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Good afternoon, Members of the Subcommittees. I am Andrew von Eschenbach, M.D., Director of the National Cancer Institute (NCI). I am pleased to present my first official testimony as the new Director of NCI before these distinguished Committees on the very important public health topic of mammography.

I would like to begin with a very concise summary of the position of NCI and the Department of Health and Human Services (HHS) on mammography and our current plans. I will expand on these later in my testimony. Let me assure you that NCI is collaborating with other agencies within the Department, including the Agency for Healthcare Research and Quality (AHRQ) and the Centers for Disease Control and Prevention (CDC), to ensure that together we are providing the latest science, clinical recommendations, and programs to prevent, screen, diagnose, and treat breast cancer.

Breast cancer mortality continues to fall, and that is very good news. Death rates from breast cancer first began to decline in 1989 at 1.4 percent per year. More recently the decrease has improved to 3.2 percent per year. This is a significant decline for all ages. Unfortunately, the decline began later (1993) and is lower for Black women, whose breast cancer death rates are 33 percent higher than rates for all women.

We feel confident that mammography has contributed to this decline, but mammography alone has not driven this trend. Advances in therapy, including adjuvant therapy (both hormonal and chemotherapy) and chemoprevention approaches (such as tamoxifen) have also played a role. Unfortunately, the current debate appears to be focused on this single component in the equation. What we need to keep in mind is that many factors taken together are responsible, all are important, and we cannot eliminate any from our current approach to breast cancer. Women need unimpeded access to prevention, screening, treatment, and supportive care to win their battle against breast cancer, and we need to keep our focus on the sum of the equation: longer life coupled with better quality of life.

NCI continues to recommend mammography screening for women beginning in their forties. This is consistent with the recently released report of the U.S. Preventive Services Task Force (USPSTF), an independent panel of private-sector experts in prevention and primary care sponsored by AHRQ. On February 21, 2002, HHS Secretary Tommy Thompson released an updated recommendation from the USPSTF that recommended screening mammography every 1-2 years for women ages 40 and over. As Secretary Thompson stated, "I believe that this recommendation reaffirms the importance of mammography and should substantially allay concerns about its value in safeguarding the health of women."

Everyone agrees that mammography detects early tumors when they are smaller, detects more tumors, and gives a woman more options for treatment. These

benefits are substantial by themselves. The controversial issue is whether it saves lives in the long run. We have reviewed the evidence and the USPSTF recommendation, and we conclude that the weight of the evidence shows that mammography saves lives through early detection and treatment at an earlier stage. We will continue to monitor and consider any new information about mammography. However, mammography as a screening technology is only one tool, and we are pursuing a strong research agenda to develop other methods, such as improved imaging techniques, to design better ways to screen for breast cancer in the future. We will continue to work closely with other Institutes and Centers of the National Institutes of Health (NIH), organizations, and breast cancer patient advocates to ensure that research findings are translated quickly into effective interventions.

How do we know what we know about mammography? The use of x-ray imaging for the detection of breast cancer came into use in the 1960s, following technological advances that resulted in better images that were easier to reproduce and interpret. Initially used to assist in diagnosis, mammography was also studied for its potential use as a screening tool. Several randomized clinical trials of mammography have been conducted since 1963, and as these studies have been completed and the data analyzed, the findings have added to the total body of evidence we have today. At various times in the past decades, different organizations such as the American College of Radiology, the American Cancer Society, NCI, and others have reviewed the available data on screening mammography, have drawn conclusions about the strength of that evidence, and have made recommendations or statements about its appropriate role and use. Specifically, in 1993 NCI convened a workshop of experts to examine the available literature and data on screening mammography and to issue a statement of the strength of that evidence. At that time, the NCI concluded that the evidence supported mammography for women over age 50 but not under age 50.

In the intervening years, more data were obtained on the women who participated in the trials, and there were now enough women who had entered the trials in their 40s to more accurately assess the impact of mammography for women in their 40s. In 1997, there was a National Institutes of Health consensus conference where an extensive review was reported of all of the available information on screening mammography. Following that meeting and subsequent deliberations by our respective boards of advisors, both NCI and the American Cancer Society (ACS) released modified breast cancer screening recommendations. As of 1997, both NCI and ACS recommend mammography for women starting at age 40, although on somewhat different screening intervals. Both organizations also emphasized the importance of informed decision making about mammography.

The critique by Olsen and Gotzsche that was published in *The Lancet* last fall reviewed the seven randomized clinical trials of mammography that were done in the 1960s through 1980s. They considered technical details of the trials, such as how women were randomized into mammography and control groups, and whether breast cancer as a cause of death was determined accurately. The authors found

technical problems in five of the clinical trials, all of which had shown a reduction in mortality associated with mammography; they therefore called into question the value of mammography.

The NCI has reviewed very carefully the Olsen and Gotzsche critique, and we have concluded that their review does not warrant a departure from our current recommendation on mammography. Over 400,000 women took part in the seven randomized clinical trials that were reviewed by Olsen and Gotzsche. They examined each of these trials and identified potential flaws that could have influenced the findings in several of the studies. They gave little weight to the reported benefits from five of the seven trials and went on to conclude that the totality of evidence did not support screening mammography. However, difference of opinion among experts regarding design of these studies does not in itself prove that the conclusions are wrong. After careful deliberation of the arguments, the NCI has concluded that the value of mammography has not been refuted.

Let me give you two examples of what Olsen and Gotzsche said and why we disagree. The first clinical trial of mammography was begun in New York City in the 1960s. It was state-of-the-art at that time. Olsen and Gotzsche pointed out that after the participants were randomized into two groups, one group to be screened and the other not to be screened, a larger number of women were excluded from the group to be screened than from the unscreened group. This suggested the possibility that women diagnosed with breast cancer before the study began could be included in the screened group, but not in the unscreened group, resulting in a bias that would make it appear that mammography was useful, when this might only have been an artifact of study design. A scientific clinical trials expert who worked on this trial corroborated that during the nineteen-year follow-up period, any woman with breast cancer diagnosed prior to the onset of the study was excluded from both groups. This would correct for the potential bias suggested by Olsen and Gotzsche.

A second claim by Olsen and Gotzsche was that in several studies, the cause of death in the mammography screened group was more often called "died with breast cancer," while in the comparison group, women were classified as "died of breast cancer." They claimed that this could also be a bias in favor of mammography. However, this is also what you would see if mammography were in fact saving lives. Therefore, the NCI concluded that Olsen and Gotzsche have not refuted the evidence that mammography saves lives.

The authors also failed to consider that since the time these trials were conducted, there have been improvements in mammography and the technique of biopsy as well as in treatment. We have learned much about breast cancer biology since this time -- we now think that if tumors are detected when small in size, they have not yet developed many blood vessels, and are less likely to be aggressive or to metastasize. Mammography can detect these small tumors and also can detect the earliest form of breast cancer, called ductal carcinoma in situ, and surgery can remove these lesions.

Olsen and Gotzsche's analysis is not the first one to scrutinize the underlying data in these studies. Other expert groups have conducted intensive reviews of the studies and have reaffirmed previous findings of a mortality reduction benefit, most notably the recent report of the USPSTF.

Large workshops and consensus conferences have been convened in an attempt to reach agreement on what the data actually say, and we have all witnessed the difficulty and frustration that ensue from these efforts to both reach agreement on the meaning of the data and also to craft a statement that accurately reflects the meaning. Simply put, this is not an easy task, and the conclusions reached by Olsen and Gotzsche are at variance with other reviews by expert groups.

The National Cancer Institute has compiled a very comprehensive database about cancer called Physician Data Query (PDQ), that contains the latest available information about cancer prevention, screening, diagnosis, treatment, genetics, supportive care, and clinical trials. Independent PDQ advisory boards have been retained by NCI to carry out periodic evaluations of the body of scientific data and its usefulness for drawing conclusions about the state of cancer care.

At its last meeting, the PDQ screening and prevention editorial board discussed *The Lancet* review and felt that Olsen and Gotzsche made some valid points about the quality of the trials. However, no modifications to the current PDQ statement of evidence on breast cancer screening have been made at this time; we expect that specific recommendations will be discussed at the next meeting of the editorial board in March 2002.

What is NCI doing?

The NCI is committed to improving health outcomes for women with breast cancer. As part of the commitment, we will continue to strive to monitor new information as it emerges and to communicate what we learn. NCI has taken a number of steps to improve our effectiveness in these areas. First, I have asked two of NCI's division directors, Dr. Peter Greenwald, Director of the Division of Cancer Prevention, and Dr. Barbara Rimer, Director of the Division of Cancer Control and Population Sciences, to lead the new NCI Breast Screening Working Group. This group has three major tasks: one, to monitor and evaluate new information on mammography and how best to communicate the message; two, to monitor NCI's research program on imaging and molecular technologies for early detection; and three, to assess basic biology as it pertains to early detection (for example, molecular methods to differentiate indolent from aggressive tumors).

Second, NCI has requested that the Institute of Medicine (IOM) review the evidence related to mammography and advise us on their interpretation of the evidence. This complements an ongoing initiative of the IOM to periodically update their year 2000 report entitled, *Mammography and Beyond*. This report examines the current state of the art in early breast cancer detection, identifies promising new technologies, and how best to move the field of breast cancer screening forward.

Third, the NCI Breast Cancer Surveillance Consortium (BCSC), a cooperative agreement between the NCI and investigators at medical research centers across the country, is evaluating the performance of screening mammography in community practice in the United States. This research collaboration links data from mammography registries with data on cancer outcomes from pathology laboratories or cancer registries. The Consortium consists of eight research sites located in seven states, plus a Statistical Coordinating Center. As of April 2001, the Consortium's database contains information on 2.2 million screening mammographic examinations and 28,000 breast cancer cases. This is a tremendous resource that can tell us much more about how mammography is performed in community practice.

The Breast Cancer Surveillance Consortium supports a wide-ranging portfolio of research projects that use population-based databases to evaluate the performance of screening mammography in community practice. Researchers at individual sites conduct analyses using data collected at their sites. In addition, all sites transmit their data to a centralized Statistical Coordinating Center located at the Group Health Cooperative site. This allows Consortium researchers to conduct analyses across sites using pooled data.

Research in the Consortium examines issues such as the effect of breast density and hormone replacement therapy on the accuracy of screening mammography, the relationship of mammography assessment with final recommendations for diagnostic evaluation, biologic characteristics of breast cancers detected by mammography screening, and rates of detection of ductal carcinoma in situ among screened women. Anticipating the need to track the diffusion of new screening technologies in clinical practice, the Consortium is developing measures for tracking the use of digital mammography, which is a promising emerging technology, and will serve as a model for tracking the diffusion of other new technologies as they emerge.

Population Data Support a Benefit for Mammography

In addition to data from clinical trials, we also have data from our population-based Surveillance, Epidemiology and End Results (SEER) registries that can be used to track new cases and deaths from breast cancer and to examine these in relation to changes in mammography use over time. NCI also has created a national collaboration of some of the Nation's leading statisticians, called Cancer Intervention and Surveillance modeling NETwork (CISNET), to examine important questions about trends in breast cancer and other diseases by using the latest modeling methods. Although preliminary, recent work by the statisticians leads to the following conclusion: breast cancer incidence rates by stage showed a decline of later stage disease and larger size tumors and an increase in smaller, early stage tumors and pre-invasive cancers. Modeling this shifting of cases to earlier tumors with better prognosis predicted a decline in mortality during recent years, accounting for about one-quarter to one-third of the observed decline in breast cancer mortality since 1990. The important fact is that back in the late 1980s, our

statisticians predicted that if mammography rose over the next decade, there would be a subsequent decrease in mortality. We are now seeing that decrease.

Beyond Mammography

There is no doubt that thousands of women are alive today because their breast cancers were treated successfully after having been detected by mammography. There also is no doubt that we have plenty of opportunity for improvement. We need better ways to detect breast cancer in its very earliest stages and to prevent its further growth. While mammography is the best technology we have available today, it has limitations. Tumors that exist, especially in dense breast tissue of younger women or located close to the chest wall, may be missed (false negative), while in other women there may be indications that cancer is present when it is not actually present (false positive), leading to a series of additional procedures such as repeat mammograms and/or biopsies. The debate about the role of mammography will continue until we have a better technology that more accurately predicts a woman's risk of developing breast cancer, and NCI is supporting a broad range of research on promising new approaches to breast cancer screening and early detection.

Imaging research supported by NCI is advancing on several fronts. Along with efforts to improve conventional and digital x-ray mammography, NCI also supports research for several other technologies such as magnetic resonance imaging (MRI), ultrasonography, positron emission tomography (PET), and single photon emission computed tomography (SPECT). Already, with these technologies, scientists can "see" and monitor biological processes taking place in living tissues such as blood flow, oxygen consumption, and glucose metabolism.

A major research effort is under way to capitalize on the abundant discoveries in cancer biology and create imaging technologies that can noninvasively detect and display the actual molecular events taking place in the body. Molecular imaging will allow researchers to detect altered gene products and tumor-specific receptors or enzymes. The ability to visualize molecular pathways involved in the development of tumors is expected to enable researchers to detect and stage tumors more easily, to select more effective treatments, and to predict the effectiveness of new drugs. Some specific examples of research supported by NCI:

Digital Mammography - In 2001, the American College of Radiology Imaging Network (ACRIN), a group of researchers sponsored by NCI, launched the largest study ever to compare conventional and digital mammography. The Digital Mammographic Imaging Screening Trial, involving 49,500 women in the United States and Canada, will compare digital mammography to standard film mammography to determine how this new technique compares to the traditional method of screening for breast cancer.

Magnetic Resonance Imaging – MRI is an imaging modality making use of a magnetic field and radio-wave signals linked to a computer to create detailed

images of areas inside the body without the use of radiation. Each MRI produces hundreds of images of the breast from side-to-side, top-to-bottom, and front-to-back. A radiologist then interprets the images. Breast MRI is not used for routine breast cancer screening, but clinical trials are under way to determine whether MRI is valuable for early detection in certain groups, such as young women at high risk for breast cancer and women with a previous history of breast cancer.

Positron Emission Tomography - PET creates computerized images of chemical changes that take place in tissue. NCI-sponsored researchers are evaluating the usefulness of PET to detect tumors in dense breasts. A clinical trial is also evaluating the usefulness of PET results compared with the findings from other imaging and diagnostic techniques. This trial is also studying the effectiveness of PET in tracking the response of a tumor to treatment.

Computed Tomography (CT) - Computed tomography creates a series of detailed cross-sectional x-rays of areas inside the body taken from different angles. The images are then turned into two- and three-dimensional pictures by a computer program. This technique is also called computerized tomography (CT) and computerized axial tomography (CAT). Several NCI-funded investigators are studying the use of dedicated breast CT devices as both a screening and diagnostic tool for the detection of breast cancer.

Magnetic Resonance Spectroscopy (MRS) - MRS has the ability to distinguish cancerous tissue from normal tissue and benign growths. MRS can show the presence and relative quantities of the chemicals comprising tissues of each type, and can characterize even small tumors. As a result, MRS can make it easier to detect breast cancer at even earlier stages. A number of NCI grantees are exploring use of MRS in breast cancer.

Optical Imaging - Optical imaging refers not only to the use of visible light but also to radiation just beyond the visible -- ultraviolet and near-infrared. Several researchers are evaluating the potential of using visible or near infrared light to scan the breast for abnormalities alone and in conjunction with other imaging technologies and the possibility of combining such information with other techniques. For example, NCI is supporting projects that superimpose optical signals from small breast cancers onto MRI scans of the breast.

Computer-Aided Detection (CAD) - CAD involves the use of computers to bring suspicious areas on a mammogram to the radiologist's attention. Through a number of grants, NCI is funding research that will develop computer-aided diagnosis methods to assist radiologists in diagnosing breast cancer from mammograms. It is hoped that CAD will improve radiologists' ability to interpret mammograms so that both the number of missed cancers and the number of women unnecessarily sent to biopsy can be reduced. A number of grantees are exploring the use of CAD in breast cancer. Currently, there are two FDA-approved CAD methods that are commercially available.

Imaging Agents - The NCI's Development of Clinical Imaging Drugs and Enhancers (DCIDE) program will foster and speed the development of promising imaging agents, such as contrast agents, and their translation from laboratory to clinic. NCI will make its pre-clinical development resources available to competitively selected developers of a promising diagnostic agent or probe in order to remove a recognized barrier between laboratory discoveries and their entry into the clinic. To further aid in the development of promising imaging agents, NCI is launching a program to fund early clinical trials of novel imaging probes and agents. One of the agents under development in this program is a nanoparticle that specifically targets angiogenic vessels. This could potentially play a role in cancer detection, staging, and monitoring of therapy for breast cancer.

In addition to imaging technology, NCI is investing in new biologic tests to improve our ability to identify cancer cells in their earliest possible stages of development. Among the research being supported:

Molecular Analysis - NCI's Innovative Molecular Analysis Technologies Program (IMAT) supports the development of non-invasive techniques for identifying molecular changes that distinguish cancer cells from normal cells. More than 100 research projects are under way, focusing on new approaches to analyze DNA, RNA, and proteins.

Proteomics: Finding Protein Patterns - Proteomics is the systematic study of protein expression and function. In the Clinical Proteomics Program, a joint initiative of NCI and FDA, researchers are discovering differences in patterns of protein in the blood from cancer patients compared to people without cancer and applying this knowledge to early detection of breast cancer.

Biomarkers - NCI's Early Detection Research Network (EDRN) is the first comprehensive network to develop and validate early detection markers for cancer. Researchers are studying a variety of molecules, proteins, genes, and other biological substances that may be the earliest warning signs that normal cells are on the road to becoming cancerous. Their discoveries are then translated into methods for detecting warning signals, sometimes even before full-blown cancer can develop.

Finding Fingerprints of Cancer Cells: The Molecular Classification of Tumors - All cells have unique "signatures" – special characteristics related to which genes are active and which proteins or other products the cell manufactures. During the transformation of a normal cell to a cancer cell, the cell's signature changes, and the change becomes a signal of the presence of cancer. Researchers are developing profiles of molecular alterations in human tumors, such as breast cancer, using DNA, RNA, or protein-based technologies. This technology holds promise for improving the early detection, diagnosis, and treatment of cancer.

Over the years, researchers have focused on examination of cells shed by breast tissue into the ducts. Investigators have now developed techniques for collecting nipple aspirates and ductal lavage and hope that it may be possible to evaluate

suspicious breast masses detected by mammography by analyzing these secretions. It may be possible to spare at least some women the need to undergo a surgical biopsy.

These are by no means established techniques, and it would be more accurate to say that they are being "explored" rather than "used" in breast cancer diagnosis. There are now a number of investigators around the country who have methods that enable them to collect these specimens, but there is no consensus yet on how they should be analyzed. The NCI is currently funding research through its exploratory grant programs to determine which substances or characteristics of cells present in these specimens will correlate reliably with the presence or absence of cancer in the breast. The research also includes development of new analytic technologies to detect particular alterations. This research has not yet progressed to a stage where large-scale clinical trials are ready to proceed.

NCI also supports a number of resources for the research community ranging from tissue banks to registries to shared funding for national monitoring programs.

Communicating about Mammography

It is not enough to make discoveries. We also must turn those discoveries into interventions that benefit people and communicate that information so women can use it to make important decisions about their health. The investments that NCI, ACS, CDC, and AHRQ made in the 1980s and 1990s led to effective interventions to enhance use of mammography. There is a solid armamentarium of effective interventions, and we have seen the former Black-white differences in mammography use disappear. There still is under-use of mammography among some groups, including older and Hispanic women. We are now working with the CDC, ACS, and other organizations to disseminate the effective interventions.

NCI has several projects in place to improve the ways we communicate the results of research and to take advantage of new communication technologies. One example is a research project funded by NCI and AHRQ studying how to communicate about the benefits and limitations of screening tests. Researchers are also developing tools to help women ask the important questions and to examine their own preferences. These research efforts are exploring the capacity of new communication technologies, including online and other interactive health communication tools, to address women's questions.

Conclusion

Multiple factors come together in an equation that leads to longer and better lives for breast cancer patients. All of our current tools are important, and all must be improved because the outcome, although better than in the past, is not yet what it should be. We must retain what is adequate and appropriate but strive to discover what is better. Many of the new technologies now under development hold real promise. Detecting the molecular changes that lead to cancer will give us the

opportunity to intervene in the disease process more effectively. Like you, I am impatient for these new approaches to prove themselves. The lives of our mothers, daughters, wives, sisters, and friends are at stake. We cannot allow ourselves to become complacent, accepting the status quo. Yet, we must not ignore the fact that our best available technology today, mammography, does save lives.

I thank you for this opportunity to testify about this vitally important topic. I will be pleased to respond to your questions.