Speaker 1:

Welcome to the Cancer Wise Podcast where we'll discuss cancer prevention, treatments, the latest in research, and important news around cancer, brought to you by the University of Michigan Health Rogel Cancer Center.

Erica Reist Bass:

My name is Erica Reist Bass and I am the Rogel Cancer Center's producer here at Michigan Medicine. Today, we're here to learn more about a study called MI Cares with Dr. Dana Dolinoy, so I'll pass it over to her to introduce herself and tell us about this study.

Dr. Dana Dolinoy:

Hello, my name is Dana Dolinoy, and I'm a professor and researcher at the University of Michigan School of Public Health and I'm really excited to be part of MI Cares. My role is to help evaluate environmental chemical exposures in the population with an eye to protection later in life from cancer.

MI Cares is a brand new study, we call this an epidemiological study, for the state of Michigan in which we're evaluating environmental exposures and different intermediate health outcomes with the idea to protect individuals from cancer. Because environmental exposures may affect other things, we will also be able to evaluate heart disease, diabetes, and other disease endpoints to identify which of the thousands of chemicals that we're exposed to can impact our health.

Erica Reist Bass:

Our first question that we're going to cover today is from a scientific perspective. What types of exposures impact an individual's ability to function and carry out their everyday tasks throughout their lifetime starting from birth?

Dr. Dana Dolinoy:

When researchers are interested in human disease, we often try to look at three different factors: how an individual's genotype or genes interact with their environment, and when we mean environment, we mean chemical exposure, dietary exposures stress, many different types of things in our environment, and how these two change over time. And so often, we can design studies to hold one or more of them constant to better evaluate variability. So for example, by using monozygotic twins, so twins studies, we can hold genetics constant to better evaluate environment, and by doing so, we've identified things like lifestyle choices like smoking or exercise, and things like chemical exposures that we often don't know we're being exposed to as triggers for different health risks.

On the flip side of the coin, we can try to hold the environment constant, it's a little bit more difficult, and evaluate how genetics changes health and disease. An interesting example here is the case of childhood lead poisoning when after even carefully controlling for known risk factors like the age of the housing, the paint in the housing, the soil outside the housing, African-American race remains a significant independent predictor of elevated childhood blood levels and this is likely due to difference in gene variants that, in the African-American race, are less likely to eliminate lead from the body once it's uptake.

But over the years, it's become clear that genes and the environment don't tell the whole story. Even after carefully controlling for environmental factors, education, lifestyle choices, monozygotic twins, and in the laboratory, inbred animal strains that have the same genes, continue to display widely varying incidences of chronic disease like heart disease, diabetes, and cancer. So this means there's another

factor at play and it turns out this factor is called the epigenome. Epigenome literally means in addition to or above the genome. It's the instruction book that tells our thousands of genes when to turn on, where to turn on, how much to turn on, and how to react to all of these environmental influences that we're encountering from when we are very young in the womb to when we're adults and throughout our life.

Erica Reist Bass:

So with those environmental influences that you mentioned, can you talk to us about how the environment can change our DNA and impact and individual's long-term health and wellbeing?

Dr. Dana Dolinoy:

Sure. So ever since the DNA double helix debuted on the cover of Nature Magazine back in 1953, we've been really looking at how genes affect health. And this pioneering work of Watson and Crick and many other scientists led the way to the Human Genome Project, which back in the late 1990s, early 2000, identified some 20,000 genes that determined much of who we are, how we grow, whether we get sick or remain healthy. But it turns out the genome story didn't tell the whole picture. It failed to identify that instruction book that tells these thousands of genes when to turn on, where to turn on, how much to turn on, and of interest to us, how to react to all of these environmental influences.

And so all of that is the job of the epigenome. And it's really interesting to think of the epigenome and the genome, their interaction, like a computer. Your computer has a hard drive and that hard drive contains a lot of data. This is the genome. But that data just sits there until the software comes along and tells it what to do, and that's the epigenome. A computer works because of the combination of the genome and the epigenome, and then the environment comes into play. We know the genome is static and not modifiable, but the epigenome is plastic and potentially modifiable across our life. So therefore, it's poised to react to various environmental influences, and some of these can be positive, like really nice less stressful environments, a really good diet can impact the epigenome in a positive way.

But on the flip side of the coin, there's consequences. We can also have negative environmental influences that come in, including things like chemical exposures, physical exposures, like to radiation and radon, and these things might impact the epigenome in a negative way. And it's actually sometimes very subtle. It can happen very early in life and you might not be able to see the results of that reprogramming until later. And so that's one of the things that we're interested in for a disease like cancer, which can take many years to develop. We might be able to identify it early on by looking at epigenome biomarkers.

Erica Reist Bass:

So circling back to you mentioning a healthy lifestyle, what are some of those things that the general public can do to maintain a healthy lifestyle and a healthy epigenome for their future?

Dr. Dana Dolinoy:

So when we're thinking about how we can maintain a healthy epigenome, we know that toxicants like bisphenol A can shift the epigenetic profiles in a potentially negative direction. But some really interesting research, it started out in animal models and a mouse model, has shown that if the mother eats a diet that's high in methyl donors, these are things like folic acid and betaine and vitamin B12 that are found in green leafy vegetables, a good diet can ameliorate or reverse the effects of that toxicant.

And so therefore, it's a little bit like a tug of war. The toxicant pulls you one way, but the good diet can pull you other ways.

And so there's lots of interest in evaluating other things that might be able to pull us back from a negative toxicant epigenome, things like exercise or having less stress in our lives. I know these are all things that we can't necessarily always control, but there is some hope when we're thinking about the epigenome that we may be able to moderate it throughout our lifetime by thinking about positive approaches.

Erica Reist Bass:

And can you say a little bit more about why the epigenome is so powerful?

Dr. Dana Dolinoy:

The epigenome gives us a little bit of hope, as I've mentioned, but also some opportunities for intervention or for identifying negative profiles that might someday, and it could be two years, it could be 20 years, lead to a health consequence like a cancer endpoint. And this is because the epigenome is changing throughout our life, but it's because we don't want the same sets of genes expressed when we're four years old as when we're 40 years old.

But what happens is the epigenome is particularly vulnerable during early developments. So this includes when an individual is developing in the womb, when an individual is going through puberty, and then when individual is going through advanced aging. And during these periods, the epigenome may be negatively influenced by environmental exposures and this could accelerate aging, and in the case of positive exposures, it might decelerate aging. But because it's reprogrammed early, we may be able to identify, through looking at an individual's epigenome, people who are more likely to develop a disease years later. And in that case, there might be some options for intervention. We might invoke some of those positive things like a good diet, less stress, but there are also potentially clinical approaches where we might be able to go in and alter the epigenome in a way that says, "Hey, wait a minute. We're not ready for these genes to be expressed this way. Let's go back and think about some interventions or some pharmaceuticals that might be able to prolong life and decrease the risk of disease."

Erica Reist Bass:

Can you point out what types of chemicals and substances specifically have been shown to alter the human epigenome?

Dr. Dana Dolinoy:

So the field of environmental epigenomics is relatively young. It's about 20 years old. We've known that the epigenome was important for cancer and other diseases for a few decades longer than that. But the fact that the environment can impinge on it is relatively young. At first, people were beginning to look at things like diet, things that are found in green leafy vegetables, these methyl donors. Then people moved on to thinking about other things that were in diets like phytoestrogens, genistein. This is a component of soy. And in these cases, the impacts on the epigenome, especially in these initial studies, were positive, but it's important to realize that there's sort of a timing and a dose dependency to all of these things.

So as the field began to grow, then people started to look at toxicants. Some of the first toxicants that people looked at were things called endocrine disruptors. These are often found in consumer products such as bisphenol A, or BPA for short. BPA is the monomer that makes up hard, clear plastic. It's found in

lots of things we encounter every day, including baby bottles, water bottles. It actually lines all food cans. It's there for a good reason, to prevent bacteria, but it also leaches out of these cans and gets into the contents of the can.

So when individuals, first using animal models and then cells and then eventually human epidemiological samples, looked at whether a mother's exposure to bisphenol A could affect the epigenome, they found that there were negative changes in the offspring epigenome that persisted across life. And oftentimes, these were negative changes that could be correlated to things like cancer later in life. One important epigenetic mark is called DNA methylation. It's simply a quartet of atoms, a carbon in three hydrogens, that sits down on one of the bases of DNA and it actually turns genes off. So when bisphenol A was entering the system, it could affect DNA methylation and the long-term programming of these genes.

Erica Reist Bass:

So previously, we had spoken about the mouse model that was used, and I was curious what were the effects of adding a nutritional supplement to the mice, and can you say more about the mouse model that was used for this study?

Dr. Dana Dolinoy:

One of the tools for studying environmental epigenomics involves a really interesting mouse model called the viable yellow agouti mouse. These mice are really interesting. They are genetically identical twins, but one is brown and the other is yellow, and this is all due to a simple epigenetic change at one gene.

What's also interesting about these yellow mice is that they grow up to get adult-onset obesity, and this is because their gene lacks DNA methylation. It's on all the time when it normally should be off, and it's on in the brain and this causes the mice to not feel full after they eat. And so this is a really interesting mouse model to test various environmental exposures.

So when we fed the mouse mothers a diet that was moderately high in bisphenol A, BPA, we noticed that the number of yellow offspring went way up. These offspring lacked DNA methylation. So we did a next study. In this case, the mothers were still exposed to bisphenol A, but they were given a really good diet. Actually, we gave them two different really good diets. We gave them a diet that was high in methyl donors like folic acid and betaine, and another diet that was high in genistein, the phytoestrogen. And in both cases, the nutritional supplementation of the bisphenol A diet counteracted those negative epigenetic effects. So at least in a mouse model, in development, we were able to fix a toxicant-induced changes on the epigenome.

Now, whether we can do this in humans is a really great line of work, and that's something that we're studying.

Erica Reist Bass:

So that being said, why is BPA so detectable in most Americans? I know you mentioned a specific race for African-Americans, but why is it so detectable?

Dr. Dana Dolinoy:

Yes. Bisphenol A is the monomer that makes up hard, clear plastic. And through CDC monitoring, we can tell that over 95% of Americans are exposed to bisphenol A. It's in things that we don't even know that it's in and so it's very difficult at a personal level to avoid BPA. You can do certain things like heat up

food and beverages in glass. You can try to eat fresh fruit and vegetables, but you're really not going to be able to eliminate all of the exposure to bisphenol A.

Interestingly, there is some consumer-driven pressure to remove BPA from products and this has happened. A lot of baby products have removed BPA, but what it's being replaced with could just be a similar analog or a different chemical. This is called a regrettable substitution. So often, we really don't have a lot of tools to identify what chemicals and toxicants are in the products that we encounter every day.

Erica Reist Bass:

So that was going to be my next question for you is if there are any alternatives out there right now. Do you know if there's been any studies done recently on alternatives?

Dr. Dana Dolinoy:

Yeah. Because bisphenol A is used in a myriad of different products, sometimes there is a good substitute for a product, and other times there's not. One of the things that we want to do when we design research like this is do our research in a rigorous and reproducible way and use a various number of animal models and human approaches so that we can have an impact on policy. We are making an impact on policy. Bisphenol A has been banned in certain products including baby bottles in the United States and other places, but it's not clear that we're replacing it with anything that's better, and so we still have to now redo all of this work on the replacement chemicals.

Erica Reist Bass:

So we spoke earlier about how we can decrease our exposure to substances like BPA in very practical ways. Could you say more about our ability to decrease our exposure to these substances, specifically in the field that's moving towards our ability to identify negative epigenetic profiles and how to prevent or reverse the associated outcomes through lifestyle or behavioral changes?

Dr. Dana Dolinoy:

So avoiding bisphenol A, and this is just one example of a toxicant, there are other types of toxicants that we encounter every day, is very difficult, but there are some things that we could think about if the goal is to protect our epigenome but also protect the epigenome of the offspring.

And so we can begin to think about vulnerable periods of life. So we know that pregnancy, and actually even preconception, so this also falls on the father, we don't want to put all of the developmental origins of health and disease burden on the mom. There's also preconception exposures that happen to the dad. We can think about vulnerable periods like pregnancy and preconception as times where you might want to attempt to avoid chemical exposures. There's lots of interesting, important resources for this on government websites, but also most universities that have programs like MI Cares also have information on their website and are happy to talk to individuals about how to avoid chemicals.

So a second area that you might want to think about is when individuals are going through puberty and have lots of changes at that time. It would be another time to be particularly a guardian of our epigenome and try to avoid exposures.

Erica Reist Bass:

What are the types of health outcomes that are associated with exposure to BPA or other similar substances?

Dr. Dana Dolinoy:

Unfortunately, with chemical exposures, especially when we're thinking about developmental chemical exposures, there are a myriad of different health outcomes and that's because the epigenome is particularly important for cell differentiation, which is how all of our cells, they start as a stem cell and then they differentiate into liver, heart, brain cells, and if there's an environmental exposure that impacts very early, that reprogramming is propagated to many different lineages of cells. So things like bisphenol A can impact cardiovascular, endocrine system, they can impact our epigenome in a way that will program cancer later in life.

Other toxicants like metals, lead, mercury, they can impact the neurological system, but they also have impacts on our endocrine and other systems as well. So it's really important to think about this from a holistic point of view. When we are starting to evaluate chemicals in human populations, we may be interested in one thing like cancer, but we have to follow where the data are taking us. We may also see that other things are impacted as well.

Erica Reist Bass:

Why would you say studies like MI Cares are so important to understanding the human epigenome?

Dr. Dana Dolinoy:

One thing that's really interesting about the epigenome compared to the genome is that it's actually variable, and being variable in the epigenome is positive. It makes us all unique and different. The genome of humans is almost 99% the same as a mouse, and it's the epigenome that's helping differentiate species, and it helps differentiate you from me.

And so one of the things that's really cool about MI Cares is that it's a really big study, 100,000 Michiganders or more. And so that means we'll be able to harness the variability to understand why certain people might get sick after chemical exposures and why others may be more protected, and that may be due to different baseline variability in this epigenome.

Erica Reist Bass:

And if you had to give your elevator pitch to someone as to why they should participate in the MI Cares study, what would you share?

Dr. Dana Dolinoy:

So MI Cares will be recruiting individuals who are 25 to 44 years of age, and I will encourage all of my friends and colleagues in that bracket to think about becoming involved. It's mostly done remote. We can get a lot of information about exposures through your address by using something called geographic information systems. And we can understand what air pollution, what different types of social stressors might be present in that immediate environment. But we also will be collecting biological samples that individuals can collect themselves and mail back to us, and by doing that, we can evaluate two things. We can evaluate direct exposure to chemicals like PFAS and lead, but we also can get access to an individual's epigenome and begin to compare the two and identify biomarkers that may be predictive of future risk or perhaps predictive of future health. And by doing this in a population level, you will be contributing to future health of the state of Michigan and beyond.

Speaker 1:

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