Hello. I’m Dr. Terry Bevers, Professor of Clinical Cancer Prevention and Medical Director of the Cancer Prevention Center at The University of Texas MD Anderson Cancer Center. Today, I’m gonna talk to you about Breast Cancer Survivorship: Second Primary Cancers.

The objectives of this lecture are to identify those risks for second primary cancers in breast cancer survivors and outline the mechanisms related to their development. We will then discuss risk reduction and screening strategies for these second primary cancers.

It’s helpful to start out with a definition of second primary cancers, which are actually a new primary cancer developing in a person with a history of cancer. It is a neoplasm that arises in a tissue that is actually distinct from the first primary and develops subsequent to the initial cancer by some defined time period. The definition used by SEER is that cancer that is diagnosed greater than two months from the initial primary.

You may be surprised to find out that excluding non-melanoma skin cancers, second primary cancers are actually the fifth most commonly occurring type of cancer amongst Americans.

Since the 1980s, we have seen that while the incidence of breast cancer has been increasing, mortality is actually decreasing. This is due to early detection and improved treatments. As a result, more women are surviving their breast cancers. In addition to the risk of recurrence of their breast cancer and late effects from their treatment, these women are at increased risk of second primary cancers.

If we look at this graph here, we see that there are a number of second primary cancers that can occur in breast cancer survivors. The most frequently occurring are female breast cancers. But a number of other cancers such as ovary, uterine, and colon can be seen such that all second cancers are actually a significant problem in breast cancer survivors.

When we talk about second primary breast cancers, it’s important to realize that based upon our definition it is technically not a second primary breast cancer. Forty percent of all new cancers in breast cancer survivors are a second primary breast cancer. And they occur primarily in the contralateral breast. Risk factors include younger age of diagnosis, which is largely due to genetic predisposition, but is also black race. Risks are significantly decreased since the advent of adjuvant hormonal therapy which includes tamoxifen and now aromatase inhibitors.

If we look at this table of the observed-to-expected ratio of subsequent primary cancers after cancer of the breast, we see whether it is subsequent cancers that includes both second primary breast cancers and others, or just subsequent cancers and exclude...
female breast cancer, that the risk is greatest in younger women, those being diagnosed with their primary breast cancer under the age of 40. As previously noted, this is commonly related to the fact that these women are more likely to have a genetic mutation.

There have been three carcinogenic pathways that have been identified as mechanisms for the development of second primary breast --- second primary cancers in any survivor. And we will look at these specifically in regards to second primary cancers for breast cancer survivors. These are common lifestyle or environmental factors, common genetic pathways, and then the iatrogenic effects of treatment.

So common lifestyle or environmental factors, one of the most striking is obesity. It is a well-known and established risk factor for breast cancer. But it also increases the risk of other cancers.

Some other cancers that we see related to obesity are colon, endometrium, and esophagus all of which are increased in breast cancer survivors.

Genetics is clearly a variable to be considered in a breast cancer survivor, especially those diagnosed at an early age. A woman's lifetime risk of developing breast cancer and other cancers is greatly increased, if she develops a harmful mutation to BRCA1 or BRCA2. We can see that in addition to breast cancer, there is cancer of the ovary associated with both of these mutations as well as cancer of the pancreas. But other cancers can be specific to these two mutations. Additionally, male breast cancer survivors are at increased risk of prostate cancer. And again, this often is due to a common genetic pathway.

There are other genetic predispositions or syndromes that can be related to breast cancer. The first is the Li-Fraumeni syndrome which is related to the p53 tumor suppressor gene. And this increases the risk not only of premenopausal breast cancer often developing in the 20s, but also to sarcoma, brain cancer, leukemias, and adrenocortical cancers. Cowden’s syndrome is a rare disorder characterized by multiple non-cancerous tumor-like growths called hamartomas. And it has an increased risk of developing thyroid and uterine cancer in addition to breast cancer.

The risk of ovarian cancer increases with the younger age of diag --- at initial breast cancer diagnosis. As we can see in this table, the risk is almost four-fold increase for women who are diagnosed under the age of 40. And women who are diagnosed over the age of 70 actually have no increased risk of ovarian cancer compared to the general population. Again, this risk is commonly related to a genetic predisposition, thus the link to the young age of diagnosis. But to a lower --- lesser extent, it may relate to some of the endocrine factors that are common between the two, for example, nulliparity.

Other genetic-based second primary cancers include melanoma which is seen in BRCA mutation carriers. But it may have a possible hormonal mechanism. Stomach cancer has also been linked to a BRCA mutation --- BRCA2 mutation.
Thyroid cancer has been seen to be increased in breast cancer survivors. The mechanism at this time is largely unknown. It may relate to Cowden’s syndrome. However, this is really a fairly rare genetic syndrome. We do note that the risks are actually similar between radiated and non-radiated women. In other words, a woman’s radiation therapy for her breast cancer does not appear to increase her risk of thyroid cancer as is seen with some other cancers.

Now, if we look at the iatrogenic effects of treatment, we see that all three of chemotherapy, radiation therapy, and hormonal therapy can produce second primary cancers.

The most common cancer linked to chemotherapy is leukemia; the most common one being acute non-lymphocytic leukemia. It is related to alkylating agents. And the risk is greater with a higher dose of these alkylating agents. Radiotherapy may, in fact, compound this risk that is related to chemotherapy.

Radiation risk for second primary cancers increases with the radiation dose and increases from time of radiation. Commonly, these cancers will not be seen until about eight to ten years after the radiation exposure. Common radiation-related second primary cancers for breast cancer survivors are lung cancers, esophageal cancers, and sarcomas.

Not surprisingly, lung and esophageal cancers are increased because they are directly in the radiation field for many breast cancer patients who receive radiation therapy. We do note that it is primarily occurring in post-mastectomy radiation in those receiving high --- because they receive higher doses of radiation to the thoracic organs. We don’t actually see an increased risk of lung cancer in women who are treated with radiation therapy after lumpectomy. The risk is of course greater for the ipsilateral lung where the radiation dose is the highest. And the risk is actually compounded by smoking which provides an opportunity for intervention. The esophageal cancer risk is greatest in the upper and middle sections, again where the radiation dose is the highest.

Sarcomas are also seen occurring in the radiation field, the most common one being angiosarcoma. But we also see osteosarcoma, fibrosarcoma, and soft tissue sarcomas. Lymphangiosarcomas of the upper extremity are rare and may be more related to chronic lymphedema due to an axillary lymph node dissection than to radiation exposure. As we mentioned, risk factors for sarcomas as a second primary cancer include radiation therapy. But we also need to keep in mind that there could be a genetic component, as Li-Fraumeni syndrome individuals not only are at increased risk of breast cancer but also at increased risk of sarcomas.

Uterine cancer is increased in women who have had a previous history of breast cancer. The risk is increased by about 35% and is actually highest in older women. The risk may be related to tamoxifen therapy which is --- increases the risk of uterine
cancer two- to three-fold, but it may be related to other common risk factors such as low parity, obesity, or prior hormone therapy use.

To manage the lifestyle risk for the development of secondary primary cancers, the first step is to help our patients control obesity through energy balance. That means the calories in needs to match the calories out. It’s a diet and exercise balance. We attempt to maintain the body mass index or BMI between 18 and 25. So it's important to identify our patients who have a body mass index greater than 25, offer them resources and support for weight reduction, and offer them an exercise prescription. Reducing their weight will reduce not only second primary cancers, but the risk of recurrence of the initial breast cancer.

In managing genetic risk for second primary cancers, it’s important to identify those who have a personal or family history that is suggestive of a genetic predisposition. These individuals should be referred for genetic counseling. Some factors that we look at include: a personal history of breast cancer that was diagnosed early age, typically under the age of 50, if they had bilateral breast cancer at diagnosis, or, men who are diagnosed with breast cancer is actually a significant red flag. We look to see if there is a family history of a relative who has actually undergone genetic testing and has been identified as having a genetic predisposition syndrome.

Other variables include the personal history of breast cancer diagnosed at any age and one or more of the following variables, such as: early onset breast cancer in a family member, having two or more relatives with breast cancer at any age, family history of male breast cancer, personal or family history of ovarian cancer, or family history of pancreatic cancer. These would all be related to a possible genetic predisposition for a BRCA1 or BRCA2 mutation. The last three, the last --- the next two bullets actually identify individuals that would be at increased risk for Li-Fraumeni syndrome, such as those with a family history of sarcoma, adrenocortical cancer, brain tumors, or leukemia or for Cowden’s syndrome, if they have a personal family --- personal or family history of follicular thyroid cancer, endometrial cancer, or dermatologic manifestations of Cowden’s syndrome. Individuals of Ashkenazi Jewish ancestry are also at increased risk for BRCA mutations.

Individuals who are identified as having a genetic mutation should be counseled on risk reduction strategies. They can be counseled regarding prophylactic mastectomy to prevent --- [speaker intended to say “prevent”] --- a second primary breast cancer. Prophylactic mastectomy can lower the risk of developing a breast cancer by as much as 90%. They can also be counseled about bilateral salpingo-oophorectomy, which not only lowers the risk of ovarian cancer significantly, but also lowers the risk of breast cancer by one-half. For women not electing to undergo prophylactic mastectomy or bilateral salpingo-oophorectomy, aggressive surveillance can be done. We can perform CA-125 and transvaginal ultrasound every six months until they are through child-bearing at which time we would want to consider performing the BSO. Additional screening for second primary breast cancers can be performed with annual breast MRI.
In managing radiotherapy risk of second primary cancers, one way is to limit the toxicity by minimizing the radiation exposure. We now have improved techniques for whole breast radiation such as hypofractionation or IMRT, intensity-modulated radiation therapy. We can also radiate smaller portions of the breast and for shorter periods of time as an accelerated partial breast irradiation. At this time, we’re not clear on how these new approaches will modulate SPC risk. But clearly, it provides an opportunity by lowering the dose and radiating smaller portions of the breast. As previously mentioned, smoking is --- has a carcinogenic effect on radiation --- radiotherapy. For this reason this provides us an opportunity to target our smokers who are undergoing radiation therapy and encouraging them to quit. Offering assistance through tobacco cessation strategies is critical.

Now while we have talked about a number of second primary cancers related to the carcinogenic pathways, it’s important to realize that many women will develop a second primary cancer simply due to the fact that they are getting older. For example, as a woman increases unrelated to her risk of breast cancer, she is at increased risk of colorectal cancer. For this reason we encourage women to follow the current screening recommendations.

In summary, breast cancer survivors are at increased risk of second primary cancers. We can manage the risk of these second primary cancers by identifying those risks, modifying those risks, and implementing appropriate screening to identify SPCs early. I thank you for your time and attention. We welcome feedback on this lecture series. Thank you.