Fabrication Techniques for Mems-based Sensors: Clinical Perspective

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Lecture – 17
Cancer Diagnostic Tool

Welcome to this lecture. And this lecture is our lecture that is focused on developing a Cancer Diagnosis Tool. So, what we mean by cancer diagnosis tool and how is it really helping or aiding a clinician to diagnose the cancer in a better way than the current existing tools.

So, we are talking about tissue related cancers alright. And when we talk about tissue related cancers, there are several cancer, which has tissue related cancer. And amongst those we will be focusing on breast cancer. So, let us see what we are talking about. And at the end of this course, at the end of this particular lecture you will be able to fabricate or at least understand the process flow, for fabricating a biochip that can measure certain properties of tissue, which can lead to a particular diagnosis alright.

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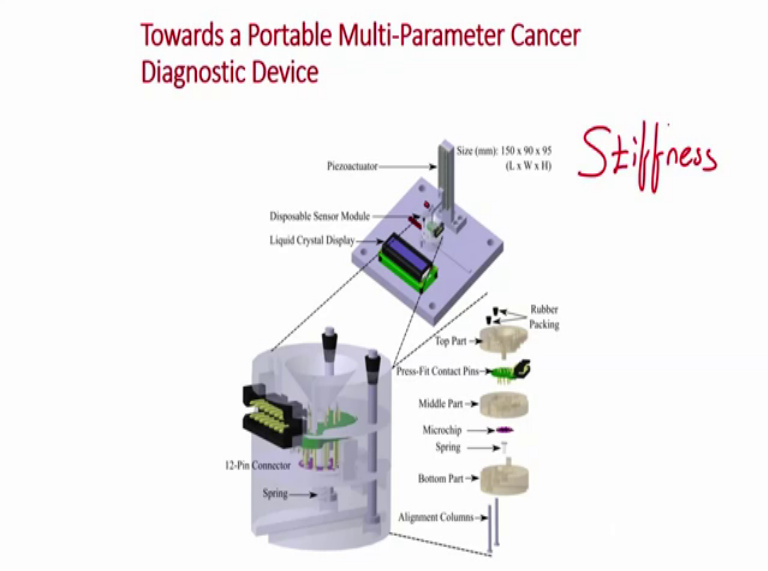

So, if you see this slide for this particular course right, we are talking about cancer diagnosis tool. So, we will be developing a tool right that can measure multi-parameter of tissue. What are multi parameters? Multi parameter can be stiffness of tissue right or in another way mechanical properties of tissue right; mechanical properties of tissue.

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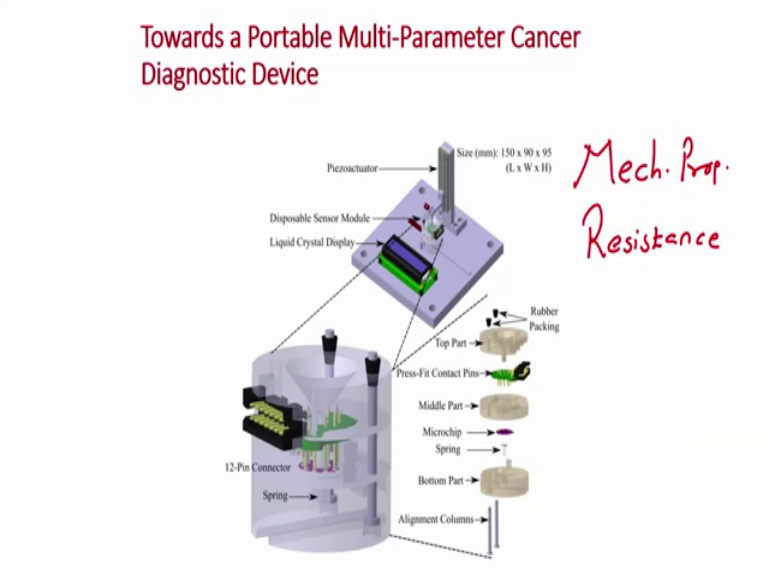

Then will we measuring resistance of the tissue or in another way we are measuring electrical property of tissue; electrical property of tissue.

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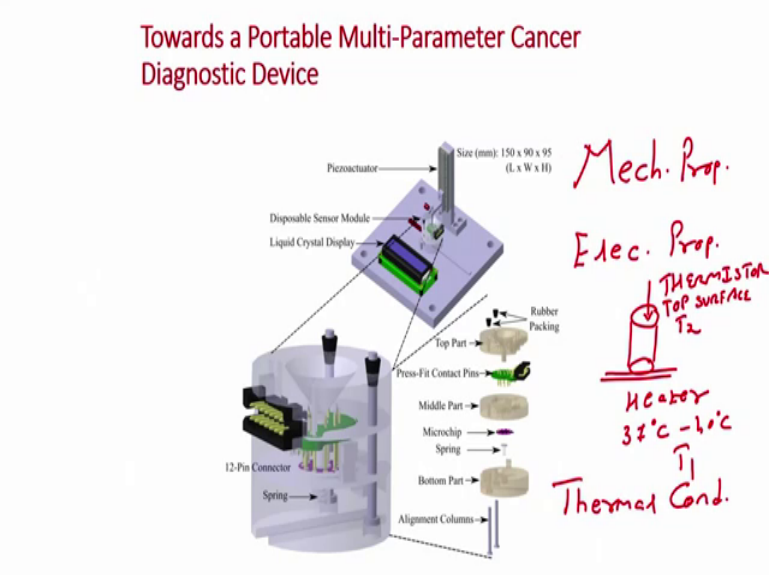

Third we will be measuring the change in the temperature of the tissue, when we heat the tissue from the bottom see where place the tissue on a heater. And I keep it at 37 degree centigrade to 40 degree centigrade, I keep a thermistor here. And I measure the temperature at the top surface let us say this is T 2, this is T 1 right. And I see that how much is a variation between T 2 and T 1. And from that what we are measuring, we are

measuring the thermal conductivity of tissue, thermal conductivity of tissue right. Or in one sentence it is we are measuring that we measuring mechanical electrical and thermal properties of tissue, this is what I mean by multi-parameter alright; measuring the electrical property, mechanical property, and thermal property of tissue in one go is a multi-parameter diagnostic device.

Now, another point is, so if I just rub it off another point is that this diagnostic tool. Diagnostic tool should be portable that means I can take it to from one dispensary to another dispensary from one hospital setting to another hospital setting without any problem right.

And what is the use of this, so what are the gold standards that are used in diagnosing cancer. Right now, let us say a patient is suffering from a breast cancer what are the parameters, how a person would know right. The first thing is self testing look at the abnormality in the breast, look at the leaky fluids alright, but what else what else we need to do right, and why we are to why to test the electrical property, mechanical property, thermal property of tissues right.

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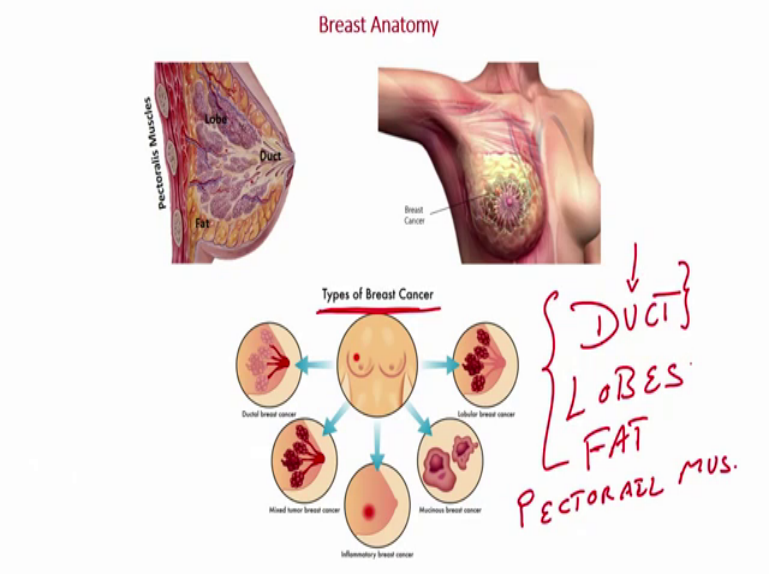

So, let us see first let us understand the breast anatomy, breast anatomy right. And see even we are designing micro engineering device or micro engineering or biochips, which can be used for cancer diagnosis. It is very important to first understand what cancer we are targeting. And if we are targeting a breast cancer, we should know right what is the

anatomy of breast otherwise it is very difficult for us to directly start fabricating the device.

So, if you see the anatomy of breast what we see that, the there is breast consists of ducts right, it consists of duct then it consist of lobes, it consists of fat right. Duct, lobes and fat this is fatty tissue here. Then these are lobular tissues this one, and then finally, there is a duct right.

So, and this whole thing is supported by pectoral muscles right. This is the anatomy of a breast just not to go in detail. So, so three things we understand, first thing is that the it consist of duct, it consists of lobes, it consist of fat, and the breast is supported by pectoral muscles right, this much we understand.

Now, if the breast if the cancer if the cancer happens in duct, then this called ductal cancer right. In case of breast cancer in the case of breast cancer, if the cancer occurs in duct, it is ductal cancer. If it happens in lobes, lobular cancer, it happens in both duct and lobes, it is called multi tumor breast cancer. Then if there is a inflammation, inflammation is a inflammatory breast cancer. And if there is a mucus, is mucinous breast cancer musinous breast cancer.

So, types of breast cancers are there right, and it is very very important to understand this, because breast cancer is second largest cause of cancer related death in women. Very important disease to understand, and thus it is very important to diagnose this particular cancer in early stage. In fact, diagnosing any cancer in early stage will double the chances of survival, then you know diagnosing at a later stage or in fact triple the chances of survival alright. So, as you can see there is a tumor formation in the breast right, and that is what we called as a cancer alright.

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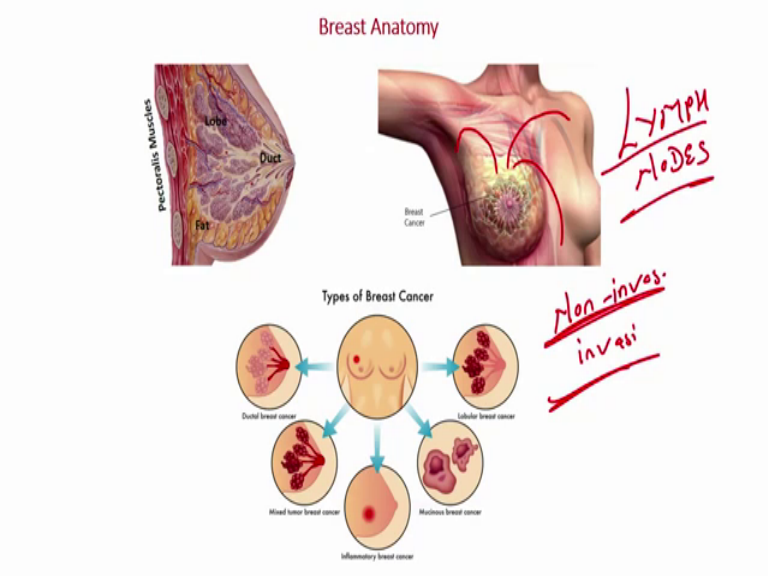

Now, there are two types of further cancer, one is called non-invasive, second is called invasive. What is invasive and what is non-invasive. So, when that when there is a tumor, and the cells comes out of the tumor, and moves to other part of the body moves to other part of the body thorough lymph node lymph node. We all have lymph nodes lymph nodes. Lymphs nodes are used to activate or to protect or to enhance our immune system. Lymph nodes are used or other part of our immune system to make it simpler.

And the cells when they are not localized, if they stay there, if they stay there if the tumor cells there cell stays there, it is non-invasive, it is not invading other part of the body. But, if the cells moves from the present location to another part of the body through lymph nodes, it is called invasive kind of breast cancer invasive breast cancer right.

So, what we understand, breast cancer two types; one is invasive, one is non-invasive. Then we understood that based on the area of the breast, it can be further classified as ductal cancer or lobular cancer. If it is in duct and lobe both, mix tumor cancer, if it is mucinous, mucinous cancer, if it is inflammatory, inflammatory cancer right, this much we understood. So, now what are the gold standards, how it is diagnosed currently. So, there is a technique, which is called mammography what is called mammography. So, let us see the next slide.

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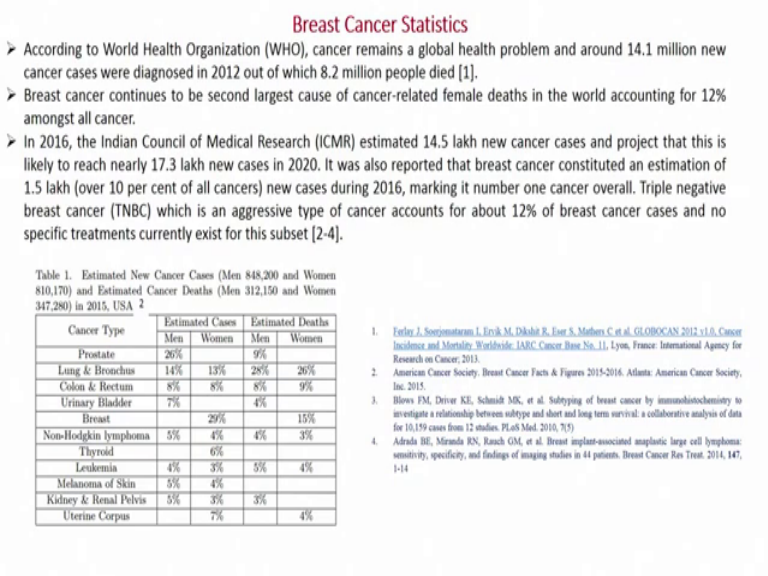

So, if you see breast cancer statistics, what is says that, according to World Health Organisation last report of it right, cancer remains are global problem around 14.1 million new cases (Refer Time: 12:02) right, or were diagnosed in 2012 out of which 8.2 million people died right. And the again it is very difficult to understand how cancer happens, what is the root cause of cancer difficult. There are lot of theories, but there are lot of speculations and theories, but not a certain answer, why it happens; what to do to stop it, what to do to prevent it right. We all learn that prevention is better than cure or precaution is better than cure precaution is better than cure right.

So, how I can be caution, that I should not do this, so that I will not have a cancer right. So, what I studied or what I found from the literature is that. If you avoid process foods, if you avoid foods that are modified genetically modified, keep it we keep our body cleaner right compared by when I say cleaner is not just taking bath, but also what food we consume. Are we consuming all the processed foods right, are we consuming all the genetically modified foods or fruits or vegetables, if so we should not we should not right.

So, again I what I am telling is from my reading my experience right, and what I will tell is avoid any process food, eat clean food is easier alright. Fortunately, as per my understanding, within our country right still there is no genetically modified food. The grains that are grown, the fruits that are grown, the vegetables that are grown, are not

genetically modified. Of course, there are use of pesticides, but not genetically modified right, except cotton. Cotton is genetically modified, and that is why there is a huge amount of cotton, we can export cotton now right.

When you modify a fruit or a vegetable or a grain right genetically, then it will stay for longer time, it is fresh for longer time, it grows faster, it yields faster yields, that the yield of the product is more right. So, in certain countries, when you go, you will find that the fruits are bigger in shape, the flowers are very bigger in shape right. And it does not stale for longer time not just because of the temperature, but because it is genetically modified.

Now, how much it defects the body, I do not know; whether it will cause cancer or not I cannot say. But, is it good to avoid that? Yes, that is the precaution that is a precaution right. And in fact, that is why the whole world is running after organic foods organic food. What is the organic food, where we use the organic material to grow or grains, fruits, vegetables right cow dung.

If you see how organic pesticides, when you say about chemical pesticides, they pesticides in particular, they also harm to a level, not only they just kill insects, but also harm the crops. Of course, when I say harm the crops, them in that crop dies, but still is a chemical. We have to wash the fruit thoroughly, vegetables thoroughly, there may be part of pesticides left in the in the leaf. Suppose, you eat spinach right, but organic way of doing it is much more safer and that is what we were doing from centuries right.

And there from someone I heard the story, and in fact it is a real story that you know, that people were making fun of our four fathers, they are using cow dung, there using coal, and salt for cleaning teeth right. And now, you see now you see MNCs have salt in their toothpaste right.

And the fruits in some of the countries, they are fruits and vegetables in some of the countries, when you when you travel, you will see organic markets. In fact, in fact in India also, we will now see organic markets right. And they sell it at much for higher price than the fruits grown by pesticides right. So, to the point that I am making is the point that I am making is that try to avoid process food, once in a while, because of our life style, we cannot avoid, and that is fine right, but try to avoid it. Try to avoid genetic originally fried foods. Try to learn what exactly this, this all things are; it is called GMO.

Anyway, so but the point is you see that, there are so many cases 14.1 million cases out of which 8.2 million died in 2012. In fact, like I said if you talk about just breast cancer, breast cancer continues to be second largest cause of cancer-related female deaths in world accounting for 12 percent amongst all cancer, 12 percent very high number very high number.

And Indian council of medical research in 2016; estimated about 14.5 lakh new cancer cases and projected that this is likely to reach 17.3 lakh new cases in 2020, which is not too far. It was also reported that breast cancer constituted an estimation of 1.5 lakh over 10 percent of all cancers cases in 16, and making in number one cancer overall you see.

Now, there is something even worst, and that is called triple negative breast cancer. What is that, triple negative, you see here. Triple negative breast cancer also called TNBC, which is an aggressive type of cancer accounts for about 12 percent of breast cancer cases and no specific treatment currently exist for this subset. And this is based on the, literature, which is right over here. I am not making my own statements; these statements are supported by the literature right.

Triple negative breast cancer, aggressive type of breast cancer, 12 percent of overall breast cancer, and no specific treatment exist for this subset. Specific treatment, it is does not meant there is no treatment, but specific for triple negative is not exist alright, now which are other cancers, tissue related cancers. And however, we are talking about this, because we want to see that if there is a gold standard, and if you see a gold standard, if you see the diagnosis, there is lot of false positive and false negative results.

What exactly false positive and false negative results means, that if a patient has a cancer, the report comes at it is ok, you are. And if a patient is not having any disease right is not suffering from the cancer, the report says that you have cancer false positive, false negative right, that false positive, false negative rates are higher.

So, if we can if we can design a tool based on our micro engineering knowledge, and little bit of additive manufacturing that is your 3D printing, laser cutting right, engineering designs, you all do engineering drawing in first year of your undergrad right, you use workshop. So, using this basic knowledge of micro engineering, additive manufacturing, can we design a tool that can add declination, and reduce the false positive and false negative signals that is the idea.

So, when we talk about tissue related cancers other than breast cancers other than breast cancer, which are other tissue related cancer. So, let us see that. You see in 2015 according to 2015 right, this is just about United States of America.

So, it is a, if the report from American cancer society, which says that just in USA, estimated cases and estimated deaths. You see estimated cases, estimated death, cancer type. Prostate cancer, prostate cancer occurs in men alright. Like breast cancer is extremely dangerous for women; prostate cancer is dangerous for men. And 26 percent is was the estimated cases in 2015 report, and 9 percent of the out of 26 percent was the estimated death for the figure for estimated amount of death and number of deaths.

Second one was lung cancer, both in men and women 14, 13 close, death 28 and 26 percent, out of 14 percent that is detected 28 percent dies, and 26 percent in women. Colon cancer and rectum cancer, 8 percent, 8 percent, look at the death 8 percent and 9 percent. Urinary bladder, 7 percent death from 7 percent 4 percent dies.

Breast cancer amongst 25 29 percent of estimated cases, 15 percent from 29 percent is the death rate. Same way lymphoma, thyroid, leukemia, like which is blood cancer; melanoma, which is a skin cancer right, kidney and renal pelvis and finally, uterine corpus. So, these are the major cancer that occurs in humans, and amount estimated death in numbers from this particular table right.

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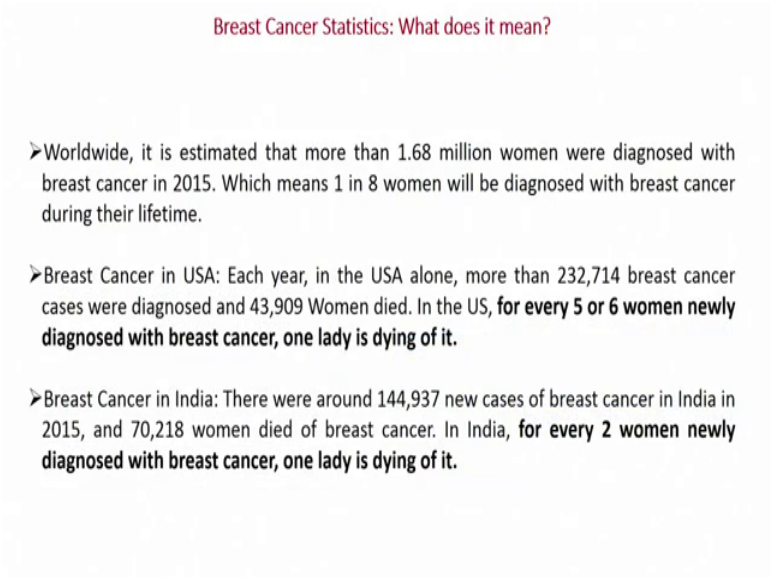

So, when we talk about this, what does exactly this statistics that we were about means that means that worldwide, it is estimated that about 1.68 million women were diagnosed with breast cancer in 2015, which means 1 in 8 women will be diagnosed with breast cancer during their lifetime 1 in 8 right, because it is 1.68 million women were diagnosed with breast cancer in 2015.That means, approximately 1 in 8 women will be diagnosed with breast cancer during the lifetime second.

Breast cancer in United States: each year, in the USA, the more than 23 how much is this 232,714 right 232,714 breast cancers were diagnosed amongst with 43,909 women died that means, in US, for every 5 or 6 women newly diagnosed with breast cancer, one is dying. For every 5 one is dying.

Now, let us talk about our country right. So, there were about 144,937 new cases of breast cancer in India in 2015, amongst with 70,218 women died of breast cancer in India 70,000 right the big number big number. And in general, nobody should die that is what we want right, nobody whom we love should die, but the real truth of our life is a death, nobody can deny it right.

So, the point the point that I am making is a loss of a family member is a great loss, and that too a woman, because it is a pillar of a family, she is a pillar of a family. Men is there, but woman has multiple roles, you see mother, sister, daughter, right, and that role no men can replace, in fact that is a great role that only a only a woman can do. A loss of a woman in our society a loss of a woman in a family, is a great loss is a great loss.

Same stance tense same stance true for men as well, but my point is, why to lose anyone just because of some disease. And we have the medicine to cure. We have the curing pills, we have the all the all the tools to cure, but we do not have a tools to diagnose it early. Is not that, we do not know how to cure, but by the time we know there is something, it is too late, and that is why this engineering design our understanding of engineering, we can apply to solve and diagnose a cancer. That is why we are learning this particular topic alright.

So, if you see back the statistics in India, for every two every two women newly diagnosed with breast cancer, one is dying of it. First of all, we are not aware right. Unfortunately the awareness program is not reaching to each and you know person in the society awareness program, we should be aware right. What happens, how to do self-

testing, self-examining, where to go, what kind of diagnosis we should do, primary health care.

And when I am talking about self-awareness, you will see in the next slide what I mean by that what I mean by that, but the situation is even worst, when we talk about our country. And what is that, for every two movement newly diagnose, one is dying one is dying.

So, if you talk about the awareness what is awareness, that the woman should go for mammography, if she is below 54, every year mammography is testing the breast to understand, if there is any suspicion region or not, gold standard. Exactly I cannot say gold standard, because there is a pathology also it was next to after mammography. Whether they would take the biopsy, and then they would take the I H C, and then measure the biomarkers, so it is not a really gold standard, but this is a standard diagnosis tool mammography.

Women between 40 and 54 or below that right, every year they should go and do this examination. Do we know that, how many of us know that, very few right, self-awareness or awareness about this disease. When we are aware, we can test, we can diagnose early, we can be healthy, we can live longer. A woman who is above 55; 55 and above right every 2 years, once we she should go and do this testing right.

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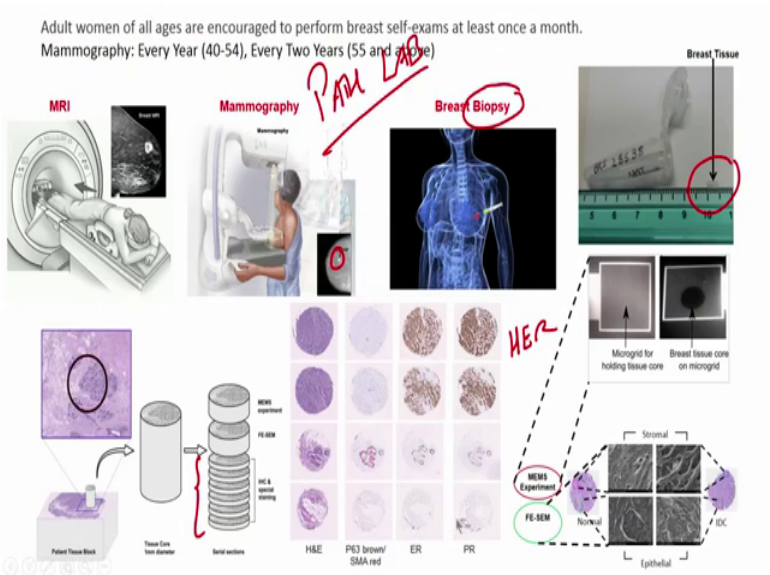

So, if you see the slide that is what is written. All adult women of all ages are encouraged to perform breast self-exams at least once a month once a month self-examination like I said right, stiffness liquor fluids, inflammation that is all self-examination. And mammography, every year 40 to 54 right, (Refer Time: 29:48) this age should go every year, in fact less than that should also go every year, and every two years, 55 and above 55 and above right.

So, you see if you go for MRI, if a patient who is suffering from breast cancer, and goes to MRI. And you can see in MRI, the suspicious region suspicious region right. Same the for mammography, you see this is mammography right. And here you can see this suspicious region, this spot, this white spot that you see is a suspicious region right. So, what happens what happens, once we e see that, there is suspicious region or not be, but the clinician looks at this suspicious region.

What is the next step what is the next, the next step is the next step is that the patient is advised for biopsy. Biopsy is, when you take out the tissue from the suspicious region, you take out the tissue from the suspicious region. So, when you take out the tissue from this suspicious region, which is your tumor.

What next, next is the tissue is sliced tissue is sliced and sent. So, tissue is sent to the pathology lab pathology path lab pathology lab, tissue is sent to pathology lab. So, when you when you do the biopsy, this a tissue, you can see tissue right over here. And it send to path lab, where it is sliced further, you can see here. Slicing for immunohistochemistry and special staining IHC and special staining, you see here, this one alright.

So, when you do this IHC and special staining, you are looking for certain biomarkers. And if the biomarkers are present, then the diagnosis would be that ok, the patient is suffering from cancer or the patient is not suffering from cancer. So, when we talk about biomarkers, what are these biomarkers, the biomarkers are H and E, estrogen, progesterone, SMA P63, and one is called HER.

These are the biomarkers that the path lab or the pathologist will be looking at, what H and E, P 63 SMA, estrogen biomarkers, progesterone and HER alright. This much is easy, very easy right to understand this easy, but the diagnosis is not so easy, it is difficult alright.

Now, what we want what we want is, can we design a tool, can we design a device that can measure other properties of tissue, except biomarkers or the optical way of understanding, which the mammography is also using it. So, here the idea is, can we measure the stiffness of the tissue, that is a mechanical property; can we measure the resistance of the tissue, electrical property; can we measure the thermal property of tissue, that is thermal conductivity of tissue. And to do all three things, we need to design now a biochip that can perform all three experiments together or all three it can detect all three parameters of the tissue right.

So, if we if we see that if we see the slide, what we see, that the tissue is sliced further, and it is given for our experiment. And another tissue is send for FE-SEM is a scanning electron microscopy. (Refer Time: 33:32) three of tissue here. If you see the tissue here, now there are two regions, one is epithelial region, another is stromal region. If the cancer is in stromal region, is called stromal cancer. Epithelial region: epithelial cancer 70 percent of cases are most of the cases in epithelial region. 70 percent of cancer breast cancer is induct and skull ductal cancer right. So, ductal cancer about 70 percent, and that is again based on literature.

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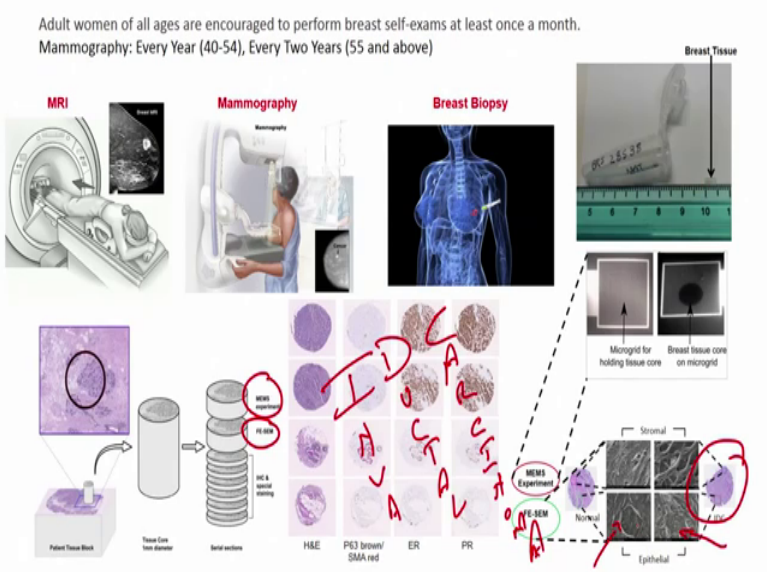

So, if we perform the FE-SEM, what we see is that, the structure of the tissue from normal. And this is IDC Invasive Ductal Carcinoma IDC IDC invasive invasive ductal carcinoma alright. This is IDC.

So, if you see the morphology or this topography using the SEM image using the SEM right what we what we see, we see that we see that the IDC, which is invasive ductal carcinoma, the tissue is much more ruptured, and the normal tissue is smoother compared to this is smoother, compared to this one IDC. This is normal, this is normal, and this one this one is cancer carcinoma. So, when you look at the images, will look at the normal and (Refer Time: 35:08) carcinoma, then you can see that the normal tissue is smoother, and the tissue which has carcinoma is rough or it is ruptured alright. This is what we see.

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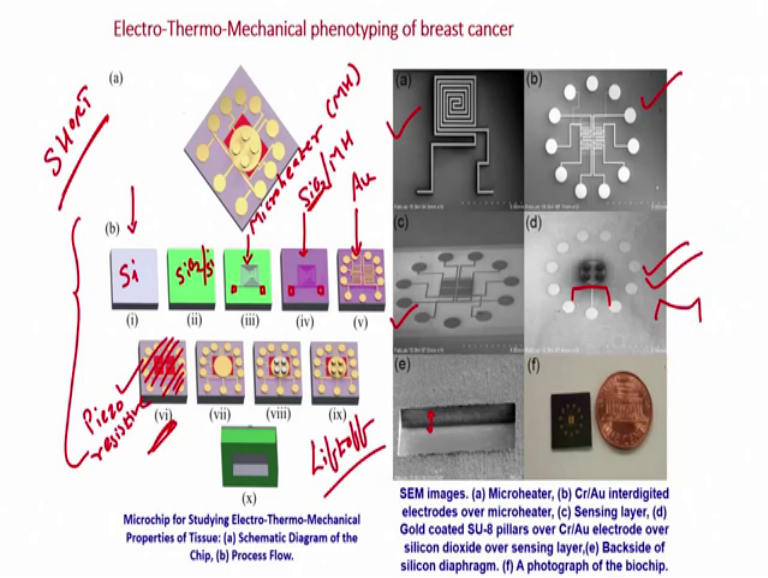

Microchip for Studying Electro-Thermo-Mechanical Properties of Tissue: (a) Schematic Diagram of the Chip, (b) Process Flow.

SEM images. (a) Microheater, (b) Cr/Au interdigited electrodes over microheater, (c) Sensing layer, (d) Gold coated SU-8 pillars over Cr/Au electrode over silicon dioxide over sensing layer,(e) Backside of silicon diaphragm. (f) A photograph of the biochip.

Now, what we want to do, we want to measure electro thermos-mechanical phenotyping or we want to phenotype the breast cancer; so electro thermos-mechanical phenotyping of breast cancer alright. So let us see what should our biochip consists of, biochip consist of a bottom layer, which is microheater which is a microheater.

On this microheater, so you can see here process flow ok. Look at the process flow here, and then we will see how we can fabricate this thing, that I will show you the process flow in detail right. Now, just concentrate on this particular slide on this particular image, process flow. First stage you take a silicon wafer, this is silicon alright. Second step is you grow oxide, this is S i O 2 on silicon. Then you form a microheater, you can see here you deposit a metal, do lithography do lithography, and form a microheater ok. On

microheater, you again deposit a insulator S i O 2 on microheater, I will say MH just to make it easy.

You get it what where are we, right now silicon silicon oxide that is grown on silicon on which we have using photolithography, we have patterned microheater. And then, there is a insulator on microheater. The reason of placing this insulator is that next would be our interdigited electrodes, you can see here right, this one this step. But, I cannot directly pattern interdigited electrodes on microheater, because metal of microheater, and metal of interdigited electrodes will get shorted will get short electrical short right.

So, to ever this short, we are depositing or we are growing insulator on the microheater, and then we are forming the; we are depositing gold. And pattern it pattern it using lithography using lithography to obtain interdigited electrodes. Now, in between there is a step, where you open the contact, you do not deposit the material, so here also there should be a contact like this. You do not deposit you deposit silicon dioxide, then you perform lithography, such that the contact area is open, only the window here you can see that one, there should be open that means, there silicon dioxide should not be there otherwise we cannot take contact to the heater right.

So, after this, you perform you deposit Au, and perform lithography, so that you will obtain this particular step. After this, you deposit you deposit in this step piezoresistive material; piezoresistive material, and pattern it pattern it, so you get this four squares, and you can see right over here right over here.

After this, after piezo resister, there is one more step, which is which is not mentioned here, but there is one more step very again grow after step 6, you take this one, and then grow a silicon dioxide alright. Then you deposit, then you deposit gold, and form a pad, which is here. And this pad, you deposit SU-8; SU-8 in and pattern it in form of pillar, and then you make SU-8 conductive by using lift of technique lift of technique again. When you get when you do this, you will obtain this.

From the backside, if I etch the silicon using bulk micromachining, that we are learned early, then I will have you see I have etch the silicon from backside. So, what will I have, I will have a diaphragm; I will have a diaphragm on which the entire structure is there. So, if you see this particular structure this one, then below this below this circle below the circle on the backside, there is a etching. So, when I press it, there will be a bending

right you get it. So, the frontside is the pad, so here if you see the pad is somewhere like this on the frontside, backside there is etching. On that pad, this structure is there right. So, we have etch the silicon from backside, using bulk micromachining.

So, let us see, quickly once again, what we are have done what we are done here, we had take we have started with the silicon substrate right, then we are grown oxide, which is number 2, then we have deposited metal for microheater, and pattern the microheater. Then we deposit silicon dioxide, which is an insulator. And we pattern the insulator, such that the contact area is open here. On that, we deposit gold. And we pattern the gold to form interdigited electrodes. On interdigited electrodes, we deposit piezoresistive material, which is 6 number here, and pattern it to form this squares.

On that, we have an insulating material, on which we have a gold pad, and gold pad is patterned, on which there is an SU-8 there are SU-8 pillars. And these SU-8 pillars are made conductive using lift of technique, which is number 9. And on the backside, we create the etch silicon to create a diaphragm. To obtain finally, this particular this particular design right. And the chip is right over here chip is right over here. So, what is the use of this right what is the use of this, we should know what is the use of this.

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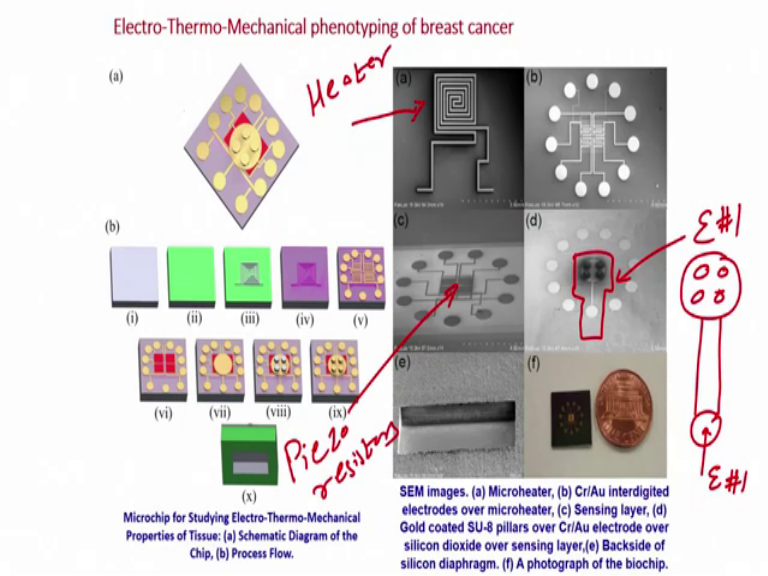

Let us see what is the use of this; we have now three things. If you have noticed, we have three things, what first is I have a heater, second thing I have a piezo resistors, third thing

I have a electrode, you see this one, this is the electrode. If you see this one, let us say electrode 2. Just we have just giving the name, let us say electrode 1.

This electrode 1 consists of four SU-8 pillars on gold pad, and this everything is conductive. And this gold pad is connected externally so that from here, we can apply or we can we can we have one point, which is our electrode 1 one contact pad for electrode 1. Three things we have right, heater, piezo resistor, electrode. Now, let us see how we will use this one, and where we will place this thing.

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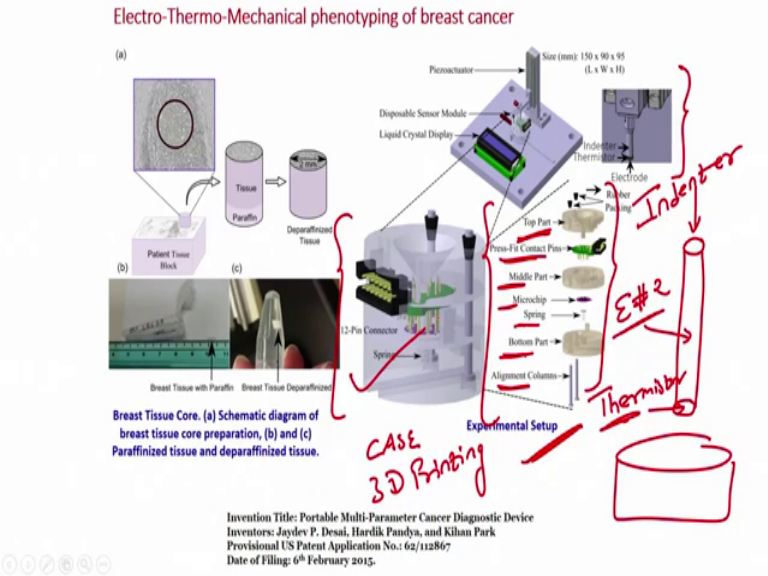

So, see this structure see this structure, and look at this structure in particular first. What is it, it is an rod right. That has that has conductive is conductive is conductive rod sorry conductive rod. And it is a thermistor thermistor. And this is conductive, so it can be our electrode number 2. There is a thermistor here, and it is conductive right. So, this is our indenter, what we say indenter. Indenter is used to indent like let us say if I have a material or of a tissue, this can press it, this can indent it indenter alright. Conductive electrodes, because it is a conductive, and we have thermistor at the tip of the indenter, understood this much.

Now, what we will do now what we will do, so we will design a case using 3D printing. Such that these case consist of top part, which is right over here, you can see this particular portion, it consists of top part right. And in the top, there is a rubber packing, then there is a press fit contact pins press fit contact pins. Then there is a middle part,

then there is a microchip or biochip, then there is a spring, then there is a bottom part, and then there are alignment columns right. What is that, let us see once again top part, press fit contacts, middle part, microchip or biochip, spring, bottom part, and alignment columns ok, this much we have.

Now, what we will do, if I press with everything, if I bring everything together, if I break bring this whole structure together, it will look like this, you get it. If I press this structure together, what it will look like, it will look like the one that I have shown it to you here, which is this particular structure. You can see spring, the you can see twelve pin connector, you can see the biochip within it right, you can see the biochip, see twelve pin connector, biochip, there is a spring, and then there is a conical flask like thing here right here you can see here. The top part, we have created this structure.

So, what exactly we have done. Here we have made a 3D printed case, such that it consist of or integrated with a microchip, there are no shoulder there are shoulder no; shoulder wires. There is there is no shouldering, there is no wire bonding; no shouldering, no wire bonding, but there is a press fit contact press fit contacts right.

This particular design is such a design, that it makes our life so easy. We do not have to do well shouldering, we do not have to go for wire bonding, and we just have to load our chip within this 3 D printed case. And we press it press fit it because of the press fit contacts, we can take out we signal or we can measure the signal from the external pins directly, one thing one advantage.

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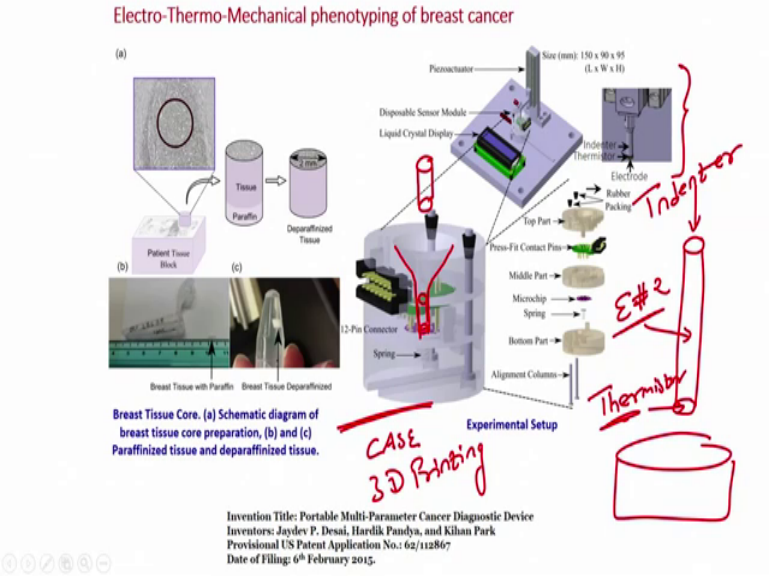

Second is that now you can load the tissue you can load the tissue in this particular section, and this tissue when you when you press fit everything, this tissue will be you can see this funnel going all the way around, like if we I see draw here, it goes all the way around like this right. And why, where does it end, it ends in the centre of the biochip it ends in the centre of the biochip that means, if I load that tissue here, if I load that issue here right, I bring the tissue down right, so what will happen. Finally the tissue will be placed on the biochip, you get it. The tissue will be placed on the biochip.

So, if I place the tissue, you can see this funnel right funnel. And we at the bottom of the funnel, there is the centre of the tissue is there, this one. So, the tissue is placed directly in the centre of the biochip, using this particular mechanism alright, you got it.

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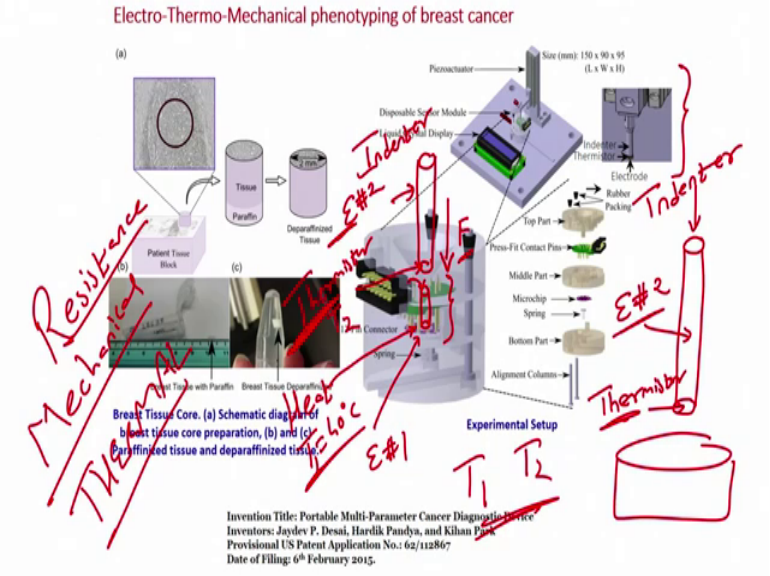

So, if I place the tissue like this, and if I place this indenter, so there is a tissue let us say this is a tissue on the biochip. And now what I am doing, I am using an indenter this indenter, which is our electrode 2 right. And on the biochip on this biochip, what we have, we have electrode 1, right. Let us see back, we have this electrode 1. So, if I apply voltage between electrode 1 and electrode 2, then the current will pass through the tissue right based on the tissue resistance, you get it.

If I have electrode 1 on biochip, electrode 2 is on indenter, if I press it, if I apply voltage between E 1 and E 2, then the current will passed through the tissue based on the tissue resistance. And that is why, I can measure the resistance of the tissue I can measure the resistance of the tissue, one thing. Second, if I press this indenter, if I indent the tissue down, then the tissue will the force exerted by this indenter will be transferred to the will be transferred to the piezo resistors via tissue right.

If I indent this indenter in this direction with the particular amount of force in micro nano newton, this force will be transferred to the biochip, and the biochip has piezo resistors. So, how much force will transferred to biochip, based on the stiffness of the tissue. So, the amount of force applied and amount of force transferred to the biochip that will help us to determine what is the elasticity of the tissue or stiffness of the tissue right.

If the tissue is stiff, then the amount of force will be different. If tissue is smoother, if tissue is less stiff; sorry not smoother, less stiff, if the tissue is less stiff, then the amount

of force transfer would be different right. So, now we can measure the mechanical properties of tissue, you got it, two things you got it right.

Third thing what is there here, thermistor. What is our biochip consist of, our biochip consist of heater right. So, now if I heat the tissue from the bottom the bottom of the tissue, I heat it with the help of the heater, which is integrated on my biochip. And let us say the temperature is 40 degrees centigrade. I can measure the top surface of the temperature the top surface of the tissue. See the bottom surface has 40 degree. I can measure the temperature at the top surface of the tissue with the help of thermistor with the help of thermistor.

So, now I have T 1, which is let us say T 1 is 40, and with help of thermistor T 2 right. From this, since I know the temperature the bottom surface, the amount of temperature at the top surface. So, if the there is a temperature difference and based on that, I can measure the thermal conductivity of the tissue, I taken can measure thermal properties of tissue or thermal conductivity of tissue, you get it.

So, now if I place this tissue; if I place the tissue in this particular set up, I can measure the mechanical, electrical, which is resistance, and thermal properties of tissue, cool. So, what will I do with this, if I can measure electrical, thermal, mechanical properties of tissue, and how it is really helpful right; how it is really helpful.

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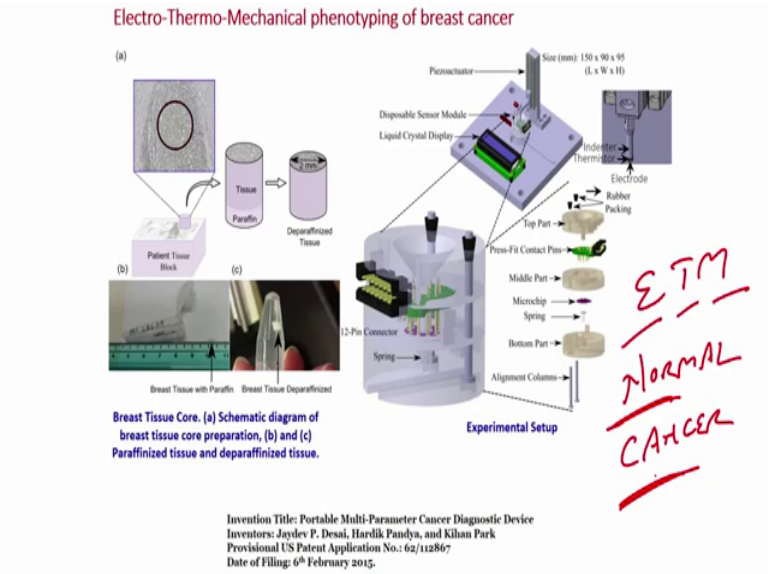

So, let us see first of all, when we measure electrical property and thermal property, is it different my point was, that If we develop this biochip, and we measure the electrical, thermal, and mechanical properties of tissue, or the electrical, thermal, and mechanical properties of normal tissue different than cancer tissue right, or the electrical, thermal, and mechanical properties of normal tissue different than cancer tissue.

And if there are difference, then we can understand that the tissue is changing is property, the disease is progressing. And we can diagnose that is the change in the tissue property. And thus, we can diagnose the cancer possibly at earlier stage right. So, but can we understand the signature can we understand the signature of the tissue or properties that is changing in the tissue.

So for that let us see the result let us see the result. So, what we see here again is, so one way is that you take the life live biopsy, means when you take the biopsy; biopsy is when you take the a tissue from the suspicious region out right. And directly place the tissue on to this system on to this tool; or you can you can save this tissue in the tissue bank right, which is using the paraffin block using the paraffin block. This is the standard way of storing the tissue in a tissue bank.

And whenever you want to use it, whenever you want to test it, you can deparaffinized tissue means you remove the paraffin right. Take the tissue out, and place a tissue on this device on this tool. You see here is a deparaffinized tissue; it is white one, deparaffinized tissue. This is paraffinized tissue paraffinized tissue alright. So, there is one thing.

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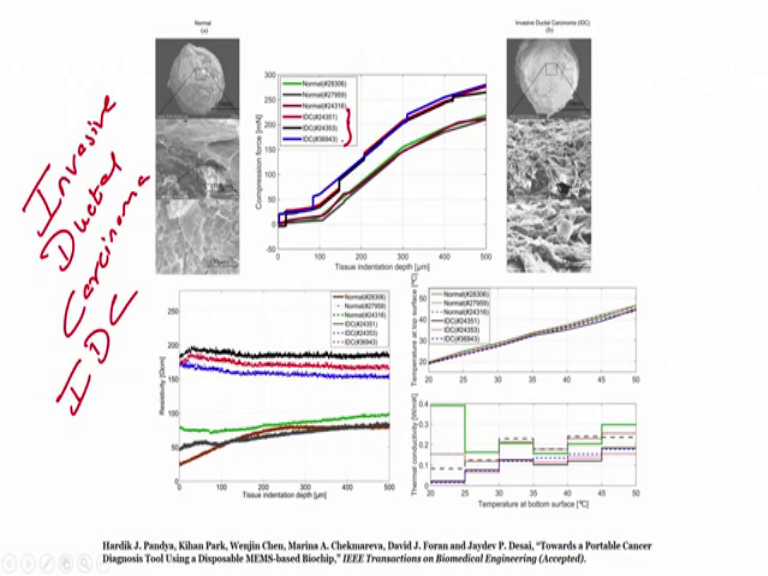

Now, when we measure the normal tissues and cancerous tissues, in here we have taken case of Invasive Ductal Carcinoma or I D C that is all you can see here I D C all right I D C. So, here we have used invasive ductal carcinoma or I D C.

And with the help of indenter, when we indent the issue with depth of indentation with the depth of indentation in micrometers, we could see the compression force compression force. And we can clearly see we can clearly see that the force obtain the compression force obtained from normal tissues normal tissues is different than cancerous tissue is different than carcinoma.

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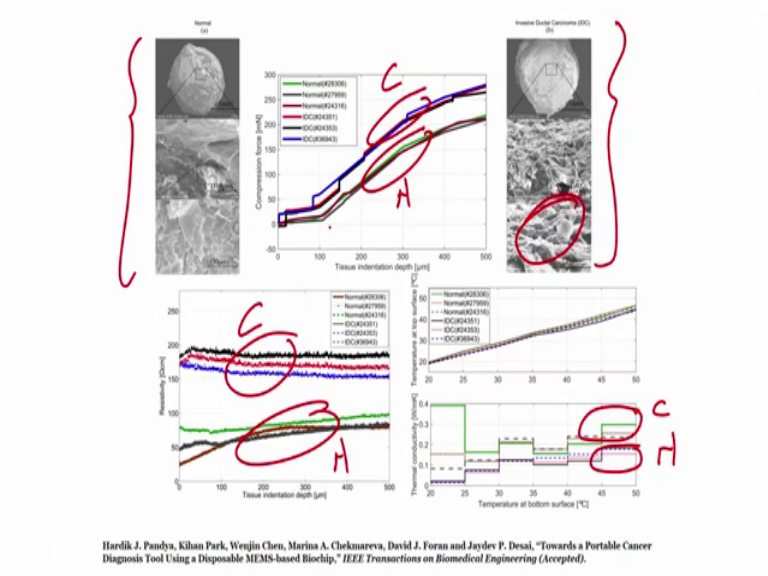

Hardik J. Pandya, Kihan Park, Wenjin Chen, Marina A. Chekmareva, David J. Foran and Jaydev P. Desai, "Towards a Portable Cancer Diagnosis Tool Using a Disposable MEMS-based Biochip," *IEEE Transactions on Biomedical Engineering (Accepted)*.

Second, the resistivity the resistivity of the normal tissues is different than the resistivity of the cancerous tissues. Third, the thermal conductivity, you can see this three lines here. The thermal conductivity of cancerous tissues is different than thermal conductivity of normal tissues. What we see, that the there is all three properties changes all three properties changes.

In fact, when you see the normal tissues, and you take the SEM, did the cancerous tissues, and you take SEM. You will see that the cancerous tissue shows much more ruptured structures. What is rupturing, what is not smooth, when something is not smooth, the resistance would increase. Where resistance is increasing, the thermal conductivity also would be different right. And that is what we have measured here that is what we have measured here.

So, if you see that from mechanical, electrical, and thermal property of tissues, we can get a sense that. When we will be measuring lot of samples, we would have a particular signature that will help us to diagnose whether there is cancer or not or you can diagnose cancer, in fact in a earlier stage in a earlier stage right, because the properties of tissue would be different as the disease progresses as the disease progresses alright.

And all the things that, I am talking about is from the publication IEEE transactions or biomedical engineering, which is published which was published earlier in 2016 and or 17, 16 probably. And these are all the results that is from the same publications.

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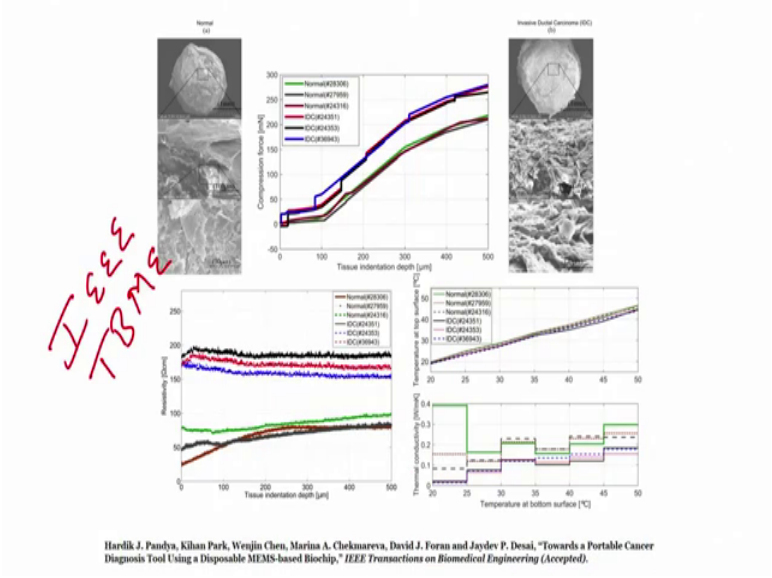

So, if you want to just go back, and see this paper towards the portable diagnosis tool using a disposable MEMs based biochip from IEEE TBME, you can go, you can read in detail, what exactly we have done, IEEE transactions on biomedical engineering ok.

So, now the point is if we know this things, now if we know that we need to fabricate we need to fabricate the biochip right, we need to fabricate the biochip, which will have the heater, which will have piezo resistors, and which would have electrodes. Then we have seen here process flow, but let us now see, how we can fabricate each of this component each of this sensor on the biochip all right.

So, in the next module, in the next module, we will be looking at each of this sensors that we can fabricate on a biochip right. From heater, then interdigited electrodes over with there is a piezo resistor over with there is a electrode on which there are S U 8 pillars on which we are making S U 8 pillar conductive, because S U 8 it is a polymer non-conductive polymer. And finally we are creating a diaphragm by etching the silicon from the back side right bulk micromachining.

So, we will see in the next module the fabrication or the process flow for fabricating this biochip. What I will like you to do is go through this module once again also read about types of cancer, read about breast cancer. In fact, when you go to YouTube and write down breast cancer and its stages breast cancer and its stages. You will be able to understand thoroughly or slightly better how exactly the cancer progresses. And what are

the stages of cancer then by understanding that you may get more problems, and probably with that problem you may have more solutions, and the solutions can be or may be based on the knowledge that we are acquiring, by understanding the micro engineering, right.

Can you come up with a new device, a novel device, a better device what I am showing it to you that is a idea. The idea of you know discussing and exchanging the viewpoints, the knowledge is that we increase we make our research better, you we come up with new ideas, new technologies. There can be better than the existing one or what I am performing on. What whatever I am doing is what I know? Can you come up with a better solution, then what I know then it is a worth of you know talking, and discussing and understanding the micro engineering right that is the idea.

So, think about it read and learn this videos once again then go through this module once again. And in next module, let us see how we can draw process flow, what should be the recipe, so that we can fabricate this biochip right.

Till then you take care. I will see you in next module. Bye.