of uncertainties about cost-benefit ratios and about the ages at which screening should commence or be concluded. Some common tests—such as the Pap smear for cervical cancer and colonoscopy for colorectal cancer—are not routinely recommended for people over certain ages (65 and 75 in the two instances mentioned), because there are harms (direct effects, such as colon perforation during colonoscopy, or over-diagnosis and over-

[1] http://wonder.cdc.gov/cancer.html

treatment), as well as the obvious advantages, associated with most screening tests; because overall life expectancy (and hence benefit) declines at increasing age; and because certain cancers (such as cervical cancer) are less frequently diagnosed at advanced ages.

For some tests, there is simply inadequate information to make an evidence-based recommendation. For example, use of helical CT scanning for lung cancer is now being adopted in the United States, with guidelines based mostly on the findings from the NCI's Lung Cancer Screening Trial (New Engl. J. Med 365: 395-409, 2011). In that trial, subjects were smokers or former smokers in good general health between the ages of 55 and 74 at the start of the study. Hence, it is difficult to make recommendations for individuals over the age of 74 or for those with co-morbid conditions, a common situation among tobacco smokers. Current guidance, based upon statistical modeling rather than direct evidence, suggests lung screening until the age of 80, but additional studies will be required to make secure recommendations for still older populations.

(3) Extensive pooled analysis of several studies of people who have taken low-dose aspirin for many years shows a highly significant reduction in incidence and mortality of several types of cancer, including gastro-intestinal and lung cancers (Lancet 377:31-41, 2011; 379:1602-1612, 2012). However, adoption of long-term chemoprevention of cancer with aspirin has been limited by concerns about the major side effect—gastrointestinal bleeding—especially in older individuals. NCI is collaborating with the National Institute on Aging (NIA) on a five-year study of aspirin's preventive attributes and side-effects in 19,000 individuals over age 65 in the United States and Australia, in hopes of providing information that will better guide the use of aspirin for chemoprevention.

Treating cancer appropriately in older patients

Historically, there has been a tendency to use less aggressive therapies in older patients with cancer, but that approach has been changing in response to several observations. First, many have noted the importance of distinguishing between chronological age (one's age in years) and physiological or functional age, especially in the oldest population groups, when making decisions about a therapeutic strategy. Patients who have a high chronological age are often resilient physiologically and able to withstand the rigors of most aggressive forms of cancer therapy.

In current practice, elderly cancer patients who are otherwise in good health—unlike those with severe co-morbidities or advanced neurological deficits—are now likely to receive surgery, radiotherapy, and/or drug therapy indistinguishable from that provided to relatively young patients.

This is being done because ample evidence suggests that healthy but chronologically old patients are capable of withstanding such therapies; because improved methods exist for controlling the symptoms (such as pain, nausea, and bone marrow suppression) that often accompany cancers or cancer treatment; and because benefits from rigorous therapies have been well documented in patients of advanced age. Moreover, it is anticipated that fewer side-effects of cancer therapy will occur as improved surgical methods are developed, radiotherapy is delivered with greater precision and better division of doses, and drug therapy shifts from traditional chemotherapy to the more targeted approaches of "precision medicine". In addition, the several new

immunotherapies—from the use of therapeutic antibodies to methods to strengthen the activity of immune cells—may be quite well tolerated by patients at advanced ages.

To obtain the evidence that supports the use of these therapies in elderly patients, it will be essential to insure that such patients are included in clinical trials. However, about two-thirds of patients in clinical trials are 65 or younger, even though over half of cancers are diagnosed in patients over 65. Despite some increases in the numbers of patients aged 65 to 75 who now participate in trials, the numbers of patients over age 75 who are enrolled in trials remain low, in the range of 10 percent or less. These numbers reflect the prevalence of co-morbidities that may disqualify such patients from enrollment; the difficulty of travelling to the sites of trials; and a persistent prejudice against inclusion of very old patients in trials. These factors require further examination, and the newly reorganized National Community Oncology Research Program (NCORP) is committed to studying patients at older ages and with the common co-morbidities.

Social and psychological aspects of the care of older patients, including the heavy burden often placed on familial caregivers, also deserve increased attention. It is often no easier to make decisions about when to abandon aggressive, curative measures in favor of symptomatic care and referral to hospice for aged patients than for younger ones. These decisions have important effects on quality of life and on economic costs of care.

Learning More About Cancer and Aging

Because NCI studies cancers of all types and because most cancers occur predominantly in older people, NCI is inherently heavily invested in research on this major cause of morbidity and mortality in aging populations. I have already mentioned a number of ways in which our research specifically addresses the relationship between cancers and aging: through studies of the epidemiology of many kinds of cancer; through efforts to address the utility of preventive measures, like daily aspirin, in older patients; and through attention to the numbers of elderly patients in our clinical trials. Furthermore, we use CISNET (NCI's Cancer Intervention and Surveillance Modeling Network) to analyze existing data and make predictions about optimal use of screening tests, such as helical CT scanning for lung cancers. And other commonly used agents, like metformin for diabetes and statins for lowering blood lipids, as well as aspirin, are being studied for their possible chemo-prevention activity.

NCI is also supporting work on more fundamental aspects of aging and its relationship to cancer. For example, NCI's Provocative Questions initiative has called for applications to study how life span relates to cancer incidence in animals, starting from the observation that certain short-lived animals, like mice, have relatively high rates of cancer, whereas some much longer lived animals, like naked mole rats or reptiles, have very low rates. Other Provocative Questions ask how biological mechanisms might influence susceptibility to cancer risk factors at different stages of life or what aspects of aging, other than mutations, might promote or protect against cancers.

Other features of the biology of aging are also under investigation. The lengths of telomeres, the specialized DNA sequences at the ends of chromosomes, have been implicated in aging and carcinogenesis by many investigators, and both NCI and NIA have significant investments in telomere biology. The immune system is known to undergo functional changes with aging,

and (as mentioned earlier) there is renewed interest in immunotherapies for cancer, so NCI is interested in effects of waning immune potency on cancer incidence and on opportunities for therapeutic intervention in older populations. New technologies allow a detailed description of an individual's microbial population, and numerous ideas about the contribution to diseases like cancers made by the microbes we carry during life, including late life, are being tested. Genetic diseases associated with premature aging ("progerias") have recently been examined for cancer incidence; some do not show increased rates of cancer, while those (like Werner Syndrome), characterized by high mutation rates, do. Studies of the effects of aging of mutation rates in different cell types and of the consequences of exposures to known carcinogens are among some of the other aspects of NCI's research program on aging and cancer.

One especially intriguing observation is the inverse relationship between cancer incidence and a diagnosis of degenerative neurological diseases (such as Alzheimer's and Parkinson's Diseases) that are common at advanced ages. In other words, compared to the general population, people with those neurological diseases are less likely to develop cancer, and vice versa. This observation forms the basis of yet another Provocative Question and has attracted the attention of other NIH institutes as well.

Finally, NCI has assembled or joined standing groups of investigators dedicated to the problems posed by aging and cancer, such as TRAC-I (Translational Research at the Aging and Cancer Interface), the Gerosciences Interest Group, and the Chronic Inflammation and Age-Related Disease group.

I would be pleased to respond to any questions you might have.