THE FURTHER SURVIVAL OF FIVE YEAR SURVIVORS OF CHILDHOOD AND ADOLESCENT CANCER

Daniel Green, MD

Figure 1

INCIDENCE RATES FOR PEDIATRIC CANCER
SEER PROGRAM, AGES 0 - 14 YEARS

<table>
<thead>
<tr>
<th>DIAGNOSIS</th>
<th>WHITE</th>
<th>BLACK</th>
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<tbody>
<tr>
<td>ACUTE LYMPHOMATIC LEUKEMIA</td>
<td>33.4</td>
<td>26.2</td>
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<tr>
<td>BRAIN AND NERVOUS SYSTEM</td>
<td>23.6</td>
<td>11.1</td>
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<tr>
<td>NEUROBLASTOMA</td>
<td>10.5</td>
<td>9.2</td>
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<td>NON-HODGKIN LYMPHOMA</td>
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<tr>
<td>WILMS TUMOR</td>
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<td>HOODGIN DISEASE</td>
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<td>5.2</td>
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<td>3.3</td>
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<td>RETINOSARCOMA</td>
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<td>OSTEOSARCOMA</td>
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<tr>
<td>Ewing sarcoma</td>
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<td>TOTAL</td>
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(CANCER 1986; 58:598-592)

Figure 2

CANCER INCIDENCE
UNITED STATES - 1994

<table>
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<tr>
<th>PRIMARY SITE</th>
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<tr>
<td>PROSTATE</td>
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<tr>
<td>BREAST</td>
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<tr>
<td>LUNG</td>
<td>172,000</td>
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<tr>
<td>COLON &amp; RECTUM</td>
<td>107,000</td>
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<td>ALL PEDIATRIC CANCERS</td>
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(CA: A CANCER JOURNAL FOR CLINICIANS 1994;44:7-26)

DR. BAKER: When we were preparing for this meeting a year or two ago I wanted to parallel Gordon’s presentation with one on kids who have cancer and grow up. Are there any problems and what are the morbidity and mortality statistics?

I spoke to a friend whom I’d known at Great Lakes and went into pediatric hematology and oncology. He was starting to prepare for this meeting and while he was preparing, he kept noticing a Dr. Daniel Green, who had done a lot of work on the subject we’re going to hear about this morning.

So he said to me, “Why not try to get Dr. Daniel Green?” which we did and we’re very fortunate to have him. He flew in this morning and has to leave again today but he consented to talk to us because he knows that it’s important for him to tell us his information. He’s the associate chief of the department of pediatric oncology of the Roswell Park Cancer Institute in Buffalo.

He’s a professor of pediatrics at the School of Medicine, University of Buffalo, State University of New York. Dr. Green, it’s an honor to have you here. Come up and tell us what you have.

DR. GREEN: Good morning. It’s a real pleasure to be here. I have wanted for a long time to be able to speak to a group of physicians who also are experts in insurance policies because it’s been clear to those of us who treat these children that they have tremendous problems obtaining health and life insurance, in particular life insurance.

Although I’m not certain at this point that we’re going to be able to make great strides in changing the approach which you all have to take to these people because unfortunately it seems to be a business decision rather than a humanitarian decision.

DR. GREEN: I’m going to speak with you today about further survival and causes of death in children who have been treated for cancer. I don’t know what all of your familiarity is with childhood cancer so I want to first review with you, very quickly, the kinds of diseases that we see in children.

Figure One. The most common cancer that we see in children is acute lymphoblast leukemia. The second most common group of disease is tumors of the brain and central nervous system. The overall incidence rate annually in white children less than 15 years of age is 129 cases per million children. And it’s slightly less common in black children.

Figure Two. Just to put this in perspective, Figure Two shows an annual number of new cases of prostate carcinoma, breast carcinoma, lung, colon and rectal, and in the sum total of those cases of childhood cancer that were diagnosed in 1990, I think you can appreciate that as a public health problem, childhood cancer ranks quite low compared to some of the common adult cancers. The reason that these cancers have attracted the interest of a lot of us is they have tended to be very responsive to both chemotherapy and radiation therapy.
Figure Three. Again looking at data that have been accumulated by the National Cancer Institute, you can see that five year survival rate is very dramatic even over the relatively brief period of time between 1974 and 1987, where the five year survival rate increased from 55 percent to almost 70 percent. It’s expected at the present time that if current survival rates remain stable, rather than continuing to improve, that in the year 2000 approximately one in 900 adults, age 15 to 44, will in fact be a survivor of childhood cancer.

The question that we, and all of you, I’m sure have had is what does this really mean? Does five year survival mean cure? Do these patients still have an excess risk of either morbidity or mortality once they have achieved their five year survival status?

At the present time there are four good studies which give differing views of this particular issue. Each of these studies has flaws which make them difficult to generalize, but I’ll present the data from each of them and try to give somewhat of a synthesis of the conclusions from the studies.

Two of the studies, by the Childhood Cancer Research Group have been conducted using population based registers in England. The middle study here from National Cancer Institute was based on five population based registries that are part of the Sear program and we have been conducting a study in Buffalo for a number of years now, which is an institutional cohort.

Figure Four. The oldest of the four studies is one which was conducted in Britain. It’s a retrospective cohort study of approximately 4,000 five year survivors of cancer diagnosed prior to age 15 years and diagnosed between 1940 and 1971. The way this particular study got patients whose diagnosis occurred earlier was we went back to several institutions that had fairly strong institutional registries and data on the entire cohorts.

This population was derived from population based childhood cancer registry, the National Register of Childhood Cancers and this is for the period of 1962 to 1971. The way this particular study got patients whose diagnosis occurred earlier was we went back to several institutions that had fairly strong institutional registries and data on the entire cohorts.

Now, there are several important points about this particular study. The most important is that the distribution of diagnoses in this cohort of five year survivors is very atypical from what you would observe at the present time.

You can see that this cohort, the commonest diagnosis was CNS tumor, whereas the distribution I showed you at the beginning of the talk (Figure One), the commonest childhood cancer is in fact acute lymphoblast leukemia. And perhaps ever more interesting is the second most common diagnosis in this cohort was retinal blastoma.

If you were to look at a typical diagnostic distribution in childhood cancer, retinal blastoma accounts for between two and three percent of all the patients. So this is a very atypical group of survivors. This particular finding of all the retinal blastoma patients is really due to the experience at a single institution in England with a treatment of retinal blastoma that went back many, many years. I think you’ll notice that there are not a large group of survivors in this particular cohort.

When one examined the causes of death of patients who in fact survived for the first five years after diagnosis, perhaps the most important finding is that still the primary neoplasm means the primary subsequent cause of death. The other important point in this series is that the second most common cause of death in this cohort is the occurrence of a second malignant neoplasm.

And then interestingly accidents or homicide are the third most important cause of death. This just details the types of accidents and homicides that occurred. Five of these were suicides, 22 were accidental deaths, three were medical misadventures, patients who have died of operative complications for surgery which is performed because of the medical complication of the origi-
nal tumor or its treatment and in three patients the cause of death, exact type of traumatic death was uncertain.

Less common causes of death were neurological problems, ischemic heart disease and other cardiac problems, cerebral vascular disease and pneumonia. In that particular study they examined the number of observed and expected deaths according to different periods of time post-diagnosis and they found that only for a couple of small groups of patients did the number of deaths observed ever come anywhere close to the number that were expected.

For almost all categories in periods of follow up, the number of deaths would in fact statistically and significantly have exceeded the number expected. The groups for which there was relatively normal mortality included the group that had non-Hodgkin’s lymphoma who were observed ten to 19 years post-diagnosis, where the expected was 1.5 deaths.

Two groups of patients, only beginning at 20 years post-diagnosis, those with juvenile astrocytoma, where the expected was 0.7 and those with fibrous sarcoma, where the expected was also 0.7. The fact that in those three groups there was no difference found should not be taken as a sign that we can relax with. The reason is that the expected numbers are so low that the statistical power of those particular groups is really quite small.

The next study, one which includes a little more recent group of patients is the five center study. This again is a retrospective cohort study of about 2,300 patients. These were all five year survivors of cancer diagnosed prior to age 20 years, and they were diagnosed between 1945 and 1974.

Again the starting point for this cohort is quite a long time ago. This does have one advantage over the previous study from England in that this was relatively population based and did not include strictly institutional based cohorts.

This study had another strength which is it collected a group of 3,200 siblings of the cancer survivors and used this control group of siblings for a number of the comparisons which were included in the study. The follow up of this study was conducted between 1980 and 1983.

In this particular cohort there are approximately an equal number of males and females. The number of patients over 14 years of age at diagnosis was about two thirds of the entire cohort and this is actually not typical of the distribution of the incidence of cancer in children between zero and 20 years of age.

**Figure Five.** The reason for this excess of older patients is the most common diagnosis in this particular study which is Hodgkin’s disease. The fourth most common diagnosis was thyroid cancer and you can see again that there is no mention of acute lymphoblast leukemia on this particular slide.

The treatments which these patients received, you can see that approximately one half of the patients were treated with surgery only. So again this is a very atypical cohort. It would be unlikely at this point in time that a randomly distributed group of children with cancer would have half of their cancer successfully treated with surgery only.

**Figure Six.** One need only think of the fact that acute lymphoblast leukemia is treated with chemotherapy only to realize that this is a very unusual distribution of therapies. Relatively few of these patients received any form of chemotherapy as a part of their treatment for cancer.

The major point I want to make is that as in the British series, the primary neoplasm remains the most important cause of death in this cohort of patients. The second malignant neoplasm is again assumed considerable importance and then all forms of traumatic death also is quite important in this series.

Among the traumatic deaths, suicide was again most common, accidental deaths was slightly less common, homicides, poisoning and medical misadventures. Then very uncommon causes of death were neurological problems. Heart disease was relatively uncommon, as were other cardiac problems, cerebral vascular disease and pneumonia.

**Figure Seven and Figure Eight.** Now, the importance of this study is this was the first one to actually publish information in a form which was useful to you. And that is that these people examined relative risks of death compared to the sibling population. I’ve indicated the mortality rates, the number of deaths...
per thousand, in years of follow up, for the males and females according to the age at which they were evaluated, 21 to 25 year olds, 26 to 30, 31 to 40 and 41 to 55. Not indicated on this slide are the mortality rates for the sibling control group.

In general the mortality rates for the sibling control group were approximately one. So then in all of these situations, for 21 to 25, 26 to 30 and 31 to 40, the ratio of observed over expected greatly exceeded one and was statistically highly significant.

The mortality rates for these patients who had apparently been successfully treated for their first cancer episode greatly exceeded those in the sibling control. The only situation where the mortality ratio did not differ dramatically than that of the siblings was for the males age 41 to 55, where the control population had a mortality rate of 5.7, compared to that among the former patients of 6.53.

Figure Nine and Figure 10. The mortality rates were examined by diagnosis and it was found that among the different diagnostic categories of those with Hodgkin's disease had very high mortality rates compared to those with CNS tumors and those at all other sites, the mortality rates were still those of the general population.

These mortality rates remain elevated for Hodgkin’s disease throughout the entire period of follow up. For CNS tumors there’s at least a suggestion that that’s when these patients get to be older that their mortality expectations decline somewhat compared to the first few years after diagnosis.

And similarly for the other sites, the mortality rate is much higher when the patients are 21 to 25 years of age than when they get much older.

The third study is again one from England. This includes a cohort of approximately 9,000 five year survivors diagnosed prior to age 15. These patients were diagnosed more recently, between 1971 and 1985. And this study, now in contrast to the first study, is based entirely on a population based childhood cancer registry, the National Register of Childhood Cancers. And in this study the follow up is through 1990.

Figure Nine and Figure 10. The diagnoses in this cohort differ considerably from those in the first British cohort. Acute lymphoblastic leukemia is now the most frequent diagnosis, central nervous system tumors are the second most frequent diagnosis.

But here you begin to see an indication of the difference between incidence rates and success of therapy. Wilms tumor which is a tumor we have had success in treating for many years, is actually the third most frequent diagnosis in this particular population of survivors, and Hodgkin’s and non-Hodgkin’s lymphoma which would be the third most common diagnosis in the incidence series. In fact, they’re somewhat less frequent in the survivor series.

The causes of death in this cohort. Again the most important cause of death still is the primary cancer, and the second most important cause of death are second malignant neoplasms. Third are accidents and homicides.
In the second British study they unfortunately did not publish a crude relative risk of death. In other words, a non-cause specific cause death rate. What they did do was to publish the deaths due to non-medical cause, non-neoplasm cause.

In other words, they ignored the fact that many of these patients still died because of their primary cancer. And they found that there were excess non-neoplasm deaths still in non-Hodgkin's lymphoma, retinal blastoma, Wilms tumor, soft tissue sarcoma and other diagnostic categories.

The reason that there were not tremendous successes of non-neoplasm deaths in the other categories in which acute lymphoblast leukemia was is that there was still a tremendous excess of deaths due to acute lymphoblast leukemia. They did not publish in the study a non-cause specific mortality rate, so it's very hard to present the data from this study using the same kind of framework as I presented early on the five center study where you could show a clear excess of mortality for patients in virtually all age ranges post-diagnosis.

We’ve conducted a study in Buffalo where we examined a group of 695 five year survivors of childhood cancer. They were diagnosed between January 1st of 1960 and December 31st of 1988 and all these patients were less than 20 years of age at diagnosis. Approximately two thirds of the patients were less than 20 years of age at diagnosis. Approximately two thirds of the patients at diagnosis were between ten and 19 years of age, slightly less than that were between zero and nine years of age. The age of follow up was almost 27 years of age and the mean duration of survival post-diagnosis was almost 16 years. So it's a cohort with actually fairly significant follow up.

Again, as in all the other studies, the primary cause of death in this particular cohort was still the first cancer and the second most important cause of death was second malignant tumors. In our cohort already we were beginning to see the importance of cardiovascular disease as an important cause of death in these people who have been successfully treated.

We calculated standardized mortality ratios for this group and compared them to the New York State population including New York City and these present the standardized mortality ratios for the white males in the cohort stratified on the basis of their initial relapse, free interval.

Figure 12. Patients who had had their first disease free interval exceeding five years, compared to those whose first disease free interval was less than five years. As you can see, although there are significant differences between those whose relapse free interval was more than five years versus less than five years, the SMR's of both of these groups are quite different from the general population, with relative risks of death of between 4.6 in 26 times out of the general population for the white males and similar data showing a relative risk of death of between six and 54 times that for the females.

So that no matter how we stratify this particular group of patients, we still cannot show that there is any group of these patients that have a mortality experience which is the same of that of the general population.

Why are these patients dying? Well, clearly their primary cancer is the most important cause of eventual death. If you in fact successfully treat the first cancer, the two most important causes of death that have emerged thus far have been death due to cardiac disease and death due to second malignant tumors. I’d like to review these issues with you a little bit.

First of all, in regard to cardiac disease, we have ischemic heart disease and cardiomyopathy. In terms of ischemic heart disease, this has been studied most thoroughly in patients who have received radiation therapy to their chest. The most uniformed treated groups of these patients are those who have been treated successfully for Hodgkin's disease.

The largest study of cohort of Hodgkin's patients is a study of 635 patients diagnosed between January 1961 and April 1991,
all of whom are less than 21 years of age and were treated for Hodgkin's disease at Stanford University.

In this particular cohort, slightly more than half of the patients were males, slightly less than half were females. The mean age of diagnosis was 15.4 years and the mean follow up is 10.3 years. I point out only to show that the mean follow up for the study of childhood cancer is still relatively brief compared to the expected life span of these patients.

In this cohort, looking at the number of patients, the persons years at risk and then over here, the relative risk of dying of ischemic heart disease. In this particular study death was due to acute myocardial infarction on the basis of death certificate registration. You can see that just on the basis of sex, that there's a clear excess of death due to acute myocardial infarction for both the males and females, with the confidence intervals for these two overlapping, although the point estimates in fact are about twice as high in females as for the males.

If one examines the relative risk of myocardial infarction by therapy, the only two groups for which there have been acute myocardial infarctions are those who received radiation therapy only and those whose treatment included both chemotherapy and radiation therapy.

The relative risk was about 50 times that of the general population compared to about 21 times that of the general population; however, when you look at these wide confidence intervals, which are due to the fact that there were a very small number of events in this entire population, the confidence levels overlap so it's not clear that the chemotherapy either adds to or reduces the risk of acute myocardial infarction compared to treatment with radiation therapy only. In the group who had no radiation there are no deaths due to myocardial infarction.

We cannot estimate either the relative risk or the confidence level; however, the number of cases that were expected due to the small number of person years is only .005, so that again the power to actually show any excess or lack of excess in this particular number of patients is relatively quite small.

Now, there are a couple of important points to raise regarding radiation therapy technique and these might influence your decision in terms of weighting the risk for a patient whose been treated successfully for Hodgkin's disease. One is that patients who were treated many years ago were treated with a technique which usually involved only an anterior radiation therapy field and the cardiac and pericardial radiation dose with such a field was actually much higher than that which the patients receive now, using modern technique.

Modern technique is to use equally weighted anterior and posterior fields and treat both of these fields every day. The pericardial and coronary dose is somewhat lower with that than with the older techniques.

The other issue, which has been recognized only recently, is the issue of cardiomyopathy. There are a number of drugs that we use called the anthracycline antibiotics, doxorubicin and donrubin which are known to produce a dose related cardiomyopathy. The drugs directly kill myocardial cells.

There are a couple of studies, one of which is a fairly large study from Memorial Sloan-Kettering Cancer Center which have examined cardiac function using fractional shortening as the end point in long term survivors of childhood cancer who are treated with these agents. This study includes patients who have now been followed for almost 25 years post-diagnosis and when this particular paper was published the average follow up post-treatment was about ten years.

If you look at the cumulative dose and the percentage of patients who have a fractional shortening of less than 29 percent, it's very clear that there's a relationship between cumulative dosage and impaired fractional shortening which correlate with impaired left ventricle function.

The other point which is clear from the study of Sloan-Kettering is the frequency of abnormal fractional shortening does in fact increase as the duration of time post-diagnosis increases, with the highest percentage of patients with abnormal fractional shortening being in that group more than 15 years post-diagnosis.

The anthracycline antibiotics do cause a dose related cardiomyopathy. That point is crystal clear. What's unfortunately not clear at the present time is what the relative risk of mortality is from this particular treatment. The results were obtained largely in patients who have been clinically and completely asymptomatic. These are only imaging findings and we really do not know at the present time what the mortality risk is of patients who have received the anthracycling as successful treatment for their cancer.

A couple of points which we do know is first that the onset of congestive heart failure may be many years after the completion of treatment and unfortunately, at the present time we do not have any screening of mortality available which will adequately stratify patients into those who have a high versus a low risk of developing congestive heart failure having gone through a previous period of X years when they were asymptomatic and had normal screening tests.

The other point is the congestive heart failure may be precipitated by the initiation of vigorous physical training or pregnancy. There are a number of case reports in literature now describing both of these events and the one recommendation which we usually make to our patients is that they do not initiate a training program which would involve any significant amount of an aerobic exercise. So, we encourage things such as running or using rowing machines but really strongly discourage use of weight training.

In addition we recommend that, although there is no generally accepted way of screening such patients for their risk of subse-
quent congestive heart failure, we do recommend that patients considering pregnancy and those who intend to do vigorous aerobic physical exercise undergo tests of left ventricular function and Holter monitoring to determine that their heart function is in fact normal at that point.

I should, as an aside, say that the fact that it’s normal at that point is in fact no guarantee that they will not in fact have an adverse event occur should they either become pregnant or initiate vigorous physical training.

The last issue I’d like to discuss with you is the issue of second malignant tumors. I think what we are beginning to get a glimpse of is the importance of this first factor. Second malignant tumors are multi-fac-torial. Genetics undoubtedly plays a role. Radiation therapy clearly plays a role in the occurrence of these tumors, and chemotherapy plays a role.

I’d like to first of all review with you the impact the genetic predisposition can have on the occurrence of a second cancer. There’s been one very large study of approximately 1,600 survivors of retinal blastoma who have been diagnosed over a very long period of time at a number of institutions that collaborated in a multi-institutional study.

Basically these were two large cohorts of patients who were treated either at Cornell Medical Center in New York or at the various hospitals in Boston.

**Figure 13.** A break down of the patients in this particular study by sex and bi-laterality. You may not know the fact that virtually all unilateral patients in fact have non-hereditary disease, whereas all bi-lateral patients do in fact have germ line mutations that have been responsible for their getting the disease.

**Figure 14.** The important point is that unilateral patients are usually treated with a enucleation so they receive neither radiation nor chemotherapy. So the estimation of such things such as the occurrence of second cancers in this group of patients would in fact give you a fairly good estimate of what role the tumor might have had or good estimate of the lack of importance of non-genetic factors.

Patients who have bi-lateral disease are rarely treated with surgery only, although this particular group, 66 who were treated with surgery only, might give you an estimate of the importance of the genetic factor only. In here you’re going to always have the carcinogenic effect of the therapy added on top of the potential carcinogenic effect of the underlying genetic defect. This particular study was a study of mortality due to second malignant tumors. So it does not give an indication of the incidence. Ignoring for the time being the fact of unilateral versus bi-lateral disease, there were a tremendous number of second malignant tumors observed, a relatively small number expected and tremendous excess of second malignant tumors.

When you look at all other causes of death in this group, comparing the observed versus the expected number of deaths, that in none of these other situations was the ratio of the observed to expected different from what you would expect in the general population. These were not significant differences. Only the occurrence of second malignant rumors was significantly different from what you would expect.

Now, these are incidence ratios, looking at the year after diagnosis. There are a couple of important points. One, is that if you look at all second malignant tumors, that you might say that the risk of second malignant tumors appears to finally have reached a plateau and the excess risk to finally be decreasing by the time...
these patients are 40 years after diagnosis. But you clearly have a prolonged period of time when there is still a tremendously increased risk of death due to a second malignant tumor.

For most of the other possible tumors, bone tumor and in particular osteosarcoma, connective tissue tumors and melanomas, for most of these other diagnoses, risk of death due to that cancer remains tremendously increased compared to the general population for many years post-diagnosis.

Now, in striking contrast, are these data on the patients that have bi-lateral disease wherefore, all cases in which you received radiation therapy there’s a tremendous excess both of second malignant tumors in general, specifically to logical subtypes of second malignant tumors among those bi-lateral patients.

You can see also that even if you were unradiated you would have bi-lateral disease, there’s a tremendous excess of death due to second malignant tumors and that excess is due largely to tumors which occur in bone and of the skin, melanoma. This I think illustrates the importance of the genetic component and the high degree of penetrance of this particular genetic defect in patients.

In terms of radiation therapy, it’s been known for many years that radiation was a risk factor for second cancers. The bombs we dropped on Hiroshima and Nagasaki I think helped to demonstrate the carcinogenicity of radiation.

There have been a number of studies published looking at the effect of radiation with respect to the occurrence of second cancers. Perhaps the most uniform body of data again are those that have been derived from the follow up of patients who have been treated for Hodgkin’s disease.

Again, the largest cohort of those patients have been treated at Stanford University. This is a study of 2,100 patients. This now ignores the effect of age, so this now includes patients more than 20 years of age at diagnosis, as well as those who were younger. 25 of the 885 women that were included in this particular cohort were subsequently diagnosed with invasive breast cancer. No cases occurred in any of the roughly 1,200 men that were included in the cohort.
Figure 17. Figure 17 shows the relative risk of developing breast cancer. Utilizing an incidence series rather than a mortality series. These are observed over expected incidence rates compared to the US population.

It examines this risk versus the age of diagnosis, and the reason I wanted to include this, is that this particular finding here actually replicates that from a number of studies of patients who were radiated for benign diseases, radiated in the chest, which shows that those who are younger at the age of radiation, have a dramatically increased risk of subsequently developing breast cancer, compared to those who were radiated at an older age. For those who were radiated over age 30, there does not appear to be an excess risk of developing breast cancer.

Figure 18. The data in Figure 18 examines the impact of the interval from diagnosis of Hodgkin’s disease to subsequent development of breast cancer. The important point here is that only with prolonged follow up do you begin to see the dramatic increase in risk of the patients developing breast cancer. There is an increase and the confidence interval does not include ones that at even at five to nine years there probably is an excess risk, but at 14 years the confidence interval does include one, so that although the point estimate in fact shows an increase versus the confidence interval including one suggests this may be due either to shortfall or small number of cases.

Finally it examines the data trying to take into consideration both the duration of follow up and the age of the patient at diagnosis. The important points here are that if you look at the group that is less than 20 years of age at diagnosis, that regardless of the time of follow up, whether they were less than 15 years or more than 15 years after treatment, that they have dramatically increased risk of developing breast cancer.

Figure 19. The bottom line in Figure 19 is that those over 30 at diagnosis, again, emphasizes the fact that the older group of women do not demonstrate the same excess risk of developing breast cancer.

Figure 20. They also examined their data to determine if there was a dose response relationship and they were unable to identify a dose response relationship. I think it is important to keep in mind here that the low dose group was in fact very, very small both in terms of absolute number and in terms of person years of follow up compared to the high dose group.

Figure 21. So this study actually had relatively low ability to be able to discriminate a dose effect. What was important here was there did not appear to be dramatically increase the risk. If one received greater than 40 as part of radiation therapy only. The point estimates differ somewhat, but the confidence intervals essentially overlap. Looking at the risk versus dose looking at those who had no radiation versus those who had greater mantle doses, there still were cases occurring even among those who had received no radiation therapy. But I just want to emphasize that the power of this site to detect important effects in the very low dose groups is quite small. The person years of follow up is just overwhelmed by the mantle does greater than 40 group of patients.
Finally there are not, unfortunately as well quantified data for those who received chemotherapy so I'm only going to be able to present you a couple of very qualitative pieces of information. I'm certain that these are going to be important and that as we follow cohorts of successfully treated patients in the future that we will actually be able to provide you with much more accurate estimates of relative risk for patients exposed to a variety of these agents.

On the first of a group of agents that are called the alkylating agents, these include nitrogen-mustard which is used frequently for the treatment of Hodgkin's disease, cyclophosphamide which is used in many of the solid tumors that we treat in children and melphalan which is often used as part of a preparative regime for bone marrow transplantation, and there are ample data at this point that show that both mild dysplastic syndrome and acute myelogenous leukemia can be induced in patients successfully treated for their first cancer with these agents.

What has only come to light recently are the importance of other groups of agents and the most important of these other groups are the groups which are called Topoisomerase II inhibitors. This group includes epipodophyllotoxins, the anthracycline antibiotic doxorubicin and doxorubicin that was mentioned before in conjunction with cardiomyopathy and dactinomycine. These inhibitors are associated with an increased risk of acute leukemia, especially acute monoblastic leukemia and when these particular leukemias are examined genetically, they often have deletion at the segment 11Q23. What has only come to light recently has been the impact that any of these agents would have on the occurrence of second solid tumors.

Most of the information with the alkylating agents and most of the early information with Topoisomerase II inhibitors suggest that these were leukemigen but they did not show that they were important broad spectrum carcinogens, although these drugs are all carcinogenic in experimental animals.

Recently there were two studies, one which we have published in Buffalo and another which is presently unpublished, examines the experience of what's called the National Study Group and both of these studies have shown that doxorubicin has in fact been associated with a dramatic increase in the risk of second malignant solid tumors.

So in the future it will be important in assessing the risk of second cancers to examine not only the impact of genetics and radiation therapy but also to examine in detail the chemotherapy regime which these patients have received.

I've tried to give you a broad overview and I hope that this wasn't too much information. Much to my own disappointment, we in fact are unable to show the patients who are five year survivors ever achieve a mortality experience which is not different from the general population. As a physician I am distressed by that. I think that certainly from your point of view I can understand the reasons why at the present time you would continue to have to evaluate these patients as having an excess mortality risk. Thank you very much.

(Applause.)

DR. BAKER: We all being edified and fully informed, we want to thank Dr. Green for his up to date and thorough coverage of the field. It’s been great to have him here and to get this complete summary of research and what he's done in the field. Thank you very much again, Dr. Green.

It’s lunchtime and we will go immediately across the hall to the French Room and reconvene here at 1:30 promptly, please.