SPECIFIC SLIDE POINTS FOR LECTURE 2

SLIDE 44. LECTURE TOPIC

We lecture today on the causes, prevention and screening of cancer.

Slide 45. CAUSES OF CANCER

There are seven major risk factor classes for cancer, as enumerated on the slide: 1) Old age; 2) Hereditary predisposition; 3) Geophysical factors; 4) Industrial exposure; 5) Lifestyle choices; 6) Infections; 7) “iatric”-medical treatment, including cancer medicine and radiation.

SLIDE 46. DODGEBALL

Currently 50% of all cancers, and 70% of all cancer deaths, occur in patients over 65. And the only thing you can do to avoid old age as a risk factor is something you don’t want to do-die of something else. As we learned in the last lecture oncogenes are mutations arising in essential genes that regulate growth of normal cells. Throughout this lecture on cancer prevention it is important to remember we can prevent external mutations, but not random errors occurring with normal cell division. As in dodgeball, the longer you play the game, the higher the odds you’ll be tagged. Death in old age is inevitable, though death before old age is not.

Hereditary genetic mutations inherited from the father or mother play a role in about 5-10% of cancers. Cancer is a genetic disease, but recall from the first lecture: genetic just refers to changes in the DNA of any cell. The DNA changes can be in a germ cell (sperm or egg) or somatic cell (all the rest of the cells of the body). Hereditary, or inherited, refers to changes in the DNA that are passed on through the germ cell line. All the body’s cells will reflect this mutation. Congenital means present at birth: congenital changes can be inherited, as in Down’s syndrome or not-as in fetal alcohol syndrome which is caused by alcohol induced damage to the fetal DNA. Roughly 50 hereditary cancer syndromes have been identified. Genetic counselors often play a role in advising physicians and patients in how to manage the risk (through enhanced screening, preventive medicine, and/or preventive (prophylactic) surgery.

Slide 47. BRCA MUTATION

The so-called BRCA-1 and BRCA-2 mutations, which were first identified in 1994, are archetypal hereditary mutations. When a BRCA gene is mutated, it may no longer repair broken DNA. BRCA stands for breast cancer, although these genes can also predispose their carriers to ovarian, prostate, pancreatic and melanoma skin cancer. BRCA genes are carried by 1 person in 400. People with the BRCA mutation are advised to visit with a genetic counselor and their MD about their risks for developing cancer, and the pros and cons of modifying lifestyle, such as diet and exercise; screening mammography and/or breast MRI (magnetic resonance imaging); prophylactic (preventive) medicine; and prophylactic surgery, such as removal of the breasts and/or ovaries.

Slide 48. ANGELINA JOLIE

The actress Angelina Jolie carries the BRCA-1 mutation. Her mother and grandmother died of ovarian cancer, and an aunt died of breast cancer. She had an 87% lifetime risk of developing breast cancer and annual screening testing indicated possible ovarian cancer. Ms. Jolie underwent prophylactic bilateral mastectomy in 2013 and prophylactic bilateral oophorectomy in 2015.

Carcinogens are substances which can cause cancer.

Geophysical causes of cancer are carcinogens present in the natural world. Around 3% of cancers are estimated to develop from such naturally occurring carcinogens. Arsenic in the water, asbestos in the soil, radon exposure in the home, and exposure to sunlight (UVB light) are examples.

Slide 49. RADON GAS

Radon is radioactive gas that is released from normal decay of uranium, thorium and radium in rocks and soil. Radon may cause up to 6% of lung cancers. Everyone is exposed to low levels of radon. Radon can enter homes through cracks, be released from building materials, or water from wells.

Slide 50. RISK LEVELS IN THE COUNTRY

Buffalo County is in an EPA zone 2 for radon with average radon soil content. Large areas of eastern and southern Nebraska are in areas with high risk (such as Phelps and Hamilton County). In the slide red counties are high risk, orange counties average risk, and yellow counties low risk.

Slide 51. RADON GAS KIT

Regardless of the average risk in your county everyone should test radon levels in their basement-test kits are readily available in hardware stores.

A wave of UVB light (so called ultraviolet light B) is 290-320 nanometers across-about the same distance across a DNA strand-which helps explain why UVB light is associated with the development of skin cancers.

Occupational, industrial, and air pollution exposure may lead to around 7% of cancers.

Slide 52. CHIMNEY SWEEP

In 1775, Percival Pott, a surgeon in London, noticed a marked rise in cases of scrotal cancer in his clinic. The patients were almost all chimney sweeps who spent hours in contact with grime and ash. The cancers developed after years of occupational exposure, generally after the sweeps had outgrown the chimneys. The delay illustrates the fact that damage to the proto-oncogenes which control normal cell division (and only divide 30-50 times in a lifetime) accumulate gradually, in a pathway that leads to cancer. Pott's observation that chimney sweeping was associated with scrotal cancer led to the Chimney Sweepers Act, passed by Parliament in 1788. The Act forbade children under 8 from employment as sweeps.

In our country and time the OSHA (Occupational Safety and Health Administration) monitors exposure to workplace carcinogens, such as another prototypical carcinogen: asbestos.

SLIDE 53. ASBESTOS FIBERS

Asbestos is the leading cause of work-related deaths presently. Asbestos fibers, which are pictured in the slide, actually physically spear the cell's nucleus. Physical carcinogens such as asbestos form "adducts" in the DNA. The DNA double helix is like an unzipped zipper during mitosis. Adducts prevent the "zipper" from lining up properly during replication. In the early 1970's a "case control" study identified asbestos as a carcinogen in numerous industrial workers. The EPA first regulated the use of asbestos in 1979. Since the development of cancers occur over decades, retired miners, auto mechanics, shipyard workers, and others continue to succumb to lung cancer.

Slide 54. MESOTHELIOMA

Patients exposed to asbestos also develop a cancer of the pleural outer lining of the lung called a mesothelioma. Globally, 90,000 people a year die of asbestos related disease and 125 million are at risk.

Tobacco (30%), diet (35%) and alcohol (3%) are the leading preventable causes of cancer.

SLIDE 55. TOBACCO

John Hill, a London apothecary first "cautioned against the Immoderate Use of Snuff" in 1761 due to this smokeless tobacco's association with lip, mouth and throat cancer. British soldiers exposed to Turkish cigarettes in the Crimean War in the 1850's brought the habit back to the UK. Lung cancer deaths rose markedly throughout the 20$^{th}$ century in the UK and USA. The precipitous rise in widespread tobacco use made it harder to see the connection between tobacco and lung cancer. Pollution, influenza, lack of sunshine, road tar, X-rays and other possible causes were cited as alternative explanations. In 1951 all British MDs were asked to record their smoking habits. 2 ½ years later 36 lung cancer deaths had occurred in the physician cohort-all in smokers. The Tobacco Industry Research Council mobilized to obfuscate the connection between tobacco and cancer in the USA, where 45% of Americans were smokers by 1956. In 1961 the US Surgeon General appointed a 10 member panel to address the possible links between tobacco and cancer for the public. Half the physicians on the panel were smokers. The chairman, a thoracic surgeon who initially doubted the connection between smoking and cancer,

eventually died of tobacco related lung cancer. In 1964 the Surgeon General's report affirming the tobacco-cancer connection was issued. Many auditing this course recall the old cigarette jingles. How many recall when the last cigarette ad for a sports event was presented? Give up? The last cigarette ad for a sports event was broadcast at 10:54 PM, January 1, 1971, at the end of the Orange Bowl. The Nebraska Cornhuskers had just defeated the LSU Tigers for their first national championship.

Slide 56. PROPER DIET

The FDA has done a good job of seeing that foods we ingest don't generally have carcinogens, such as the aflatoxin in peanuts that leads to liver cancer. However, only the person you see in the mirror can eat less processed red meat; consume dark green, orange, purple, and red fruits and vegetables; eat legumes such as beans, lentils and peas; exercise moderately 5 hours a week, and prevent your body mass index from exceeding 30.

Heavy use of alcohol increases the risk of mouth, esophageal, voice box and liver cancers. Moderate alcohol intake may slightly increase the risk of several cancers, such as breast cancer in women, but equipoise is achieved by improvements noted in heart health. Moderate drinkers don't have to join the Women's Christian Temperance Union.

Finally, infections may be associated with around 10% of cancers in the USA. Worldwide, infections cause 20% of cancers. The human papillomavirus (HPV) causes cervical cancer as well as head and neck cancer. As is well known, the HIV-so called human immunodeficiency or AIDS virus-predisposes to many cancers by crippling the body's immune defenses. Liver cancer is the 6$^{th}$ most common cancer worldwide due to the widespread prevalence of Hepatitis B and C virus.

Slide 57. HELICOBACTER PYLORI

A pair of doughty, creative Australian physicians discovered a heretofore unknown bacteria they named Helicobacter pylori that causes gastritis (inflammation of the stomach) leading to gastric cancer.

For centuries physicians had attributed gastritis to stress. But Dr. Robin Warren, a gastroenterologist in Perth, Australia convinced himself that gastritis was due to an undocumented bacterial infection. Dr. Warren's theory flew in the face of centuries of medical dogma that bacteria could not survive in the highly acidic environment of the stomach. Dr. Warren felt he saw a bluish haze overlying ulcer craters in the stomach biopsy specimens of his patients (which nobody else could see). Dr. Barry Marshall, a junior investigator was looking for a research project. He attempted to isolate bacteria on petri dishes, which Dr. Warren could not do. Dr. Marshall failed to isolate bacteria on his petri dishes for many weeks, but he persisted. One Easter weekend Dr. Marshall forgot to examine his plates. When he examined the petri dishes later the fastidious bacteria were growing, due to the longer incubation period. In July 1984, Dr. Marshall's grant application was in jeopardy. Dr. Marshall ingested a solution containing the bacteria. Within a few days he was nauseated, vomiting, sweating and chilling. Dr. Marshall persuaded Dr. Warren to biopsy his stomach several times. The biopsies revealed gastritis. There was a dense overlay of bacteria shaped like a helix in the area of the stomach known as the pylorus. The doctors therefore named the bacteria they discovered Helicobacter pylori. Dr. Marshall and Warren had established, beyond a doubt, that bacteria can cause gastritis. By the late 1980's the connection of Helicobacter pylori with stomach cancer was established. A treatment program for the Helicobacter pylori infection had also been devised.

SLIDE 58. WE HAVE MET THE ENEMY AND HE IS US

Radiation therapy and cancer chemotherapy may place patients at risk for treatment related cancer, particularly leukemia and lymphoma. Cancers related to earlier cancer treatments are called secondary malignancies. Secondary malignancies can be very difficult to treat, particularly when they involve the bone marrow. A variety of medications for conditions other than cancer may place a patient at risk for cancer as well. Approximately 1% of cancers are due to medicine and medical treatments.

Slide 59. AMES TEST

Have you ever wondered about the tests that raised the possibility that saccharine could cause cancer? In the late 1960's Bruce Ames, a UC Berkeley chemist, developed the eponymous Ames test to screen for carcinogens. Carcinogens are substances which cause cancer in people. Dr. Ames knew there were Salmonella bacteria which carry mutations in genes involved in histidine synthesis. He knew these strains of Salmonella normally required the amino acid histidine for growth, but could not synthesize histidine. The test relies on the fact many carcinogens are also mutagens that cause a mutation in the normal Salmonella bacteria. The mutation in the normal Salmonella bacteria allows the mutated Salmonella to produce histidine. The mutated Salmonella which produce histidine grow in a petri dish without histidine. Therefore, if Salmonella bacteria exposed to a substance grow in a petri dish without histidine, it suggests the substance to which they were exposed will be a carcinogen in human beings.

Dr. Ames's test is not perfect-it missed the fact a female hormone called DES caused vaginal cancer. On the other side of the coin, cruciferous vegetables which are good for you, such as broccoli and cabbage light up on the Ames test. Without a doubt, Dr. Ames did prove carcinogens could sometimes be identified in advance, instead of with 20-20 hindsight-an important advance.

SLIDE 60. PREVENTION OF CANCER

We turn now from reviewing the causes of cancer to prevention of cancer. There are three kinds of prevention. Primary prevention aims to prevent a disease before it occurs. Secondary prevention aims to reduce the impact of a disease that has already occurred by catching it early and treating it at a more treatable or curable stage. Tertiary prevention aims to soften the impact of an ongoing illness or injury that has lasting effects.

Other than lifestyle changes, and prophylactic surgery in patients with hereditary mutations, there is little than can be done to primarily prevent cancer.

SLIDE 61. HEALTHY MAN WITH SAFE FALLING JOKE

And, as has been said, “What makes God laugh? People making plans.” Stoic resolve may be the beginning of wisdom, but it isn’t the end of it. As has also been said, “The race isn’t always to the swift, nor the battle to the strong-but that’s the way to bet.” So eat your vegetables.

The HPV vaccine, for human papilloma virus, was introduced in 2006 and is indicated in all children aged 11 to 12 years old to prevent cancer of the uterine cervix and throat cancer. A vaccine is available for Hepatitis B and is given to people at risk for Hepatitis B, which lowers the risk of liver cancer. Daily use of two regular size aspirin a day lowers the risk of colon cancer in patients with a hereditary syndrome called Lynch syndrome. Lynch syndrome is named after Dr. Henry Lynch. Dr. Lynch identified the syndrome, practiced at Creighton, and even briefly had a hereditary cancer clinic in Kearney. Several oral anticancer hormone pills for breast cancer can lower the risk of developing breast cancer in women at high risk. Several other medications (the diabetic medication metformin, the blood thinner warfarin, and the statin drugs for cholesterol) are promising but unproven for cancer prevention.

SLIDE 61. TYPES OF SCREENING

We now lecture on screening of cancer, which is a form of secondary prevention of cancer.

Most of us have undergone some type of screening for cancer called secondary prevention. Secondary prevention is an attempt to detect cancers in an early and asymptomatic stage. We try to nip cancer in the bud through early detection with tests such as Pap smears, mammograms, colonoscopies, or PSA blood tests. Once again, this is in contrast to primary prevention, which is preventing a disease from occurring (like with the HPV vaccines). Also recall, tertiary prevention involves treatment to reduce damage from established advanced disease (such as cardiac rehabilitation for a heart attack).

Screening works if early detection reduces suffering or death from a common disease, and if the screening test is safe, widely available, and affordable.

Slide 62. SPIDER AND THE FLY

If a spider’s web is too dense it will yield many flies, but too much clutter. Such a screening test is

called sensitive for the disease. A test that is sensitive for a disease will be less specific for the screened disease. A highly sensitive test yields too many false positive tests-too much clutter, along with the flies. False positive tests lead to unnecessary patient anxiety, expense, and possible harm from confirmatory tests. If the spider's web is too thin it will yield less debris (be more specific), but fewer flies as well (be less sensitive). A specific cancer test is more likely to miss cancer on screening because it is less sensitive.

Slide 63. SCREENING TEST

This slide conveys the same point as the spider and the fly slide. The slide illustrates the point no screening test is perfect. The perfect test would always be positive if the patient has the condition for which you are screening, and is always negative when you don't have the condition for which you are screening. The more sensitive your test, the larger the number of false positives. The more specific your test, the larger the number of false negatives.

The goal of cancer screening is not to diagnose cancer early. The goal of cancer screening is to nip otherwise incurable and painful cancers in the bud. Early diagnosis may or may not improve survival, as early stage cancers may already have metastatic disease to the rest of the body that is undetectable. Frequently cancer screening will document a cancer at an early, but not curable stage. If cancer is diagnosed at an early but incurable stage it increases survival rates artificially, without helping the patient live any longer than they would have if the diagnosis had been delayed.

SLIDE 64. THE OKIE EFFECT

The name for this pitfall of screening is lead time bias-which is more colorfully known as "the Okie effect". When the most downtrodden Okies headed down Route 66 to California in the Dirty Thirties IQs increased in both Oklahoma and California.

Similarly, when patients are screened for prostate cancer, and prostate cancer is detected, the men with prostate cancer are removed from the healthy screened population (therefore improving the healthy screened cohort's survival rate). The screened patients are inserted, with their early stage, into the overall prostate cancer population containing many patients with advanced disease. The insertion of the asymptomatic, screened population also improves the survival rate of the cohort whose prostate cancer is already diagnosed, and more advanced. But, if a man's cancer recurs despite diagnosis at an early stage, the individual man doesn't necessarily live any longer than he would have if the diagnosis had been made at a later date and stage. In addition the man may experience erectile dysfunction, urinary incontinence and other untoward complications of early treatment. The pitfalls surrounding screening have not always been recognized by physicians, patients or advocacy groups.

SLIDE 65. GEORGE PAPINICOLAU

Pap smears are the most successful cancer screening test, by any measure. Pap smears are a worldwide success. Pap smears were developed by a Greek immigrant physician named George Papanicolaou who grew weary of studying guinea pig menstruation at Cornell Medical School in New York. In 1928 he published a paper documenting the presence of cancer cells in samples taken from the uterine cervix of some asymptomatic women, at an early, curable stage. The doctor achieved this proof of concept in a novel way: he performed daily Pap smears on Mrs. Papinicolaou.

Slide 66. PAP SMEAR

In 1952 Dr. Papanicolau persuaded the National Cancer Institute to perform a trial involving 150,000 women in Memphis. 557 advanced cancers were found, but 555 early cancers were detected at a curable stage. Because the benefits were so dramatic (as in the discovery of penicillin), patients were not randomly assigned to control groups in a large trial, as they have been for COVID-19 vaccine trials.

SLIDE 67. MAMMOGRAPHY

Mammography for early detection of breast cancer illustrates the promise and pitfalls of cancer screening.

This slide documents the continuum from fatty breasts (which are more likely to be present in older women) and dense breasts, which are more likely to appear in younger women and camouflage early breast cancers. There are no cancers in these mammograms.

In 1913, Dr. Albert Solomon, a Berlin surgeon, performed post-operative X-rays on 3000 mastectomy specimens to document the possible role in diagnosis of what he called mammograms. Mammography was first adopted in the UK and Europe, because American physicians at that time automatically performed mastectomies for breast cancer. In 1963 the Health Insurance Plan of New York launched a study of screening mammograms. Half the women in the trial, the so-called study group, underwent annual screening mammograms. The other half of the women in the trial, the so-called control group, did not undergo annual mammography. The investigators reported the following results: fewer deaths were noted in the mammography screened group over the next eight years. They concluded screening mammography saved lives by detecting breast cancer at an early, curable stage. However, the investigators had not designed the trial properly. The investigators had placed previously diagnosed breast cancer patients in the control group, which did not undergo mammography, on the study. The investigators did not place patients with a previous diagnosis of breast cancer in the study group who underwent mammography. Patients in the control group with a previous history of breast cancer were at higher risk for recurrence and death. Screening mammography would not have helped these women in the control group if they already had undetected micro-metastatic breast cancer at the time they were registered on the study. This flaw in trial design artificially inflated the survival advantage in the mammography screened group by comparing apples to oranges. Based on this faulty data the American Cancer Society enthusiastically recommended mammographic screening. The ACS then launched the Breast Cancer Detection Demonstration Project, which begged the question, presumed the benefit of

mammography, and did not provide for a control group. Many other worldwide studies of screening mammography were also flawed. In 1988, the results of a well-designed Swedish study, the Malmo Mammography Study were released. The Malmo study revealed screening mammography led to a 20% reduction in breast cancer mortality in patients aged 55 to 70, but did not benefit older or younger women.

SLIDE 68. CARTOON-TORTURED DATA

An important lesson had been learned. Studies must be designed properly. Don't compare apples to oranges. As the British economist Ronald H. Coase acknowledged: "If you torture the data enough it will confess to anything". I wonder if we should consider that when we listen to politicians.

SLIDE 69. COLON POLYPS.

Evaluating screening for large intestinal (colon cancer) made good sense. The disease is common and associated with much suffering and death. Most important, colon cancer generally arises from benign colon polyps, such as the two pictured here, that progress to cancer over 10 years. Indeed, colon cancer screening, in prospective, controlled, randomized trials has been effective with a number of screening tests. Colonoscopy every 10 years, fecal occult blood testing yearly, CAT scan colonography every 5 years, sigmoidoscopy (examination of the left side of the colon) every 5 years, or an annual fecal multi-targeted stool DNA test all reduce colorectal cancer deaths by about 20 out of every 1000 40 year olds.

SLIDE 70. PRESIDENT REAGAN'S CANCER SCARE

President Reagan's life may have been saved by early detection of a benign colon polyp in a screening sigmoidoscopy performed in 1984. In March 1985 a follow-up sigmoidoscopy revealed another polyp. The second sigmoidoscopy prompted what should have been done in the first place-a full colonoscopy. Four months later the colonoscopy revealed an invasive, malignant cancer on the right side of the colon.

The 25th Amendment was invoked, and the malignant right sided colon cancer was removed. The 4 month delay in the colonoscopy prompted controversy.

SLIDE 71. SCREENING CT SCAN LUNG

Annual low dose CAT scans of the chest in high risk smokers aged 50 to 80 saves lives. Regular chest X-rays are not sensitive enough to detect lung cancers at an early, curable stage.

SLIDE 72. IMAGES OF PROSTATE CANCER SCREENING

Prostate cancer screening has been on a roller coaster ride over the last four decades. From its peak in the early 1990s prostate cancer mortality has fallen by half. The reason for the fall in mortality of prostate cancer is not entirely clear. Strangely, prostate cancer mortality rose sharply in the 1970's to 1980's. This was probably a statistical artifact. During the 1970's and 1980's urologists performed more operations to treat benign swelling of the prostate gland. The tissue removed was sent to the pathologists to examine and incidental cancers were detected. By 1986, half of all prostate cancers were detected incidentally during operations for "Benign Prostatic Hypertrophy" causing slow urination. This artificial increased incidence of prostate cancer was associated with increased attribution of deaths to prostate cancer in these elderly men, even if they didn't die of prostate cancer. The prostate cancer diagnosis "stuck to them". This phenomenon was called "sticky diagnosis bias".

SLIDE 73. PSA BLOOD TEST

In the late 1980's widespread screening for prostate cancer with the so called PSA blood test was embraced. PSA stands for prostate specific antigen. Frail, elderly men with limited life expectancy received PSA testing at health fairs. Widespread PSA screening exacerbated sticky diagnosis bias. Many men die with prostate cancer, not because of it. Indeed, half of men who die over 60 have pathological evidence of prostate cancer. That being said, prostate cancer mortality has fallen somewhat since the 1970's baseline. The fall in mortality may not entirely, or even largely, reflect increasing use of surgery and/or radiation to cure early prostate cancer detected by PSA screening. The fall in mortality may

reflect the subsequent use of medical therapy with anti-androgens, which cut off the testosterone supply that fuels the growth of the prostate cancer cells. Anti-androgen medicine has been commonly used to treat early recurrence of prostate cancer detected by a rise in PSA after failure of local therapy with surgery and/or radiation to cure local disease. The medical therapy delays the time until the prostate cancer spreads widely to the bones and hence prolongs survival. Given the high rate of complications with surgery or radiation for early prostate cancer it has been argued we should not screen for prostate cancer at all. Indeed, the use of PSA screening has fallen. It has also been argued that if PSA screening is done by primary care physicians, referrals to urologists for biopsy should only be made when the PSA is > 10 ng/ml, instead of 4 ng/ml. This threshold produces a group of men approximately the same size as the group of men expected to die from prostate cancer over the next 10 years. That may be preferable to diagnosing many men early and treating them with potentially morbid surgery or radiation. After all, many of them weren't going to die of prostate cancer even without the surgery or radiation.

SLIDE 74, ZOMBIE SCREENING

"Zombie screening" is clearly inappropriate screening that should be avoided like the plague, but isn't. For instance: women with Stage 4 breast cancer which has spread to the bone often receive computer generated prompts to schedule their annual mammograms. When a woman has metastatic breast cancer the whole point of mammography-to prevent advanced metastatic breast cancer-is moot. We doctors like to say: "The cows are already out of the barn". Another example of zombie screening: an 85 year old man with a life expectancy of 3 years who undergoes PSA screening. PSA screening should be reserved for men with a life expectancy of ten years.

It is inappropriate to screen a zombie for early prostate cancer. Prostate cancer screening won't help a zombie.

With your new understanding of the causes of cancer, cancer prevention, and the use and misuse of cancer screening tools, you will be better prepared to understand the topic of the next lecture: evaluation of the cancer patient.