

## **SPECIFIC AREAS OF CONCERN**

### **6. Epidemiology of Childhood Cancer**

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MS. FIELDS: The next presenter is Dr. Melissa Bondy, who is a professor of epidemiology at M.D. Anderson Cancer Center.

DR. BONDY: Janie, thanks for inviting me. I participated in the first of these biennial meetings, and I appreciate the invitation again.

As Janie said, I'm an epidemiologist at M.D. Anderson, but last year M.D. Anderson and Texas Children's Hospital joined forces to put together a Center for Childhood Cancer Epidemiology and Prevention. We're in the process right now of building this program. So I like hearing about the opportunity again for childhood centers because maybe we'll be ready when these opportunities come up.

So who gets childhood cancer? What's the scope of the problem? First, this year, 2002, about 9,000 children in the United States will be diagnosed with cancer. (Figure 6-1) Now, that doesn't seem like a lot, but if you're a parent of one of those children, it is a devastating illness. Cancer is the second leading cause of death in children, and the number of cancers in children are increasing over time. I think that was mentioned in one of your earlier presentations.

Unfortunately we really don't understand the causes of many of these cancers. Dr. Deary asked me earlier, "Do you think it's all environment or do you think it's genetics?" I said, Well, I'm a genetic epidemiologist, I study molecular and genetic factors associated with cancers, and I believe that's it's gene-environment interaction, but I'm not willing to say whether it's 60%-40%, 50-50, etc. I can't just say that at this point. I wish that I could make a pie chart and say okay, we can attribute this percentage of childhood cancers to genes and this percentage to environmental factors, but we're not there yet, it's going to take time.

Actually the good news of all this is that the survival rate for children is outstanding; about 75 percent of the children who are diagnosed with cancer survive their illness.

It's estimated that about 4,800 children each year will be long-term survivors. Now, as the number of survivors increases, we have concerns about what happens to these children who are treated with radiation or chemotherapeutic agents (many of which are alkylating agents). What are the long-term effects of these treatments, which are in some ways environmental exposures, because you're giving them radiation to different parts of the body. Unfortunately cancers could occur many years down the road, and we've seen that now as time passes.

Let me make a comparison so we can put some of this into perspective and try to compare childhood cancers with adult cancers. (Figure 6-2) The median age for adults to be diagnosed with cancer is about 67 years; that's the median age -- obviously there are adults diagnosed much younger. The median age for children is six. Children are frequently diagnosed with more advanced stages of disease. It's not that often that you see a child with cancer, and one of the first points in Dr. Amler's talk was you have to think of the diagnosis. You have to know what you're looking for to be able to diagnose cancer. So often parents ignore the early symptoms, not knowing what it is. If the signs or symptoms are not acute, they're unlikely to bring the child to a physician immediately, so they're often diagnosed with later stages of disease.

Only about one in 100 adults show evidence of disease spread at diagnosis, while 80 percent of the children have evidence of metastasizes at presentation. Many adult cancers result from lifestyle choices—smoking, obesity, high fat diets. Some adult cancers relate to occupational exposures that predispose to cancer. With children, if you look at that window of time, they haven't had the same length of exposure, but we talked earlier about how some of these exposures could be more critical in a growing or developing child. Let's just look at the distribution of the childhood cancer. If we look at Figure 6-3, you can see that leukemias account for about 25 percent of pediatric cancers, and if you added some of the lymphomas, hematologic cancers account for almost 40 percent of the cancers. Intracranial tumors account for about another 17, possibly 20 percent. The rest are very rare types of cancers. So if one is going to study pediatric cancers -- and we know that each type of cancer probably has a different type of exposure or etiology -- you have to have very large numbers. So it's a very difficult disease to study, and I think that's one reason why little progress has been made in understanding the etiology of these diseases.

So if we look at the incidence and mortality, we can see that while the incidence has gone up slightly over time, the mortality has decreased. (Figure 6-4) We have better chemotherapeutic treatments for children, and they've benefited from these new agents. I think that when we look at some of the treatments for leukemia and other types of cancers in adults, many of these treatments have come from the childhood arena.

Epidemiologists always like to give statistics, so I would like to tell you some differences in incidence. We look at male/female differences; we look at differences by ethnicity; and we look at a lot of other things. (Figure 6-5) Cancer incidence rates in children are often described per 100,000 -- this is based on data from the CI registry, based on per 100,000 rates.

So as you can see for all sites, there's not a whole lot of difference between males and females for some of these cancers. There is a slight excess in males; we see more of brain tumors in boys than girls, and we see the same type of predominance of males to females in adult brain tumors as well, which is one of my areas of research. Non-Hodgkins lymphoma also has a difference in male to female ratios, and I'm not sure why that is.

In Figure 6-6 we see all cancers adjusted by age, from 1992 to 1996, and distributed here by males and females and by ethnicity. And you can see right here that when we look at all cases, the incidence is about 163 per million. The darker number is males compared with females. Whites obviously have the highest cancer rate compared with other ethnicities. You can see here that American Indians have much lower rates. Hispanic children have rates that are higher than African-Americans, however they're nearly similar to whites.

Now in Figure 6-7 we're looking at ethnicity by different types of cancers, and if we look at the non-Hispanic whites, we can see that the largest proportion of cancers are, of course, the leukemias/lymphomas, and then brain tumors are another large grouping right there. So numbers are fairly close in terms of distribution for Hispanics and for whites. African-American children seem to have lower rates; Asian/Pacific Islander rates seem to be fairly close to Hispanics and whites.

Here's the distribution of brain tumors. (Figure 6-8) We put all brain tumors together, but what's really difficult about studying brain tumors is that there are so many different types. Those of us who study brain tumors believe that each one probably has a different etiology, a different genetic, molecular pathology distribution, and this makes it difficult to study large numbers of children for large-scale epidemiologic studies. It's also a very fatal disease, even in children where I mentioned that survival is much better in children than it is in adults. You can see that there's small peak right here in the 0 to 4 year age, and then there's another major peak in the 60s and 70s.

The histology is very different in children than in adults. Children often get lower grade brain tumors; they get medulloblastomas and other types, and older people get higher grade tumors such as glioblastoma multiformae and anaplastic astrocytoma. So when we try to compare adults and children, we're looking apples and oranges.

What about the cancer incidence in Texas? (Figure 6-9) Between 1990 and 1998 (data from the Texas Cancer Registry), there were 8,711 children less than 19 years of age diagnosed with cancer during this time period for the whole state of Texas. That equals about 1,000 children in Texas per year for the whole state. Leukemia-lymphomas account for about 40 percent and brain and CNS cancers another 20 percent.

Now let me just tell you a little about a project that I'm pursuing. I asked the state Cancer Incidence Registry to give me some of the geo-coded information of cancers in Texas, and it turned out to be an interesting little project, which we're just getting started with.

If you look at Figure 6-10, you will see the distribution of the 8,700 childhood cancers I mentioned. The map shows the location of those cases, and I thought, this would be a great student project, because we can look at spatial clustering and we can look at environmental exposures. I was really excited and I thought this was pretty neat.

We got the data and we looked at the latitude and longitude information for residence of where the child lived at the time of diagnosis, but what happened was that a lot of families when they gave their addresses to the hospital, gave a post office box or a rural route. Some, maybe because they don't have the money to pay their bill, they don't give accurate information about their address.

So then what happened is that when we had the information about where they resided, out of 8,700, we ended up with 6,700 or so. We lost 25 percent of the data. About 2,200 cases are missing valid information about exactly where they resided. So we went back to the drawing board, which is where we are at this point in time. How do we deal mathematically with these issues? It's very important to look at geographic and spatial clustering, and so we began to look at cancers in the state of Texas and there is some indication of some specific exposures that in certain parts of the state.

You can see in Figure 6-10 that the sparsely populated area around El Paso has a lot of cancers. I think we see the same type of pattern with all these areas where the cancers are occurring. But when you're doing this type of geographical mapping, and you want to start overlaying other types of exposure maps, you really need to know, to a pretty fine point of location, the places where these people live, so you can feel fairly confident that you have good information and you can look at specific exposures.

So we have a little bit of a challenge right now, and our plan is to look at it statistically and see what we can do to try to remedy this problem. It's an interesting issue, because I thought that we really had a gold mine of an opportunity here and that we could really start looking at this. And if anybody has any ideas, I'd welcome hearing some of them.

Remember I mentioned earlier that survival is improving, so if we look at Figure 6-11 we can see, over time, that children really are surviving their illnesses. We compare two times periods, 1974 to 1976, versus 1992 to 1997, and each of these represents a certain age group: zero to four, five to nine, ten to 14, and 15 to 19. You can see that there's a big difference between the two time periods, so I think this very much shows the improvements of cancer treatment and survival of children.

Here's another way of looking at this same thing. (Figure 6-12) These data are from the CI registry, and you can see over time with each of these curves that percentages of survivors are increasing dramatically.

Currently in the United States it's estimated that approximately one of every 900 individuals between the ages of 15 and 45 is a cancer survivor. That's pretty major, and I'm sure that in many adult practices as these children age there's going to be a lot of complex issues to deal with regarding long term consequences of their cancer treatment. There is a large childhood cancer survivor study that's being conducted through the Children's Oncology Group, and Dr. Wes Robison in Minnesota is looking at the issue of complications from treatment.

So why do children get cancer? (Figure 6-13) That's the next part now that we see the scope of the problem and we see how many children have cancer. Is it diet? Is it environmental exposures? Is it some type of maternal tobacco use or paternal tobacco use? Is it occupational health exposure during pregnancy or other types of pre- and postnatal exposures? Is it genetics, or is it a combination of all these things? My guess is that it's a combination of genetics and some exposures, because the children don't have enough time to have had a lengthy exposure. Especially infants who were diagnosed with infant leukemia within the first year of life; something has to have triggered their cancer.

So we have environmental exposures, we have our gene pool, and we've got many different time periods that are critical in terms of when this exposure could occur. We talked about exposure during the gestational period when the mother is pregnant, and there was some discussion about lactation. We heard that you don't want to discourage mothers from breast feeding, but it's a time when infants get exposed to many of the pesticides and other types of toxicants to which the mothers have been exposed during their lives.

So there are a lot of opportunities for exposure during this early time, through the mother, through the father, through genetics on both sides, through some types of exposure to stored toxins that could be then transferred to the child in different ways. As a girl begins to mature, begins to develop her breast buds, it's a critical period of time when we think about breast cancer and the etiology of breast cancer as well.

What about other factors. Figure 6-14 is from a chapter that I wrote looking at different types of exposures. I think this is also reviewed in the CIR called Pediatric Cancers. You can download it from the web, and you can get a hard copy from the NCI through the internet. It's a very nice book.

To review some of these factors I'm going to go through different types of risk factors and the types of cancers that seem to be associated with each. (Figure 6-15) As I mentioned earlier, we looked at ethnic differences and we looked at race, and we saw that for leukemias, whites have about a twofold higher risk than blacks; for Ewing's sarcoma, whites have a nine fold higher risk than blacks; and for Wilms tumor, Asians have about half the rate of whites and blacks. So there is variation here by race, but we really aren't sure exactly why.

We know a lot more about genetics because we've looked at chromosome aberrations and we've looked at different types of hereditary conditions. In Figure 6-16 we can see that for some of these there's a preponderance of cancers among children in these families and in children with different types of congenital malformations.

Certain types of leukemias seem to occur in some of these children. NF-1 stands for neurofibromatosis type 1, and we've seen that many different types of cancer, brain tumors and leukemias can occur in these children. Also for acute myeloid leukemia, it seems that the NF-1 gene may be involved.

If we look at some of these others, for brain tumors, there's a strong hereditary predisposition among families with NF-1 or tuberous sclerosis. Gardner's syndrome, multiple colon polyps, has been associated with brain tumor in some children. Li-Fraumeni cancer family syndrome is another one where we've seen a clear genetic predisposition. So these are some of those cancers where we've seen specific types of hereditary conditions occurring in these types of cancers. There's a high correlation between the syndrome and the cancer. When pediatric oncologists are taking histories they're quite good at asking about these types of things.

Another big risk factor that we've seen cropping up many, many times is ionizing radiation. (Figure 6-17) This seems to be a very strong risk factor. We've seen it in acute lymphoid leukemias, brain tumors, and osteosarcomas. Ionizing radiation is pretty much a proven risk factor for cancers.

Chemotherapeutic agents are used to treat cancer, but they also have the ability to cause different types of cancers: acute myeloid leukemia and osteosarcoma. We've seen that transplacental exposure to diethylstilbesterol (DES) caused vaginal carcinomas in girls and young adults, so that's a very clear example of an exposure in utero causing later cancer.

There have been some studies of atomic bomb survivors that show excess cancers that have occurred, leukemia and brain tumors. In a follow-up study, the atomic bomb survivors seem to have an increased risk of different types of brain and other types of cancers.

What about viruses? (Figure 6-18) I think that this is an important area to address because maybe this is the tip of the iceberg in terms of what we really might see in terms of cancers occurring after some exposure. It's been estimated that 15 percent of cancers -- and this is of all ages -- have some associated bio-etiology or co-factor. It seems that we've seen lymphoma following exposure to some viruses. Hepatitis B has been associated with liver cancer, and they've seen this happening with in-utero exposure when the mother had Hepatitis B. HIV has been associated with other types of cancers as well. So there's some host factors that may modify the susceptibility and the cancer phenotype, and I think this is probably going to be a very important area of research in the future.

This was a New York Times advertisement that was put out by Phil Landrigan's group, (Figure 6-19) and I'm sure many of you have seen this. I guess it was a series of several articles that came out in the New York Times. I thought this is really incredible, because it's making a major splash, but it was "More kids are getting brain cancer. Why?" The article went on to mention different toxic chemicals and other things. I felt like this was really a public awareness kind of thing, but I wasn't sure where it was going. I do think that it helps trigger people's awareness; it makes them wonder what is really going on in terms of these exposures. Maybe, as we bring people together like this, we can start to do something about trying to understand more about this.

I've been involved with the Children's Oncology Group which is now the formation of two different oncology groups that merged together this year. It has brought all of the pediatric hospitals and different groups together. And it takes a group like this, where you have people working together. I'd say about 90 percent of all children are treated through cooperative group types of activities and through protocols that are sponsored by cooperative groups. There are a lot of childhood cancers and for us to do studies, it really helps to have all the groups working together in order to recruit sufficient numbers of patients.

I'm just going to mention one finding that came from the Children's Oncology Group. (Figure 6-20) There have been studies of leukemias, looking at exposure to electromagnetic fields (EMF). The paper I would like to mention was published in The New England Journal of Medicine in 1997, and kind of brought things together to say that EMF was not a major risk factor. The first author is Dr. Martha Linet from the National Cancer Institute. I think this is something that has come up in many discussions, whether or not EMF exposure really is a risk. Some studies have shown yes, and some studies have shown no.

I get phone calls all the time. "I'm thinking about buying a house and it's right next to power lines, what should I do?" I say "If you're thinking about buying it and you're concerned, probably the best thing to do is not to buy it." That makes sense to me, but people are living there already. They don't have that option about buying it or not buying it. Is it a concern or not? I think most of the current studies, with better exposure assessment, are showing that it doesn't seem to be a major risk factor for childhood cancers.

Then there have been some studies looking at breast feeding and whether or not it reduces the risk of childhood leukemias, ALL and AML. It seems to, so we're talking about another reason that lactation is important.

Studies looking at parental pesticide exposures found an association with increased risk of non-Hodgkins lymphoma. Other studies looking at infectious agents found there might be an association with some infectious agent exposures and disease. A study of neuroblastoma, probably the largest ever conducted in the United States or anywhere, found that vitamin supplementation reduced the risk of neuroblastoma.

Studies of children who were in daycare and had neuroblastoma suggested that there was an increased risk among children who had chronic infections as a result of being in daycare centers.

Figure 6-21 looks at the role of glutathione S-transferase (GST), a family of metabolic enzymes that can repair the damage from different types of exposures. These enzymes can repair reactive oxygen species damage related to chemotherapy or radiation. Looking at the different gene types, here's a control group and here's the different m3/m4 allele types, we can see that there seems to be an association with those that have these particular alleles compared to controls -- they have an increased risk of developing leukemias. This was a case controlled study.

I want to end with one point. As part of the Children's Oncology Group, the NCI has given pilot funds to test a national registry for childhood cancers, and it seems that the pilot testing went well. What will happen is that each child with cancer in the United States would then be entered into this registry and would be available for studies. It looks like the pilot was a success, and if the NCI agrees to fund it, it will probably be initiated in the near future. (Figure 6-22)

This population-based registry would provide a lot of research opportunities as well as more precise estimates of incidence and trends. It would be good for Global Information System methods if we can get this information pinpointed to exactly where people live, and I think it would be important for enrolling people in epidemiologic studies because we need large numbers. When a parent signs the informed consent, it simplifies the IRB process to go back to them, because they have signed that they can be contacted for future studies. That's really important given the situation right now, and how difficult it is with all the IRB changes and the HIPPA rule. At times it's almost impossible to do research trying to go through the hoops of Institutional Review Boards.

Another thing I get called about is clusters. I think this was addressed by the ATSDR, but the NIH gets contacted as well. We get calls like "I think there are about six people in my neighborhood who have cancer. Are we being exposed to something?" It's often alarmed mothers who are concerned. Some of these clusters are real, but many times they aren't. People sometimes call this the Texas Sharpshooter phenomenon. If you keep expanding your area and you keep adding more cases, it looks like it's something that real. If you shoot your gun and you have a big target, then you're going to have something that looks like a cluster but it may just be by chance. And it takes a lot of effort to evaluate these cases, so I always refer people to the Texas Registry, because I think that it is their job to evaluate these clusters.

So what are clusters? (Figure 6-23) They're large numbers of cases in one area. Usually we want to find large numbers of one specific type of cancer rather than brain tumors and leukemias and Wilms tumor and neuroblastoma. (Figure 6-24) When there is an increase in the more rare types of cancers, it's more indicative of a true cluster rather than when it's a bunch of different common types of cancer.

And also what an epidemiologist would look for is whether or not this type of cancer usually occurs within this age group. And another thing that we investigate is whether or not the cancer is primary or metastatic, whether or not some suspected exposure has the potential to cause this type of cancer. Then we have to do a statistical analysis to determine whether or not, based on age, gender, and race, there really is an excess risk and is this really a cluster. This is important work, and that's why I refer them on to people who are more adept at evaluating these types of clusters.

As I mentioned earlier, children are surviving their cancers and this is what we want to see for the future of our children -- that they do survive their cancers or better yet, that they don't get cancer. How many cancers are too many? Most of us would say one.

So I think we have our work cut out for us in trying to understand the etiology of this disease. Thank you for inviting me.