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0:00:13.4 -> 0:00:42 Welcome to Yale Cancer Answers with doctors Anees Chagpar and Steven Gore. Yale Cancer Answers features the latest information on cancer care by welcoming oncologists and specialists who are on the forefront of the battle to fight cancer. This week, it is a conversation about global oncology with Dr. Donna Spiegelman. Dr. Spiegelman is the Susan Dwight Bliss Professor of Biostatistics at the Yale School of Public Health, and Dr. Chagpar is a Professor of Surgery at Yale School of Medicine.

0:00:42 -> 0:00:49.6 Donna, maybe we can start off by you telling us a little bit about yourself, your research and the work that you have been doing in global oncology?

0:00:49.6 -> 0:01:39 I am by professional training a joint biostatistician and epidemiologist. Meaning, where biostatistics is the use of statistics and even more broadly mathematics to address and solve public health problems and problems in medicine, in healthcare, epidemiology traditionally has been the study of the distribution and causes of different diseases, both in the United States and around the world. And biostatistics is basically the primary tool that is used by epidemiologists to address questions such as what are the causes of cancer, how can we prevent them, and so forth.

0:01:39 -> 0:01:48.1 And so, your work kind of melds biostatistics and epidemiology. Tell us more about the research that you have been doing and the work that you have been interested in, in global oncology in particular.

0:01:48.1 -> 0:02:40 I came to Yale a little over a year ago to start a new center called The Center for Methods on Implementation and Prevention Science. And the focus of our center is exactly as the name says, we want to work on biostatistical methods as well as other sorts of research methods, health economics and so forth to strengthen our ability to learn about how best and how efficiently and cost effectively we can prevent diseases such as cancer, which is responsible for the deaths of at least a quarter if not a third of all Americans today and a rapidly increasing number of people around the world.

0:02:40 -> 0:02:39.4 And so, tell us more your research.

0:02:39.4 -> 0:03:58.5 Before I came to Yale, I was one of the lead statisticians for 3 large epidemiologic cohorts based at the Harvard School of Public Health and the Harvard Medical School called the Nurses Health Study, the Nurses Health Study II, and the Health Professionals Follow-up Study, and between these 3 studies, we have been following over 250,000 male and female health professionals in many cases since 1976, and every 2 years, these health professionals answer questions about their diet, their exercise, any kind of health events that have happened, mental health issues, substance abuse issues, exercise and so forth, and between the 3 of these studies, they have been a major source of in-

formation about the risk factors for cancer, maybe one of the strongest sources in the country if not the world, and we have learned a lot about diet and cancer, exercise and cancer, all sorts of things. And I have been a researcher and contributor to many of these studies.

0:03:58.5 → 0:04:03.7 And so, tell us how that transitions to global oncology?

0:04:03.7 → 0:12:01.8 That's a great question because in fact what happened for me personally is I got to a certain point in my life where I had worked on basic research on the causes of cancer for I would say 30-35 years and I felt like I now wanted to move on to how do we translate the information that we have learned to actually prevent cancer, and I felt that we have learned so much already, not that there is not more to learn, there very much is, but I would like to move on to this next phase of my career and maybe being involved more directly in sort of saving lives, making a difference, preventing cancer. So, I happened to know that there are certain cancers that are very highly preventable and others that we still need to learn more about. For example, and now we will get into global oncology, one of the most preventable cancers in the world is cervical cancer. In fact, it is so preventable that except in very low income pockets around the United States, almost no women get cervical cancer anymore in this country and even fewer die of it, but that is not true at all in the rest of the world. We have what are called low and middle income countries, a World Health Organization, maybe a United Nations designation, and it is based on the gross national product of countries and the high income countries are basically those in North America, excluding Mexico, and Western Europe, and middle income countries are countries like Mexico, Argentina, I think India is now a middle income country, China is a middle income country, countries in Eastern Europe are middle income countries, and then there are low income countries such as say some of the other countries in Central America, Nepal, many of the countries in sub-Saharan Africa. And basically, in these low and middle income countries, in which probably a good, probably four-fifths of the world's population resides, cervical cancer is the first or second leading killer of women. So, here is a situation where we know how to prevent it because nobody is getting it here, I should not say nobody, but very few women are getting it here, and yet these preventive interventions are not taken up to prevent four-fifths of the women in the world to also not get and die from cervical cancer, so that is where we get into implementation and prevention science and global oncology, and the two ways to prevent cervical cancer, one probably most women in the audience would know about because most of us have had many Pap smears and through the Pap smears, they can detect what are called early precancerous lesions of the cervix and do a very local removal of those lesions so that cervical cancer never develops, and then once a woman has had some of this, then she is screened more frequently and we make sure she does not redevelop the lesions, and if she does, we remove them and so forth and that is the main reason why women, say in the United States, very few of us get cervical cancer. It has turned out for reasons that are not well understood, that Pap smears do not work well in low and middle income countries. I actually personally feel that it could be studied

more, but the reason given when I talk informally with colleagues is that it requires a high level of training, very strong laboratory infrastructure, very good linkages between the clinical wards and the laboratories so the cells are looked at in a timely manner and so forth. So, other methodologies have been proposed for preventing cervical cancer in low and middle income countries instead of the Pap smear. And one of these is called VIA, which involves painting of the cervix with acetic acid that is what the IA part is and acetic acid is actually just vinegar, like the vinegar that you can buy off the shelf in a supermarket and is reasonably well available in most low and middle income countries. If a woman's cervix has precancerous lesions, parts of her cervix for some reason turn white and the health provider whether it is a doctor or a nurse or even a lower level position, can see that through standard methods of performing gynecological exams and then a procedure called cryotherapy can be performed, which involves taking a pen attached to a tank of liquid oxygen or some other cooled gas and basically killing those areas of the cervix where the white cells were. And that method is very low technology we are talking about, vinegar and a tank with a little tube at the end, so it does not require electricity, it does not require power, it does not even require running water in order to perform this procedure and it has been shown in fairly large clinical trials in India to be very safe and effective in preventing the development of cervical cancer in large populations of women. So, you might think, okay end of story we are done but actually it is not that simple because even after we find an alternative more culturally and economically sustainable approach to Pap smears, that does not mean that women all over the world are going to be lining up to have this test or that providers still have to be trained, they have to be trained to perform the acetic acid aspect, they have to be trained to detect what are the white areas if any versus not and then they or some higher level health provider needs to be trained on cryotherapy. So, it still requires various aspects, it is not just a matter of say pushing a button, but it is believed to be a promising approach in low and middle income countries where there might be uneven laboratories and training of health providers and so forth, and in fact, I along with Dr. Sangini Sheth, who is a OB/GYN at Yale Cancer Center, who is involved in the screening and treatment for cervical cancer right here in New Haven, and then 2 colleagues in Nepal, who just visited at the end of August, Dr. Archana Shrestha and Dr. Sunila Shakya have a pilot grant from Yale Cancer Center where we are looking at the barriers and facilitators to the implementation of this VIA screen and treatment approach in the hill areas outside of Khatmandu in Nepal where there is a fairly high cervical cancer incidence and mortality rate.

0:12:01.8 -> 0:12:03.9 What have you found so far?

0:12:03.9 -> 0:13:24 Well, it is the very beginning of the study. I really cannot say too much about it. We just received our funding maybe 3 or 4 months ago and the way things work, which I think is a good thing, is researchers cannot just, say in the United States, cannot just say oh! we are going to do a study in Nepal, let's go, pack your suitcases, there is a lot of ethical oversight to conduct such studies to ensure that we do not subject people who are maybe

more vulnerable, poorer, not as educated and so forth in other parts of the world to unnecessary procedures, so right now we are in the process of filling out our institutional review board applications, both at Yale, at Dhulikhel Hospital in Nepal and with the Nepal Research Council to get permission to do this study and ensure all these various parties that provide oversight that this is a study that would be beneficial to its participants and provide useful knowledge to Nepal and ideally others around the world.

0:13:24 -> 0:13:43.3 Clearly it sounds like promising research that can help us to understand cervical cancer and means of finding it at an earlier stage when it is most treatable. We are going to take a short break for a medical minute and then when we come back, learn much more about global oncology with my guest, Dr. Donna Spiegelman.

0:13:43.3 -> 0:13:53.4 Medical Minute Support for Yale Cancer Answers comes from AstraZeneca, working to eliminate cancer as a cause of death. Learn more at astrazeneca-us.com.

0:13:53.4 -> 0:14:40.3 This is a medical minute about lung cancer. More than 85% of lung cancer diagnoses are related to smoking and quitting even after decades of use can significantly reduce your risk of developing lung cancer. For lung cancer patients, clinical trials are currently underway to test innovative new treatments. Advances are being made by utilizing targeted therapies and immunotherapies, the BATTLE-2 trial aims to learn if a drug or combination of drugs based on personal biomarkers can help to control non-small cell lung cancer. More information is available at YaleCancerCenter.org. You are listening to Connecticut Public Radio.

0:14:40.3 -> 0:15:50.1 Welcome back to Yale Cancer Answers. This is Dr. Anees Chagpar, and I am joined tonight by my guest Dr. Donna Spiegelman. We were talking about her research and global oncology, and right before the break, Donna you were talking about cervical cancer, a cancer that very few women die from here in the United States, and one of the reasons you mentioned that was that we have Pap smears and that really has not been something that has taken off in the third world, and many low to middle income countries suffer from a lack of infrastructure, a lack of highly trained medical professionals such that Pap smears have not really taken hold, but one of the methods that have become popularized and that you are studying in Nepal is visual inspection with acetic acid or VIAA, which is simply painting the cervix with vinegar and finding these precancerous lesions that then can be essentially frozen so that they can be treated at an early stage. Are there other prevention strategies for cervical cancer that we have here in the US that might not be available in low to middle income countries?

0:15:50.1 -> 0:20:30.7 Yes, and the other one is HPV vaccination. Cervical cancer is caused by the human papillomavirus, that is what HPV stands for. And what that means when I say caused is that it is a necessary cause, meaning it seems to be almost impossible for a woman to get cervical cancer unless she

has been infected with HPV, but many, many, many, many, many, in fact the majority of women who are infected with HPV do not go onto get cervical cancer, and it also turns out that HPV virus has multiple subtypes and some subtypes have been found to be more virulent than others and one thing we do not know, that is an objective research around the world is do the malignant subtypes vary from one country to another since viruses are like eco systems and how they may grow and evolve in different subsets of populations might be different. So, we do not really have the answer to that right now, but it does seem like there are several at least, I think 4 if not more, that have been identified as the most malignant HPV subtypes around the world. And so, this is a vaccine, many of you in the audience might know if you have daughters that it is a vaccine that young girls, it is recommended that they get around the age between 12 and 13 with the idea that to be absolutely the most maximally effective, it should be before girls initiate their sexual debut, but obviously many girls do not initiate their sexual debut that early and it is also an objective active interest whether even after the sexual debut, it seems that the vaccine might still be effective, may not be as effective, but it still seems to be effective, and I am saying all of this because I want to encourage parents, mothers, and fathers in the audience whose daughters have not been vaccinated even if they might have been past their sexual debut or they might be 16 or even beyond, it appears that the vaccine could still be beneficial, and I would encourage you to seek that out for your daughters. Around the world, there have been trials of the vaccine, and maybe we do not know for sure what the endpoints are in terms of giving a vaccine to a girl at the age of 12, she may not develop cervical cancer, precancerous lesions until she is 35 or 40. So, the way the research has gone, it is get the vaccine to the girls, show that the vaccine is beneficial at least in some subset and then very long-term follow-up, we will hopefully reap the benefits, in say 15 or 20 years from now in lowering cervical cancer rates and lower rates of precancerous lesions and so forth. So, there are studies around the world, again not of the vaccine itself because the vaccine is already proven safe and effective, but their implementation trials about what is the best way to get this vaccine out to girls around the world, is it through schools, is it through health clinics, is it going house to house in communities and villages, what are the barriers, are people refusing the vaccine, what are the issues if so, how can we address them, but in the United States, I think the vaccination rate is disappointingly low, like maybe 20%, whereas say in Australia, it is extremely high like 80 or 90%, it is very high in Brazil, a catholic country, of something like 80 or 90%, so there is quite a lot of variation around the world and another area of research for us in the Yale Global Oncology program is looking at the distribution of vaccination rates around the world and trying to ascertain what are the factors even within a country that explain differences in vaccination rates as well as between countries.

0:20:30.7 -> 0:21:03.5 And do you have data on that because I know I would be very curious when we think about and you had mentioned before the break that in low to middle income countries cervical cancer is often the #1 or #2 killer of

women, particularly when it comes to cancer. And so, one would wonder in low to middle income countries whether there is an uptake of the vaccine or whether there are barriers, whether that is cost related to the vaccine or whether that is cultural barriers that are at play?

0:21:03.5 -> 0:22:58.9 I have been working with some colleagues using data from Brazil, which is well known to have a very high vaccination rate, but there is still quite a variability from state to state within Brazil, and as we might guess, all around the world where the rates are lower are the states that are lower income, that are more rural and have higher proportions of indigenous people living in them. So, to have more equity in HPV vaccination uptake, and for Brazil, first of all, it is good to note this, and then ideally stakeholders and policy makers and even politicians might devise strategies to even the playing field in terms of access to this important health intervention within Brazil. In India on the other hand, and this is a little bit of hearsay, but what happened is sort of similar to what happened here, which was that there was a big HPV vaccine trial and a girl died who was in the trial. It has been very well looked at and the cause of death of the girl seems by all possible reviews of her medical records and so forth had nothing to do with the HPV vaccine, but there is a lot of fear in countries about these kind of newer technologies and medicines and so forth being exported from say the United States or Europe into other countries and the word got out throughout the country of India that this vaccine killed somebody and so there is a lack of enthusiasm in India for a vaccination at this time from what I understand even though cervical cancer is the first to second leading cause of cancer death among women in India.

0:22:58.9 -> 0:24:43.1 Yeah. It is certainly tragic, and I think that beyond that there were issues with regard to the trial and you had mentioned the importance of ethics for example in that India trial, one of the other things that had happened was that there was some questions as to whether one patient had, I think it was actually 3 patients who had had their informed consent form signed after the fact and so there were all of these issues, on top of which from a cultural perspective, there was the whole issue of cervical cancer being sexually transmitted and of course parents do not think that their kids could possibly be sexually active and therefore the vaccine would not be needed, because of course their children are not sexually active. And those kinds of issues and layered on top of that was all of these trials that you mentioned, which have proven the efficacy of the cervical cancer vaccine have largely been done in the United States, in European countries, but have not really been proven in the Indian population, and on top of that, let us just layer on while we are at it, was the cost of the vaccine, and so this whole issue we finally have something that is very effective in preventing cervical cancer but how do we actually get it into a population where it can be of benefit and so peeling back all of the layers of the onion really becomes problematic.

0:24:43.1 -> 0:24:56.8 It is very complicated and interestingly some of the reasons you are giving for the lack of uptake in India are very similar to reasons

for lack of uptake in the United States.

0:24:56.8 → 0:25:08.2 Yeah. Tell us about other research that you have done in other cancers in terms of prevention and the strategies for improving global cancer care.

0:25:08.2 → 0:28:31.9 I want to bring up in the limited time that we have even though my own personal focus is focus towards prevention, there are really big issues in treatment in cancer around the world as well. For example, we have the term palliative care, which is very important for cancer and other diseases as well, and it usually involves taking people out of the terrible pain they might otherwise be experiencing in their last stages of cancer and even in the United States with all our technology and medicine that is so fantastic, a quarter to a third of the population is still dying of cancer, so at some point we all may need this palliative care and it is very good. It involves the use of opioids and opioids are banned substances in most low and middle income countries because as much leakage as we have had in the United States that has caused our own opioid epidemic, health leaders and health policy makers and government leaders are even more afraid in their own countries to bring in these kinds of palliative care agents, they are afraid they are not going to be able to control what happens to them and the next thing they know, maybe they will be sold on the black market or they will be sold or traded in different ways, they are very, very fearful of it. So, they would rather just completely ban them right now than do anything else. Even I can just say personally I have colleagues say in Mexico in other countries who have had relatives who have progressed to late stage cancer and these are very well-paid in the highest echelons of society and they could not get palliative care for their own relatives without going out of the country. So, that is the kind of kind of situation it is. So, just think of all of the millions of people who around the world are dying in pain because there is literally no palliative care. Similarly, I know that even in terms of cancer treatment, things like surgery, there are great surgeons all around the world, I think that has been very well documented where surgeons can perform their craft without a lot of technology, good surgeons, and good surgeons in low and middle income countries are really good surgeons oftentimes because they have learned to perform surgery without all of the aids and CAT scans and MRI and lasers and everything else that we have and that we even take for granted, but in general, things like radiation and chemotherapy are also unavailable in a very uneven way in many low and middle income countries around the world, and then in addition, the training of oncologists, what is the point of learning how to use an MRI machine if you are not going to have one in your hospital.

0:28:31.9 → -0:00:00.001 Dr. Donna Spiegelman is the Susan Dwight Bliss Professor of Biostatistics at the Yale School of Public Health. If you have questions, the address is canceranswers@yale.edu and past editions of the program are available in audio and written form at YaleCancerCenter.org. We hope you will join us next week to learn more about the fight against cancer here on Connecticut Public Radio.