

Special Edition 2010

THE BURDEN OF SOUTH DAKOTA'S
FOUR MAJOR CANCERS:
COLORECTAL • FEMALE BREAST • LUNG • PROSTATE



South Dakota
medicine

SPECIAL EDITION

THE JOURNAL OF THE SOUTH DAKOTA STATE MEDICAL ASSOCIATION



L to R: Luis A. Rojas, MD; Kelly McCaul, MD; Addison R. Tolentino, MD; Anwarul Haq, MD, FACP

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*Thank you to the outstanding staff of the SDSMA for their hard work in
preparing this special issue and in distributing task force information.*

Cancer's Impact on South Dakotans

By Thomas J. Huber, MD
SDSMA President



As a physician, I see the impact of cancer on my patients every day. Cancer will touch each of our lives either directly or indirectly.

This special edition of *South Dakota Medicine*, focusing on breast, lung, prostate and colorectal cancer, highlights the very latest in screening, diagnosis and treatment of cancer in South Dakota. I'm proud to say these physicians and researchers on the cutting-edge of cancer care are my peers.

As a physician, I urge you to take these articles in this special issue into careful consideration to learn more about these four cancers and how we can continue to fight the battle against them.

Thanks you, and congratulations to the SDSMA staff, the South Dakota Department of Health and the contributing physicians and researchers who have worked so hard to create this special issue of *South Dakota Medicine*.

F R O M T H E D E P A R T M E N T O F H E A L T H

Dear Fellow South Dakotans:

On behalf of the Department of Health, it is my pleasure to welcome you to this very special issue of *South Dakota Medicine*.

Each year, more than 3,800 South Dakotans receive a cancer diagnosis, and 1,600 die from cancer. The impact of cancer reaches deep and none of us are immune. This special edition features the four primary sites of cancer that are consistently diagnosed most often in our state.

In the world of cancer risk factors, prevention and treatment, patients understandably rely heavily on their physicians. Physician recommendations to reduce cancer risks by healthy lifestyle choices or to undergo available cancer screenings carry considerable weight. A cancer diagnosis can present patients and their families with overwhelming and unfamiliar medical decisions. As patients seek information and choose treatment plans, the advice of a trusted physician can provide much-needed support and solace. The purpose of this special issue is to arm physicians with information about cancer in South Dakota to help them, and in turn, their patients to prevent and control cancer.

The Department of Health welcomes the partnership of the South Dakota State Medical Association and others involved in cancer prevention and control as we work together to attain the ultimate goal of reducing death and illness due to cancer. It is an enormous job and requires the dedication of many. We are pleased to have joined in the effort of developing this special issue.

Sincerely,

Doneen B. Hollingsworth
Secretary of Health





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Dear Reader,

This special edition of South Dakota Medicine is devoted to the four major cancers that affect South Dakotans and the U.S. population: Breast, colorectal, lung and prostate.

This special edition begins with a discussion of the epidemiology of these cancers in South Dakota and the impact they have on our state. This is followed by a timely piece on the heritability of these cancers and the importance of obtaining a good family history. This article also highlights the advantage of having genetic counselors available to obtain a detailed pedigree as well as counsel the patient on the genetics of these diseases. Genetic counselors recently received licensure by the state of South Dakota and join our team in the fight against the four major cancers. The next manuscripts are a series devoted to screening, diagnosis and treatment of breast, prostate, colon and lung cancer. This series finishes with an article on the impact that genomics may have on diagnosis and treatment of breast and prostate cancer. The explosion of information which has followed mapping of the human genome has the potential for allowing early diagnosis and individualized treatment of cancer depending on the cancer genotype. The final article discusses the South Dakota Cancer Registry and its importance for the people of South Dakota.

In the continuum of rural-urban communities South Dakota faces many challenges as our population is estimated to be 42.1 percent from "frontier" areas. Fifty-four South Dakota counties are considered frontier as defined by the Census Bureau as being sparsely populated and a long distance in miles or time from a service or market area. The definition used by the Census Bureau can be found at www.frontierus.org/documents/matrix.htm.

There are numerous challenges that face frontier communities, including health care. It is estimated that 30 percent of U.S. frontier areas lack a hospital, which requires patients to travel long distances for health care. In terms of cancer, this often results in patients not getting important screening tests and having to make decisions between treatment or their job due to the large amount of time required to travel. In this special edition, the importance of South Dakota physicians in providing access to frontier and rural health care is clear. The South Dakota Department of Health has also launched innovative programs and funding to improve screening and treatment of Cancer for South Dakotans.

We hope you enjoy the third special edition of South Dakota Medicine on the four major cancers.



H. Bruce Vogt, MD, and Keith Hansen, MD
Co-Editors,
South Dakota Medicine

SPECIAL EDITION 2011



Epidemiology of the Four Major Cancers in South Dakota

By Jacy Clarke, PhD

Abstract:

This report presents the findings of epidemiological analyses of cancer incidence and mortality for the top four cancers in South Dakota: female breast, colorectal, lung and prostate during 2002-2006. Throughout this report, the South Dakota Cancer Registry Data were used to obtain South Dakota specific rates. From 2002-2006, there were 10,834 new cases of female breast, colorectal, lung and prostate cancers identified among South Dakotans. Specific to the type of cancer itself, there were 2,656 women with breast cancer, 2,271 colorectal cancers, 2,596 lung cancers and 3,311 prostate cancers. From 2002-2006, there were 4,019 deaths due to female breast, colorectal, lung and prostate cancer. Specifically, there were 546 female breast cancer deaths reported, 827 colorectal deaths, 2,132 lung cancer deaths and 514 prostate cancer deaths.

All incidence and mortality rates referred to in the text are age-adjusted according to the U.S.2000 standard population. The national rates were obtained from the Surveillance, Epidemiology and End Results (SEER).

Background

This report presents the findings of epidemiological analyses of cancer incidence and mortality for the top four cancers in South Dakota: female breast, colorectal, lung and prostate during 2002-2006. Throughout this report, breast cancer statistics refer to female breast cancer only. South Dakota rates are compared with national rates from the Surveillance, Epidemiology and End Results (SEER) Cancer

Statistics Review, which is produced by the National Cancer Institute. All incidence and mortality rates referred to in the text are age-adjusted according to the U.S.2000 standard population. Also presented are data on the stage at diagnosis for cases reported to the South Dakota Cancer Registry, as well as an analysis of years of potential life lost due to the selected cancers. Comparisons of age-adjusted mortality and incidence rates between gender and racial

Figure 1. Female Breast Cancer in South Dakota, 2002-2006

	Incidence	Age-adjusted incidence rates	Mortality	Age-adjusted mortality rates
Total 2002-2006 number of cases	2656 (average 531 per year)	*127.9	546 (average 109 per year)	*24.4
2002	605	145.4	109	24.5
2003	548	132.3	120	27.2
2004	483	117.2	105	23.3
2005	547	129.8	117	25.7
2006	473	115.0	95	21.2
White	2510	127.8	522	24.5
American Indian	120	129.8	23	26.8
Other races	26	189.2	1	10.2
Median age at diagnosis	64	N/A	Median age at death: 71	N/A
Age range at diagnosis	24-101	N/A	Age range at death: 28-104	N/A

*Rates are per 100,000 persons, age-adjusted to 2000 U.S. standard population

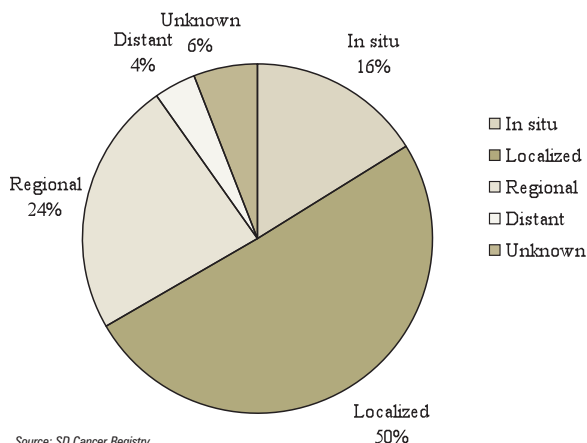
Source: SD Cancer Registry

groups are presented. The proportion of cases diagnosed at different stages are compared between gender and racial groups to highlight disparities where they exist.

Female Breast Cancer

A total of 2,656 new cases of female breast cancer were diagnosed during 2002–2006 in South Dakota (on average 531 cases per year). The age-adjusted incidence rate was 127.9 per 100,000 women. Breast cancer is reported among females and males. Among females, 2510 cases (95 percent) occurred among white women, 120 (5 percent) were among American Indians and 26 (<1 percent) were among other races (Figure 1). The 2006 U.S. SEER age-adjusted incidence rate was 120.8 per 100,000.

Figure 2.
SEER Summary Stage at Diagnosis- Female Breast Cancer



A total of 546 breast cancer deaths were reported during 2002–2006 (on average 109 deaths per year). The age-adjusted mortality rate was 24.4 per 100,000 population. Of that number, 522 (96 percent) were among white women, 23 (4 percent) were among American Indian women, and 1 (<1 percent) case was reported among other races (Figure 1). The 2006 U.S. SEER age-adjusted mortality rate was 23.4 per 100,000.

Among reported stages of breast cancer, 16 percent were in situ; 50 percent were diagnosed at localized stage; 24 percent at regional; 4 percent at distant; and 6 percent were unknown (Figure 2).

Whites have a high age-adjusted incidence rate of early stage breast cancers (in situ and localized) compared with American Indians, which subsequently reduces their age-adjusted

death rate (Figure 3).

The age-adjusted death rate was higher for American Indians than for whites (26.8 vs. 24.5 respectively) (Figure 5).

Figure 3. Age-Adjusted Rates by Race- Female Breast Cancer

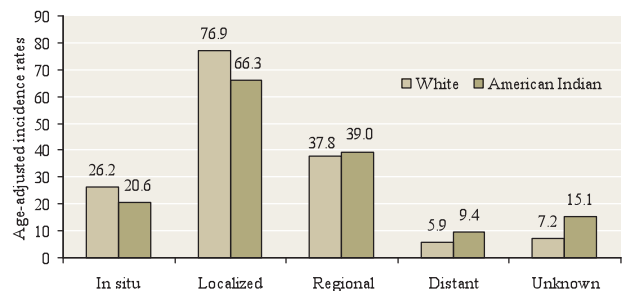


Figure 4. Years of Potential Life Lost Before Age 75- Female Breast Cancer

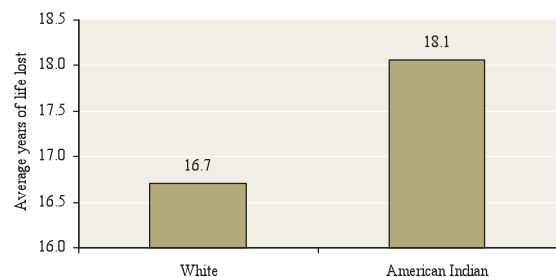
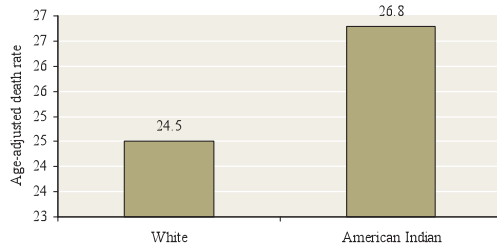
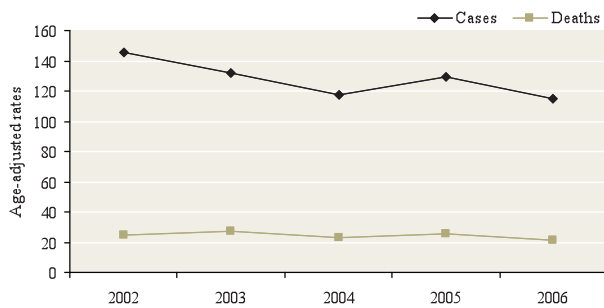


Figure 5. Age-Adjusted Death Rate- Female Breast Cancer

Source: SD Cancer Registry

Figure 6. Age-Adjusted Female Breast Cancer Cases and Deaths by Year of Diagnosis/Death**Figure 7. Age-Adjusted Incidence and Mortality Rates by Region- Female Breast Cancer**

	Age-adjusted incidence rates	Age-adjusted mortality rates
Northeast	110.8	19.5
Southeast	144.2	27.3
Central	115.7	25.7
West	136.4	25.6

*Rates are per 100,000 persons, age-adjusted to 2000 U.S. standard population

Source: SD Cancer Registry

Breast Cancer Prevention

Estrogen (endogenous)

Endogenous estrogen is a hormone made by the body. It helps the body develop and maintain female sex characteristics. Prolonged exposure to estrogen may increase the risk of breast cancer. Estrogen levels are highest during the years a woman is menstruating. A woman's exposure to estrogen is increased in the following ways:

- Early menstruation: Beginning to have menstrual periods at age 11 or younger increases the number of years the breast tissue is exposed to estrogen.
- Late menopause: The more years a woman menstruates,

the longer her breast tissue is exposed to estrogen.

- Late pregnancy or never being pregnant.

Hormone replacement therapy/Hormone therapy

Hormones that are made outside the body in a laboratory are called exogenous hormones. Estrogen, progesterin or both may be given to replace the estrogen no longer produced by the ovaries in postmenopausal women or women who have had their ovaries removed. This is called hormone replacement therapy (HRT) or hormone therapy (HT) and may be given in one of the following ways:

- Combination HRT/HT is estrogen combined with progesterone or progesterin. This type of HRT/HT increases the risk of developing breast cancer.
- Estrogen-only therapy may be given to women who have had a hysterectomy. It is not known if this type of HRT/HT increases the risk of breast cancer.

Exposure to Radiation

Radiation therapy increases the risk of breast cancer, starting 10 years after treatment and lasting for a lifetime. The risk of developing breast cancer depends on the dose of radiation and the age at which it is given.

For women who are at risk of breast cancer due to inherited changes in the BRCA1 and BRCA2 genes, exposure to radiation, such as that from chest x-rays, may further increase the risk of breast cancer, especially in women who were X-rayed before 20 years of age.

Obesity

Obesity increases the risk of breast cancer in postmenopausal women who have not used hormone replacement therapy.

Alcohol

Drinking alcohol increases the risk of breast cancer. The level of risk rises as the amount of alcohol consumed rises.

Inherited Risk

Women who have inherited certain changes in the BRCA1 and BRCA2 genes have a higher risk of breast cancer, and the breast cancer may develop at a younger age.

Source: National Institutes of Health, National Cancer Institute. <http://www.cancer.gov/>

South Dakota Department of Health Screening Programs

The Well-Integrated Screening and Evaluation for Women Across the Nation (WISEWOMAN) is a comprehensive program for medically underserved women to reduce morbidity and mortality from chronic diseases. WISEWOMAN

is a companion program to the National Breast and Cervical Cancer Early Detection Programs (NBCCEDP) and All Women Count! program funded by the CDC. South Dakota's BCCEDP program serves women ages 30 to 64. The population of low-income women in South Dakota aged 30 to 64 is 39,823 (South Dakota Department of Social Services, 2006).

Since September 2000, the South Dakota BCCEDP and All Women Count! program has enrolled 15,250 women. There have been 190 cancers detected (166 breast cancers and 24 cervical cancers). According to the 2008 Behavioral Risk Factor Surveillance Survey (SD BRFSS), 24.6 percent of female respondents aged 40 and older indicated that they had not received a mammogram in the past two years, while another 21.9 percent had not had a clinical breast exam in the past two years (SD BRFSS, 2008).

Colorectal Cancer

A total of 2,271 new cases of colorectal cancer were diagnosed from 2002–2006 in South Dakota (on average 454 cases per year). The age-adjusted incidence rate was 54.9 per 100,000 population. Of those cases, the white population comprised 2,159 (95 percent) cases, 91 (4 percent) cases were reported among American Indians and 21 (1 percent) among other races. In addition, 1,158 (51 percent) cases were reported among males and 1,113 (49 percent) among females (Figure 8). The 2006 U.S. SEER age-adjusted incidence rate was 45.9 per 100,000.

A total of 827 colorectal cancer deaths were reported from 2002–2006 (on average 165 deaths per year). The

Figure 8. Colorectal Cancer in South Dakota, 2002-2006

	Incidence	Age-adjusted incidence rates	Mortality	Age-adjusted mortality rates
Total number of cases from 2002-2006.	2271 (average 454 per year)	54.9	827 (average 165 per year)	19.2
2002	549	66.3	169	19.4
2003	471	56.9	180	21.1
2004	432	52.1	153	17.7
2005	435	52.8	176	20.7
2006	384	46.6	149	17.3
White	2159	54.4	790	19.0
American Indian	91	60.1	34	25.7
Other races	21	92.3	3	16.6
Male	1158	65.0	410	23.3
Female	1113	46.5	417	15.9
Median age at diagnosis	73	N/A	Median age at death: 77	N/A
Age range at diagnosis	25-105	N/A	Age range at death: 28-100	N/A

*Rates are per 100,000 persons, age-adjusted to 2000 U.S. standard population
Source: SD Cancer Registry

age-adjusted mortality rate was 19.2 per 100,000 population. Of that number, 790 (96 percent) were white, 34 (4 percent) were American Indian and 3 (<1 percent) cases were reported among other races (Figure 8). The 2006 U.S. SEER age-adjusted mortality rate was 17.1 per 100,000.

Among reported stages of colorectal cancer, 6 percent were in situ; 38 percent were diagnosed at localized stage; 31 percent at regional; 13 percent at distant; and 12 percent were unknown (Figure 9).

Figure 9. SEER Summary Stage at Diagnosis- Colorectal Cancer

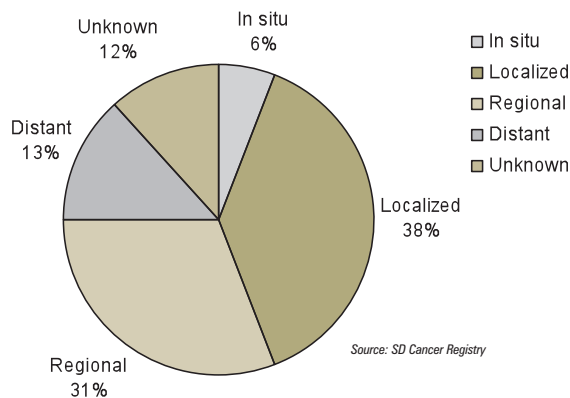


Figure 10. Age-Adjusted Incidence Rates by Race- Colorectal Cancer

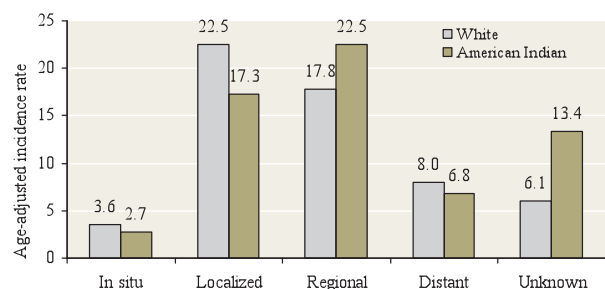
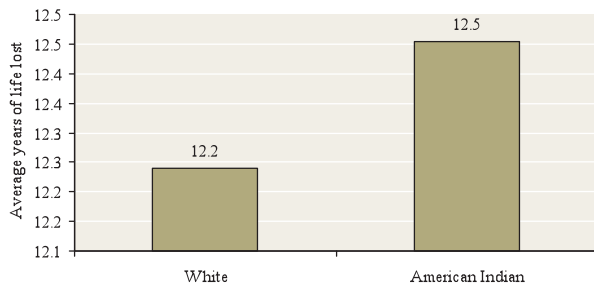
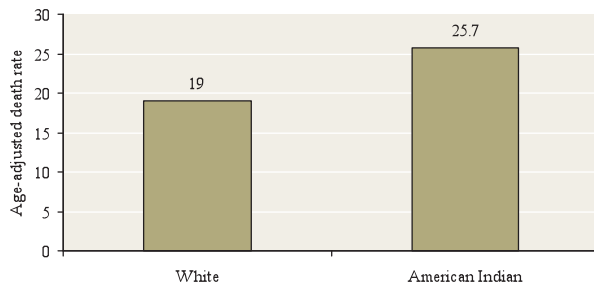


Figure 11. Average Years of Potential Life Lost Before Age 75- Colorectal Cancer



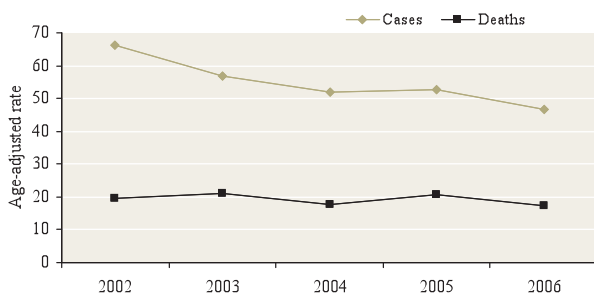
Source: SD Cancer Registry

Figure 12. Age-Adjusted Death Rate- Colorectal Cancer



Source: SD Cancer Registry

Figure 13. Age-Adjusted Colorectal Cancer Cases and Deaths by Year of Diagnosis/Death



Source: SD Cancer Registry

Figure 14. Age-Adjusted Incidence and Mortality Rates by Region- Colorectal Cancer

	Age-adjusted incidence rates	Age-adjusted mortality rates
Northeast	56.3	19.9
Southeast	59.1	19.0
Central	48.1	17.7
West	54.2	20.5

American Indians died younger: average years of life lost were higher among American Indians than among whites (12.5 vs. 12.2 respectively) (Figure 11).

Age-adjusted mortality rate was also higher among American Indians than among Whites (Figure 12).

The age-adjusted incidence rate was the highest in southeast region and the age-adjusted death rate was the highest for the west region (Figure 14).

Colorectal Cancer Prevention and Risks

Avoiding risk factors and increasing protective factors may help prevent cancer.

Avoiding cancer risk factors such as smoking, being overweight and a lack of exercise may help prevent certain cancers. Increasing protective factors such as quitting smoking, eating a healthy diet and exercising may also help prevent some cancers.

The following risk factors may increase the risk of colorectal cancer:

Age: The risk of colorectal cancer begins to increase after age 40 and continues to increase as people age.

Obesity and lack of exercise: Obesity is linked to an increased risk of colorectal cancer. A lifestyle that does not include regular exercise may also be linked to an increased risk of colorectal cancer.

Smoking: Smoking cigarettes is linked to an increased risk of developing colorectal adenomas and colorectal cancer. Cigarette smokers who have had surgery to remove colorectal adenomas have an increased risk for the adenomas to recur .

Alcohol: Drinking alcoholic beverages may increase the risk of colorectal cancer.

Source: National Institutes of Health, National Cancer Institute. <http://www.cancer.gov>

South Dakota Department of Health Colorectal Cancer Screening Program

The SD Department of Health (SDDOH) received funding from the CDC to implement a colorectal screening (CRC) program in January 2010. In addition to a strong patient education component stressing the need for CRC screening for all individuals, the department has identified a priority population of persons aged 50-64 living at or below 200 percent of the federal poverty guideline who are uninsured or underinsured for colorectal cancer screening and who are asymptomatic and at average risk for developing colorectal cancer. The program will use the Immunochemical Fecal Occult Blood Test (iFOBT) as the initial screening test for all participants. The iFOBT test was chosen for the screening because it is the least invasive to the participant. There are no dietary restrictions and there is a longer amount of time for the person to send the kit into their provider, thus allowing for a follow-up contact to be made if the client fails to send in the kit. Follow-ups for positive iFOBTs will have a colonoscopy. Health care providers will be urged to recommend CRC screening for all of their patients over 50 years of age. If cancer is found, a number of providers throughout the state have agreed to provide free treatment to the individual. According to the 2008 BRFS, 79.3 percent of respondents aged 50 and over had not had a blood stool test in the past two years, while 37.6 percent had never had a sigmoidoscopy or colonoscopy (SD BRFS, 2008).

Lung Cancer

A total of 2,596 new cases of lung cancer were diagnosed during 2002–2006 in South Dakota (on average 519 cases per year). The age-adjusted incidence rate was 64 per 100,000 population. Of those cases, the white population comprised 2,451 (94 percent) cases, 128 (5 percent) cases were reported among American Indians and 17 (1 percent) among other races. In addition, 1,516 (58 percent) cases were reported among males and 1,080 (42 percent) among females (Figure 15). The 2006 U.S. SEER age-adjusted incidence rate was 60.7 per 100,000.

A total of 2,132 lung cancer deaths have been reported during 2002–2006 (on average 426 deaths per year). The age-adjusted mortality rate was 51.8 per 100,000 population. Of that number, 2017 (95 percent) were white, 109 (5 percent) were American Indian and 6 (<1 percent) deaths were reported among other races (Figure 15). The 2006 U.S. SEER age-adjusted mortality rate was 51.7 per 100,000.

Among reported stages of lung cancer, 19 percent were diagnosed at localized stage; 20 percent at regional; 47 percent at distant; and 14 percent were unknown (Figure 16). A high proportion of cases diagnosed at distant stage (47 percent) might explain the small difference between median age at diagnosis and the median age at death (72 and 73 respectively).

The age-adjusted incidence rates for all stages were higher for American Indians than for whites (Figure 17).

Whites had 11.1 average years of life lost before age 75 as opposed to 10.9 years of American Indians (Figure 18).

Figure 15. Lung Cancer in South Dakota, 2002-2006

	Incidence	Age-adjusted incidence rates	Mortality	Age-adjusted mortality rates
Total number of cases from 2002-2006.	2596 (average 519 per year)	64.0	2132 (average 426 per year)	51.8
2002	516	63.3	402	49.0
2003	518	63.8	405	48.9
2004	520	64.8	423	51.5
2005	518	63.8	467	57.1
2006	524	64.4	435	52.6
White	2451	63.1	2017	51.0
American Indian	128	94.6	109	80.9
Other races	17	75.2	6	29.6
Male	1516	84.5	1250	70.0
Female	1080	49.0	882	38.8
Median age at diagnosis	72	N/A	Median age at death: 73	N/A
Age range at diagnosis	30-100	N/A	Age range at death: 30-101	N/A

*Rates are per 100,000 persons, age-adjusted to 2000 U.S. standard population
Source: SD Cancer Registry

Figure 16. SEER Summary Stage at Diagnosis- Lung Cancer

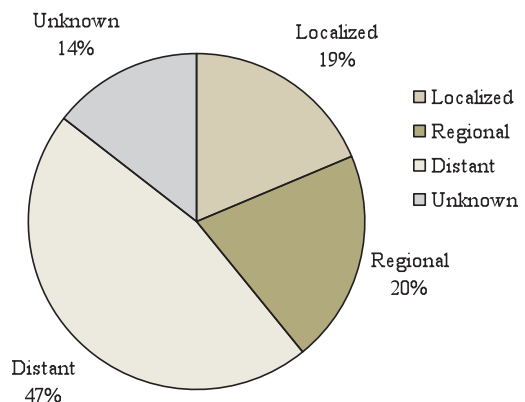
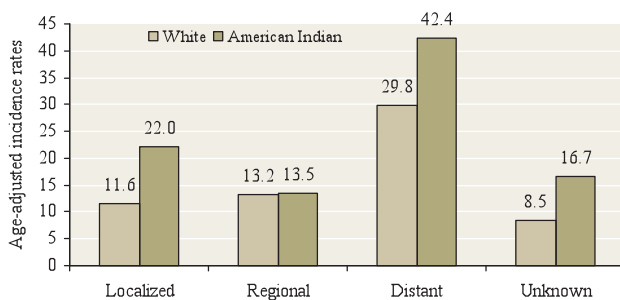
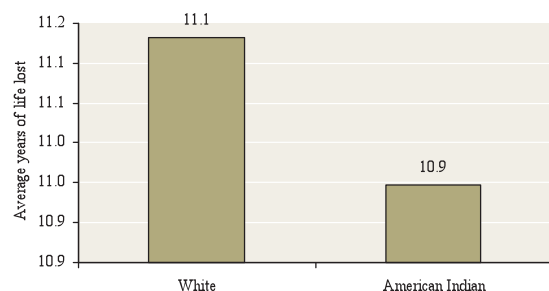


Figure 17. Age-Adjusted Incidence Rates by Race- Lung Cancer



Source: SD Cancer Registry

Figure 18. Average Years of Potential Life Lost Before Age 75- Lung Cancer



Source: SD Cancer Registry

The age-adjusted death rate was 1.6 times higher among American Indians than among whites (Figure 19).

Figure 19. Age-Adjusted Death Rate- Lung Cancer

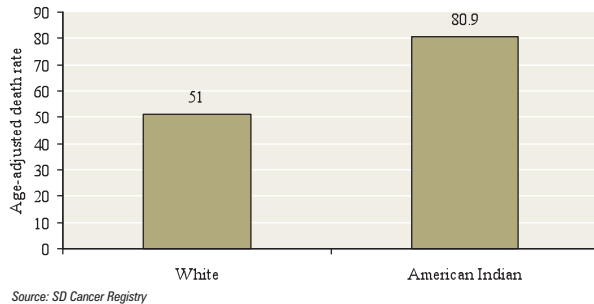


Figure 20. Age-Adjusted Lung Cancer Cases and Deaths by Year of Diagnosis/Death

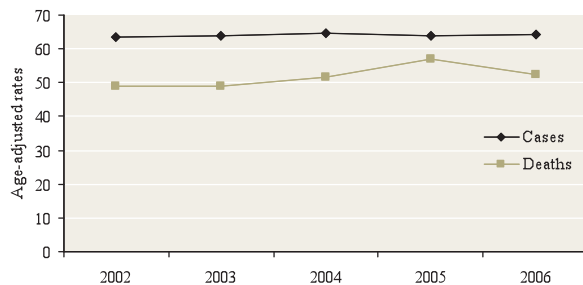


Figure 21. Age-Adjusted Incidence and Mortality Rates by Region- Lung Cancer

	Age-adjusted incidence rates	Age-adjusted mortality rates
Northeast	57.9	47.0
Southeast	74.3	58.5
Central	54.9	43.7
West	69.4	59.3

*Rates are per 100,000 persons, age-adjusted to 2000 U.S. standard population

Source: SD Cancer Registry

The age-adjusted incidence and mortality rates were the highest in west region (Figure 21).

Lung Cancer Prevention and Risks

Lung cancer can often be associated with known risk factors for the disease. Many risk factors can be changed, but not all can be avoided.

Tobacco: Studies show that smoking tobacco products in any form is the major cause of lung cancer. People who stop smoking and never start again lower their risk of developing

lung cancer or of having lung cancer recur. Many products, such as nicotine gum, nicotine sprays, nicotine inhalers, nicotine patches or nicotine lozenges, as well as antidepressant drugs, may be helpful to people trying to quit smoking. Never smoking lowers the risk of dying from lung cancer.

Secondhand tobacco smoke also causes lung cancer. This is smoke that comes from a burning cigarette or other tobacco product or smoke that is exhaled by smokers. People who inhale secondhand smoke are exposed to the same cancer-causing agents as smokers. Inhaling secondhand smoke is called involuntary or passive smoking.

Environmental Causes: There are other causes of lung cancer in the environment, but the effect on lung cancer rates is small compared to the effect of cigarette smoking.

Cancer-causing agents that may be found indoors, especially in the workplace, include asbestos, radon, arsenic, chromium, nickel, tar and soot. These substances can cause lung cancer in people who have never smoked and combine with cigarette smoke to further increase lung cancer risk in smokers. Many countries are working to control these cancer-causing agents in the workplace.

Air pollution may also increase the risk of lung cancer. Studies show that lung cancer rates are higher in cities with higher levels of air pollution.

Beta Carotene: Studies show that heavy smokers who avoid taking beta carotene supplements may avoid further increasing their risk of lung cancer compared with smokers who do take beta carotene.

Diet and Physical Activity: Studies show that a diet rich in fruit, and possibly vegetables, may help lower the risk of lung cancer, while heavy alcohol drinking may increase the risk of lung cancer. In addition, studies show that people who are physically active may have a lower risk of lung cancer than those who are not, even after taking cigarette smoking into account.

Chemoprevention: Chemoprevention is the use of specific natural or man-made drugs to reverse, suppress, or prevent cancer growth. Chemoprevention is an area of active clinical research. It has not yet become standard therapy.

Source: National Institutes of Health, National Cancer Institute. <http://www.cancer.gov/>

Prostate Cancer

A total of 3,311 new cases of prostate cancer were diagnosed during 2002–2006 in South Dakota (on average 662 cases per year). The age-adjusted incidence rate was 183.9 per 100,000 population. Of those cases, the white population

Figure 22. Prostate Cancer in South Dakota, 2002-2006

	Incidence	Age-adjusted incidence rates	Mortality	Age-adjusted mortality rates
Total number of cases from 2002-2006.	3,311 (average 662 per year)	183.9	514 (average 102 per year)	30.1
2002	736	204.7	109	32.0
2003	692	192.3	106	31.5
2004	691	191.6	102	29.8
2005	602	167.1	94	27.3
2006	590	163.8	103	30.1
White	3,159	183.0	499	30.1
American Indian	105	173.2	13	36.3
Other races	47	479.0	2	15.9
Median age at diagnosis	70	N/A	Median age at death: 82	N/A
Age range at diagnosis	42-100	N/A	Age range at death: 48-100	N/A

*Rates per 100,000 persons U.S. standard population
Source: SD Cancer Registry

comprised 3,159 (95 percent) cases, 105 (3 percent) cases were reported among American Indians, and 47 (1 percent) among other races (Figure 22). The 2006 U.S. SEER age-adjusted incidence rate was 154 per 100,000.

A total of 514 prostate cancer deaths have been reported during 2002–2006 (on average 102 deaths per year). The age-adjusted mortality rate was 30.1 per 100,000 population. Of that number, 499 (97 percent) were white, 13 (3 percent) were American Indian, and 2 (<1 percent) cases were reported among other races (Figure 22). The 2006 U.S. SEER age-adjusted mortality rate was 23.6 per 100,000.

Among reported stages of prostate cancer, 77 percent were diagnosed at localized stage; 8 percent at regional; 3 percent at distant; and 12 percent were unknown (Figure 23).

Age-adjusted incidence rates for localized stage for whites were higher which means that whites are diagnosed at an earlier stage of prostate cancer compared with American Indians (Figure 24).

American Indians died younger: average years of life lost was higher among American Indians than among whites (9.33 vs. 8.27 respectively) (Figure 25).

The age-adjusted death rate was higher for American Indians than for whites (36 vs. 30 respectively) (Figure 26).

Figure 23. Stage at Diagnosis- Prostate Cancer

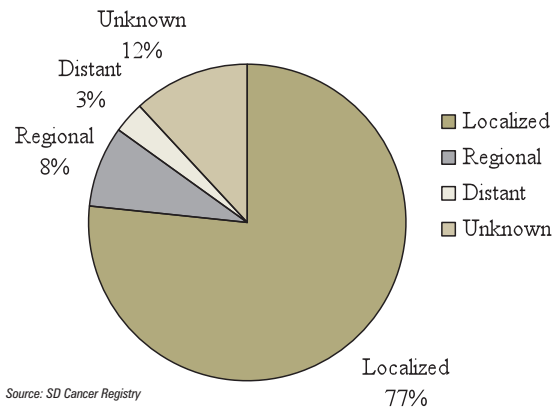


Figure 24. Age-Adjusted Incidence Rates by Race- Prostate Cancer

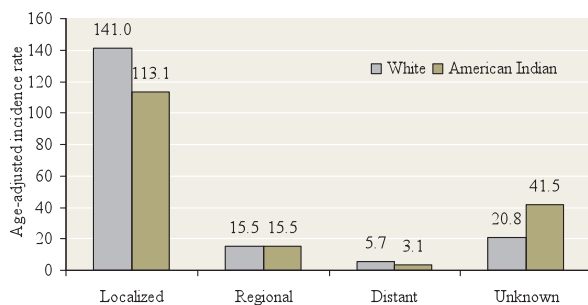


Figure 25. Average Years of Potential Life Lost Before Age 75- Prostate Cancer

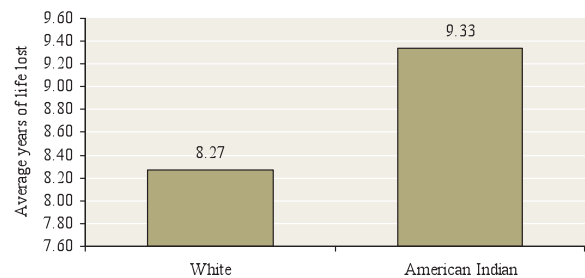


Figure 26. Age-Adjusted Death Rate- Prostate Cancer

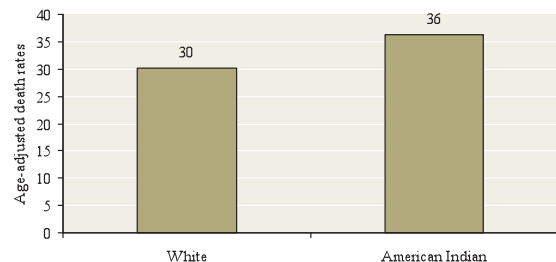
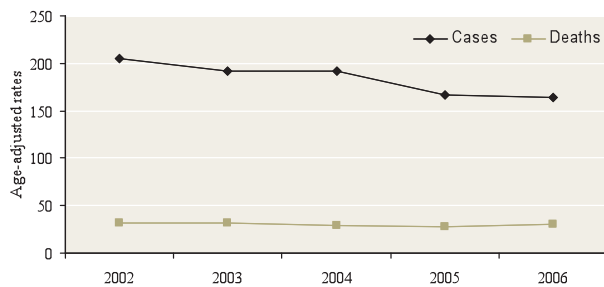


Figure 27. Age-Adjusted Prostate Cancer Cases and Deaths by Year of Diagnosis/Death**Figure 28. Age-Adjusted Incidence and Mortality Rates by Region- Prostate Cancer**

	Age-adjusted incidence rates	Age-adjusted mortality rates
Northeast	177.0	28.2
Southeast	199.8	30.5
Central	171.6	27.5
West	183.9	35.8

*Rates are per 100,000 persons, age-adjusted to 2000 U.S. standard population
Source: SD Cancer Registry

The age-adjusted incidence rate was the highest in southeast region and the age-adjusted death rate was the highest for the west region (Figure 28).

Prostate Cancer Prevention and Risks

Prostate cancer can sometimes be associated with known risk factors for the disease. Many risk factors are modifiable, though not all can be avoided.

Age: The risk of developing prostate cancer increases as a man gets older.

Diet and Lifestyle: The effect of diet on prostate cancer risk is under study. A diet high in fat, especially animal fat, may be associated with an increased risk of prostate cancer. More studies are needed to determine if a low-fat diet with more fruits and vegetables helps prevent prostate cancer.

The effect of folate on prostate cancer risk is under study. A 10-year study found that taking folic acid supplements increased the risk of prostate cancer. In the same study, prostate cancer risk was lowered in the men who did not take the supplement but got enough folate in the foods they ate. Studies show that a diet high in dairy products and calcium may be linked to an increased risk of prostate cancer, although the increase may be small.

Hormonal Prevention: Studies are underway to discover the role of certain drugs, such as finasteride, that reduce the amount of dihydrotestosterone.

Race: The risk of prostate cancer is dramatically higher among blacks, intermediate among whites, and lowest among native Japanese. However, this increase in risk may be due to other factors associated with race. Studies have shown a link between levels of testosterone and prostate cancer risk, with black men having the highest levels.

Source: National Institutes of Health, National Cancer Institute. <http://www.cancer.gov/>

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Genetic and Familial Factors Influencing Breast, Colon, Prostate and Lung Cancers.

By Quinn P. Stein, MS, CGC; Jason D. Flanagan, MS, CGC

Abstract:

Knowledge of cancer genetics is advancing our biological understanding of breast, colon, prostate and lung cancers. A family history of any one of these four types of cancer can increase an individual's personal risk to also develop a malignancy. For some families, genetic testing, in combination with genetic counseling, can be a helpful way to identify a hereditary cancer predisposition gene or establish a cancer risk management plan. In this paper, we will review the current state of knowledge surrounding genetic factors influencing breast, colon, prostate and lung cancer.

Introduction

When caring for an individual with a current or past history of cancer, the role of genetic factors and family history cannot and should not be overlooked. Although most cancer develops sporadically, as much as 10 percent of cancer is thought to be inherited. This is significant since an inherited cancer predisposition gene not only increases the chance for a primary cancer but can also increase the chance for a secondary cancer and, thus, treatment may need to be altered.

Single genes influencing the development of breast and

colon cancer have been known for more than a decade, with clinical genetic testing available. More recently, however, recommendations for cancer surveillance have been broadened to also include familial empiric risk factors, i.e., the number and ages of diagnoses of cancers in the family. In this paper, we will review the current state of knowledge surrounding genetic factors influencing breast, colon, prostate and lung cancer. We will also explore the genetic counseling process as a way to facilitate genetic testing and provide a familial cancer risk assessment.

Breast Cancer

Most cancers, including breast cancer, occur sporadically. Approximately 30 percent of the time, however, two or more family members are affected. When this occurs, the question to address is "Why are several cases of breast cancer seen in a particular family?" More generally, why do some families have more cancer in them than others? There are 3 possible explanations:

1. Chance;
2. A hereditary cancer gene mutation (e.g. BRCA); and/or
3. Shared genes/shared environment (sometimes known as familial cancer)

Hereditary Cancer

Several genes have been found to increase susceptibility to breast cancer when inherited in altered forms, but two specific genes influence risk more than all others. These two genes are known as BRCA1 and BRCA2. Both genes normally function as tumor suppressors, with the role of maintaining genomic integrity. Tumor-suppressor genes, or more precisely, the proteins for which they code, are important because of their role in DNA damage repair. Tumor suppressor genes follow the "two-hit hypothesis," meaning that both alleles that code for a particular gene must be affected before a disease is manifested. If a person is born with one germline mutation, a "second hit" is still needed before cancer can develop. Those who possess a germline mutation in BRCA1 or BRCA2 are often said to have a "predisposition to cancer" or a "cancer susceptibility gene."

The best tool to help identify families which may have a cancer susceptibility gene is an accurate family history. Health care professionals should recognize that family history is an intrinsic part of a comprehensive cancer risk assessment and as important as asking about other personal risk or environmental factors. Family history collection needs to go beyond first-degree relatives because an assessment of only first-degree relatives will not take into account paternal contribution. Also, it is a common misconception that only the mother's side of the family is important for breast cancer, when, in fact, both sides of a family history are important.

When looking at a family history, there are several "clues," or characteristics, any one of which may suggest that a cancer susceptibility gene may be present. For breast cancer, these include:

- A) Multiple close family members affected with breast cancer or ovarian cancer;
- B) Earlier than average age at cancer diagnosis (under 50, or before menopause);
- C) Bilateral breast cancer;
- D) Breast and ovarian cancer in the same person;
- E) A specific pattern of inheritance;

- F) Rare or unusual cancers such as male breast cancer; and/or
- G) A tumor which is hormone receptor negative, high-grade and highly mitotic.

BRCA-related cancers are more likely to be high-grade, poorly differentiated and highly mitotic. They are also more likely to be estrogen receptor- (ER) and progesterone receptor- (PR) negative. In most studies the overall prognosis for BRCA-related cancer is similar to that of sporadic cancer, but the risk for a second breast cancer in BRCA mutation carriers is 20 percent to 40 percent over ten years. Many affected women will opt for prophylactic removal of the contralateral breast at the time of diagnosis. Thus, knowledge of BRCA status can directly impact cancer management. Advantages of this approach are a 97 percent risk reduction in contralateral breast cancer.¹

Knowledge of BRCA status is not only important to women diagnosed with cancer, but also to family members since those who possess a mutation are at significantly increased risk to develop both breast and ovarian cancer. Current data suggests that women who inherit one non-functioning copy of BRCA1 or BRCA2 have a lifetime risk to develop breast cancer of 50 percent to 85 percent and a 20 percent to 45 percent lifetime risk for ovarian cancer.² Because of these significantly increased risks, women possessing a BRCA gene mutation need to be more active with regard to surveillance and/or treatment than compared to women in the general population.

Current recommendations for women with a germline BRCA1 or BRCA2 gene mutation include monthly breast self-exams starting between ages 18 to 21, annual clinical breast exams starting between ages 25 to 35 and annual mammography starting between ages 25 to 35. More recently, it has been recommended that women also be offered breast MRI as an adjunct to mammography.³ Breast MRI is known to be more sensitive than mammography, therefore it can be a useful tool to detect breast cancer in young women including BRCA mutation carriers. In addition, prophylactic bilateral mastectomy has been shown to reduce breast cancer risk by greater than 90 percent in women with a BRCA mutation. In our professional experience, many women in South Dakota do not originally initially opt for bilateral prophylactic mastectomy after they first find out they are BRCA positive. They will, however, often choose bilateral mastectomy as a surgical option later when diagnosed with for a unilateral breast cancer diagnosis.

Ovarian cancer risk is also increased by a BRCA gene mutation, but unfortunately good screening methods for ovarian cancer remain elusive. Conversely, prophylactic bilateral oophorectomy has been shown to reduce ovarian cancer

risk by 96 percent in women with a BRCA mutation. Oophorectomy is generally recommended after 35 years of age or after childbearing is completed. Additionally, if this procedure is performed pre-menopausally, it also reduces the risk of breast cancer by more than 60 percent.⁴

In general, BRCA genetic testing is considered a reasonable option for those individuals who have had cancer at young ages or whose family history is suggestive of a certain type of inheritance. The likelihood of the presence of a BRCA1 or BRCA2 mutation can be estimated by licensed genetic counselors. When a patient/family decides to pursue genetic testing, an affected relative is the best candidate in the family to be tested. It is best to first test an individual who has had cancer, whenever possible, in order to give the greatest chance of finding a mutation in the family. If a mutation is identified, usually by full gene sequencing, other family members at risk may be tested for just the known single gene mutation. This is significant, since sequencing currently costs several thousand dollars while known mutation testing costs only a few hundred.

Appropriate use of genetic testing along with MRI and mammography could improve breast cancer detection in young women. To date, almost all BRCA gene mutations detected have been familial rather than *de novo*. Identifying mutation carriers and testing unaffected women may identify high-risk women who should undergo additional screening and be offered preventative options.⁵

Familial Breast Cancer

In some families, the incidence of breast cancer is more than one would expect by chance alone, yet the family doesn't fit a clear a pattern of inheritance, and a single gene mutation is not identified. In these families, the cancer is said to be familial. These histories may be the result of small family size, skewed distribution of the higher-risk gender or multifactorial influences. For these families, genetic testing is less likely to be informative, yet the families may still be in need of increased surveillance if the risk is deemed to be "high."⁶ The cancer models BRCAPRO, Claus and Tyrer-Cuzick are often used by genetic counselors to help determine risk. All three models rely heavily on family history including both affected and unaffected relatives.

The American Cancer Society recommends screening by breast MRI for those women with a lifetime risk of 20 to 25 percent (or greater) of developing breast cancer. There is an increasing amount of literature demonstrating that breast MRI screening can identify cancer in patients of specific risk groups. Several studies have demonstrated the ability of MRI screening to detect cancer with early-stage tumors that are associated with better outcomes. While survival and mortality data are not yet available, it has been proven that MRI has higher sensitivity and finds smaller tumors com-

pared with mammography, and these types of cancers found with MRI are the typesones that respond to therapy and that contribute to reduced mortality.³

Colon Cancer

Colorectal cancer is the third-most commonly diagnosed cancer in both men and women. It is estimated that 146,970 new cases are diagnosed annually, with 4 to 6 percent of these cases being caused by a hereditary cancer susceptibility gene.⁷ This sizeable disease burden is made even more complex by the fact that several different cancer susceptibility syndromes are associated with colon cancer. Some of these cancer syndromes include: hereditary non-polyposis colon cancer (HNPCC) which is also known as Lynch syndrome, familial adenomatous polyposis (FAP), attenuated familial adenomatous polyposis (AFAP), Muir-Torre syndrome, Turcot syndrome, Gardner syndrome, Juvenile polyposis syndrome, Peutz-Jeghers syndrome, PTEN hamartomatous syndrome and MYH-associated polyposis.⁸ Of these, HNPCC is the most common followed by FAP & AFAP.⁹

HNPCC

Although there are a number of inherited syndromes that can increase a person's risk of colon cancer, HNPCC is the most common. An estimated 3 to 5 percent percent of colon cancers are thought to be associated with HNPCC.⁹ The syndrome is caused by an inherited mutation in one of several DNA mismatch repair genes, namely MLH1, MSH2, MSH6 or PMS2. Mismatch repair genes are critical for the maintenance of genomic stability, because of their role in identifying and excising single-base mismatches and insertion-deletion loops that may arise during DNA replication. An inability to identify and repair the "mismatched DNA" makes it more likely that mutations will accumulate and set the stage for the development of cancer. Of the mismatch repair genes causing HNPCC, *MLH1* and *MSH2* are the most common accounting for approximately 90 percent of deleted mutations.⁹

A consequence of a cell's inability to repair DNA mismatches is a tumor variation known as microsatellite instability (MSI), in which simple repetitive sequences of DNA called microsatellites demonstrate characteristic changes in their length. MSI is found in about 90 percent of HNPCC related tumors, and, in fact, can be used as a screening method for HNPCC. It is important to note, however, that evaluating a tumor for MSI is a considered a screening test only, and not an actual diagnostic test.

Individuals who carry an inherited mutation for HNPCC are at greatly increased risk for colon cancer with an estimated lifetime risk of up to 80 percent. This diagnosis is often earlier than normal with an average age of 45 years, compared to 65 years in the general population.¹⁰ The

cancers are much more likely to be found in the right side of the colon. There is also a higher chance of developing a second colon cancer; risks are 30 percent over 10 years and 50 percent over 15 years.⁹

HNPCC is inherited in an autosomal dominant manner. Therefore, men and women are equally likely to have this disorder, and their sons and daughters are equally likely to inherit this disorder. A difference exists between sexes, however, in that women have the added potential burden of endometrial or ovarian cancers. About 40 to 60 percent of women will develop endometrial cancer during their lifetimes, and 12 percent will develop ovarian cancer.⁹ The average age of diagnosis of endometrial cancer is 46 years. In addition to the above mentioned increased risks for colon, endometrial, and ovarian, and colon cancers, both men and women with an HNPCC gene mutation are at increased risk for stomach cancer (13 percent).

For some time, HNPCC was a clinical diagnosis based solely on pedigree analysis and the Amsterdam criteria – which were initially formed for research purposes, but may have missed up to 40 percent of at-risk families.¹¹ At the present time, however, the majority of the genes associated with HNPCC have been identified, and clinical testing is available to help verify cancer risk status for family members. Genetic testing for the four known mismatch repair genes is thought to have a sensitivity of approximately 70 percent (Lynch).⁹ As with all hereditary cancer testing, when such a test is being considered in a family, initial analysis should be done on an individual with who has had cancer so that it would be possible to correlate the genetic change with the occurrence of cancer.

Knowledge of a mutation in an HNPCC gene can be advantageous for individuals with and without prior histories of cancer. Because of its early age of onset, colonoscopy needs to start by age 25 and should be repeated every 1 to 2 years through age 40, and then annually thereafter. The reality that the cancers are most often found on the right side of the colon can be problematic. “Complete colonoscopies” are recommended but various studies have shown that only about 56 percent of colonoscopies can be considered “complete”.¹² Colonoscopies should be performed by specialists, who have been made aware of the familial mutation, so that extra time can be spent on the right side of the colon. It has also been suggested that spiral CT be performed on individuals with HNPCC to better visualize the right side of the colon as well as to aid in detection of extracolonic cancers.¹² Should colon cancer occur, subtotal colectomy may be necessary, because of the increased chance for multiple additional cancers.⁹

Since 40 to 60 percent of female patients will develop endometrial cancer, it is recommended that annual

screening begin between the ages of 30 to 35 and include endometrial aspiration and transvaginal ultrasound. Prophylactic hysterectomy and oophorectomy should also be strongly considered after childbearing is complete.⁹

Family history is often the key to diagnosing HNPCC. Features of which to take note should include: two or more relatives with an HNPCC-related tumor (i.e. colon, uterine, stomach or ovarian), two or more affected generations, or an individual with an HNPCC-related tumor under the age of 50 or with two synchronous or metachronous tumors. Identifying a family or individual with any one of these features may suggest that a formal evaluation for HNPCC is necessary.

Adenomatous polyposis syndromes

Adenomatous polyposis syndromes are associated with multiple polyps in the colon. Two of these syndromes, familial adenomatous polyposis (FAP) and attenuated familial adenomatous polyposis (AFAP), are dominantly inherited conditions caused by mutations in the adenomatous polyposis coli (APC) gene. A third polyposis syndrome, often referred to as MYH-associated polyposis, is a recessive condition caused by two mutations in the MYH gene.

In classical FAP, individuals develop hundreds to thousands of polyps throughout the colon, usually as a teenager or young adult. The major concern with this condition is that the polyps will become cancerous, and there is nearly a 100 percent chance for malignancy if they are not removed. The polyps often begin to form around age 16. For this reason, prophylactic colectomy is often done between the ages of 16 and 20 to minimize risk for malignancy.⁸

FAP displays variable expressivity, sometimes displaying extracolonic features. Additional manifestations can include desmoid tumors, osteomas, dental anomalies and congenital hypertrophy of the retinal pigment epithelium (CHRPE). If additional features are found in association with multiple polyps, it's possible that a separate overlapping syndrome such as Gardner syndrome or Turcot syndrome may be present.⁸ Gardner syndrome is characterized by colonic polyposis typical of FAP found together with osteomas and soft tissue tumors. Turcot syndrome is the association of colonic polyposis and central nervous system tumors.

In contrast to classical FAP, attenuated FAP (or AFAP) is characterized by fewer colon polyps. It still, however, carries a significant risk for colorectal cancer if polyps are left untreated. Most individuals with AFAP develop 10 to 99 colon polyps. These polyps tend to be found more proximally in the colon than in classic FAP.

When eliciting a family history of a patient with multiple polyps, emphasis should be placed upon: parents or siblings

with multiple colon polyps, the number of generations affected with colon polyps, childhood colon or upper gastrointestinal cancers, and rare tumors (e.g., desmoid tumors). It is also important to note if there is a lack of multiple affected generations, since this could more strongly implicate a recessive form of polyposis.

The two genes most commonly associated with polyposis are APC and MYH. APC is the more common of the two. An identifiable APC gene mutation can be found in more than 90 percent of individuals with classic FAP and in 30 percent of individuals with AFAP. More recently discovered, MYH-associated polyposis is inherited in an autosomal recessive manner. It is believed that 33 percent of individuals who have 15 to 100 polyps and test negative for an APC gene mutation will test positive for two mutations in the MYH gene.¹³

Individuals may wish to consider APC genetic testing if they have had more than 10 polyps during the course of their lifetime or if there is a known mutation in their family. Genetic testing of the MYH gene may be appropriate for families with polyposis who have tested negative for the APC gene, or those who appear to demonstrate an autosomal recessive inheritance pattern.

Medical recommendations for someone who has AFAP or MYH-associated polyposis include colonoscopy every two to three years beginning at age 12 to 20 years and colectomy if more than 20 to 30 adenomas are identified. Esophagogastroduodenoscopy (EGD) should also be done beginning by age 25 years and repeated every one to three years.¹⁴

Familial Colon Cancer

In some instances of colon cancer, a family has more diagnoses than can be explained by random chance, yet the family does not have an identifiable cancer gene mutation. In these circumstances, the colon cancer is said to be familial, and risk to family members must be based on empiric risk estimates and model-based prediction algorithms. It is believed that 20 to 30 percent of all colorectal cancers have a familial basis.¹⁵

Numerous studies have explored the risk of cancer in the context of family history and have consistently found that first-degree relatives of affected individuals are themselves at a twofold to threefold increased risk of colorectal cancer. With no family history of colorectal cancer, there is a 4 percent lifetime risk of developing the disease (by age 79). The risk jumps to 8 to 9 percent with one affected first-degree relative and to 15 percent if that first-degree relative is diagnosed under the age of 45. If an individual has more than one affected first-degree relative (at any age) the risk for colorectal cancer is 16 percent.¹⁶ Additionally, familial factors also appear to influence the age of onset of colorectal

cancer. People who have a first-degree relative with colorectal cancer are estimated to have an average onset of colorectal cancer about 10 years earlier than people with sporadic colorectal cancer.¹⁷

Prostate Cancer

Prostate cancer occurs in approximately 1 in 6 men. Of those who develop it, about 20 percent will die from the disease. In many cases, however, prostate tumors grow slowly. If the cancer is detected early, five-year survival rates in South Dakota approach 100 percent.¹⁸

Risk for prostate cancer, as well as its progression, can be influenced by many factors, including race, diet, sexual activity, age and family history.¹⁹ African-American men tend to have the highest risk, while Asian men appear to have the lowest risk. Also, men who eat a lot of red meat or high-fat dairy products appear to have a slightly higher chance of getting prostate cancer. Of all risk factors, however, age plays the biggest role. For example, only one in 45 men are diagnosed under age 59, while the risk is one in seven for men ages 60 to 79.²⁰

After age, family history is the next strongest risk factor for prostate cancer. Risk increases with both the number of diagnoses in a family as well as with any diagnoses that occur at younger ages. If a male has a brother with prostate cancer, his risk is three times greater than the general population to also develop prostate cancer. If an individual has two first-degree relatives diagnosed at any age, the risk increases to five times the background risk.²¹ Furthermore, some studies have demonstrated that men have an increased risk for prostate cancer if their mother or sister have had breast or ovarian cancer.²²

The genetics of prostate cancer have proven challenging. With the exception of BRCA, which likely only accounts for 5 percent of all familial and early onset prostate cancer, no single genes have emerged as hereditary cancer predisposition genes for prostate cancer. Twin studies, nevertheless, have determined that 42 percent of prostate cancer risk may be accounted for by heritable factors and numerous other studies have concluded that much of the risk is due to highly penetrant autosomal dominant genes.²²

While specific single genes for familial or hereditary prostate cancer have not been implicated, there are many genes that have been reported as possible candidate genes. Some of these include CHEK2, ELAC2, HSD17B3 and RNASEL. There are now laboratories testing for a number of these genes, but the current dilemma with such testing is that the risk conferred by each of these genes is not known, so meaningful interpretation is not available. In fact, each gene tested only accounts for a small fraction of the overall familial risk. As an example, CHEK2 mutations are only seen in 4 percent of all prostate cancers.²³

While various studies have suggested that a single gene mutation is the mostly likely cause of inherited prostate cancer, the fact that no single gene has been discovered leaves open the possibility of multifactorial inheritance. In other words, it is possible that there are many genes, plus environmental factors, working in combination to influence the risk for prostate cancer.

As of yet, there have not been quality studies which have determined the most appropriate screening and surveillance strategies for men with a familial/inherited risk for prostate cancer. Although the optimal timing has not been studied, the age of 40 has been suggested as the most appropriate age at which time men with increased risk should be offered PSA testing. Even though there are no clear recommendations, all men with a family history of prostate cancer should be offered genetic counseling to review family history.

Genetic counseling can help in identifying families with hereditary prostate cancer. Obtaining and analyzing a family history may determine the mode of inheritance which could help facilitate genetic testing for some. Families with three or more first-degree relatives with prostate cancer, families with three successive affected generations (either maternal or paternal), or families with two relatives under the age of 55 should be considered for referral.²¹ One study in particular surveyed sons of men with prostate cancer and found that 90 percent wanted to know if they were at increased risk and indicated they were likely to undergo increased screening or consider genetic testing.²⁴

Lung

Since smoking is undeniably the number one factor influencing the risk to develop lung cancer, it can be easy to overlook other factors. One factor that shouldn't be overlooked, however, is family history. An underlying genetic susceptibility to lung cancer has been suggested by numerous studies showing familial trends even after adjusting for family smoking habits.²⁵ These studies have suggested that smokers who have a first-degree relative with early-onset lung cancer have a lifetime risk of between 17 percent to 25 percent to develop lung cancer.²⁶

In the clinical setting, family members of individuals diagnosed with lung cancer usually recognize the influence of smoking but often do not realize the role that an inherited predisposition to lung cancer may play. Family members should be made aware that first-degree relatives of patients with all forms of lung carcinoma are at a two to three-and-a-half-fold increased risk compared to the general population, and that the risk for second- and third-degree relatives is also increased.²⁷

Lung cancer is a multifactorial genetic condition, with both environmental and genetic factors influencing its development. Although the environmental components of lung

cancer are extrinsically apparent, the genetic factors leading to lung cancer have proven much more difficult to study. A 2009 study, however, has strongly implicated a gene known as RGS17 as a candidate for lung cancer susceptibility.²⁸ This gene is found on the q arm of chromosome No. 6. RGS17 has been found to be highly expressed in tumor tissues. To date, clinical testing for RGS17 is not available and a search for other candidate genes and modifier genes remains underway.

Genetic Counseling, Genetic Testing, and Risk Assessment

Cancer genetic counseling is a process whereby complex genetic information is translated to patients in an easily understood way, typically by master's level genetic counselors. The goal of cancer genetic counseling is to provide clear and clinically important information about genetic risk factors. Genetic counselors educate patients about their chance of developing cancer, help them derive personal meaning from cancer genetic information, and empower them to make educated, informed decisions about genetic testing, cancer screening and cancer prevention.⁶ The information presented during genetic counseling may help in the prevention or early detection of hereditary cancer. Alternatively, in our personal experience, many patients find out their risk to develop cancer is much less than what they anticipated and appear reassured by the information presented.

During any genetic counseling session, a detailed family history/pedigree is collected. Eliciting and analyzing a genetic pedigree is the foundation of cancer genetic risk assessment. By analyzing the family history, the genetic counselor is able to establish the likelihood of an inherited cancer syndrome, conclude if genetic testing is appropriate and determine the risk for cancer (or cancer recurrence). In addition to this individual multifaceted cancer risk assessment, other core components of cancer genetic counseling include education, counseling and the establishment of a cancer risk management plan. It is also necessary to ascertain what the level of risk means to each individual patient and to get them to contemplate how they will act upon this risk.²⁹

A referral for cancer genetic counseling should be considered for those patients with personal or family history features suggestive of familial or hereditary cancer and should not be limited to just those individuals who are potential candidates for genetic testing. Individuals from high risk families may benefit from a detailed discussion about the heritability of cancer in their families and appropriate cancer risk management strategies. Genetic counseling does not always require genetic testing and, in fact, the majority of men or women who meet with a genetic counselor do not have a test performed.

In some families, there is more cancer than one would

expect by chance alone, yet the family doesn't fit a clear a pattern of inheritance and usually does not have a single gene mutation causing the cancers. In these families, the cancer is said to be familial. Currently, sophisticated models are available to help estimate lifetime cancer risks for familial cancer (Saslow). By taking into account those family members who have had cancer, as well as those who have not, lifetime cancer risk estimates can be calculated and discussed with the patient. While those with familial cancer may not benefit from genetic testing, they do benefit from genetic counseling as a way to understand and act upon such risks.

Finally, risk estimates themselves are not static since family histories tend to be dynamic. Because of this, it is important that patients take note of and report new cancer diagnoses or other pertinent family health history that occurs after an initial genetic risk assessment. The occurrence of additional cancers in a family after someone has initially met with a genetic counselor may alter the likelihood of a cancer predisposition gene or change empiric cancer risk estimates. Moreover, as family histories are not static, neither is genetic discovery and new genes will continue to be discovered following the primary genetic consultation. Medical surveillance and treatment options for cancer will continue to evolve as new genes continue to be discovered.

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Breast Cancer Screening Update and Evaluation of the High-Risk Patient

By Thomas M. Cink, MD, FACR, FCCP

Introduction

Breast cancer is the most common noncutaneous malignancy in women and accounts for 30 percent of the new cancer cases in American women. Approximately 180,000 new cases of invasive breast cancer are diagnosed each year, with 62,000 new cases of in situ breast cancer, mainly ductal carcinoma-in-situ (DCIS) also diagnosed annually. (American Cancer Society, 2007)

Approximately 40,000 American women die of this disease annually. Between 11 and 13 percent of US women (one out of eight or nine) will develop breast cancer if they live to age 85. Breast cancer is the second-most common cause of cancer death in women. Lung cancer is the most common cause of cancer mortality in women.

The keys to surviving breast cancer are early detection and

treatment. Survival rates depend on the stage at which the cancer is detected. The five-year relative survival rate for stages 0 and 1 are near 100 percent. The survival rate decreases with more advanced stages, in which the survival rate for stage 4 has a relative 5-year survival rate of 20 percent.

While the incidence of breast cancer diagnosis has increased, the survival has improved dramatically in the last few decades. In the 1940s, the five-year survival rate for early-stage localized, node negative disease was 72 percent. Today, the survival rate has improved to 97 percent for the same stage disease.¹ The decline in mortality from breast cancer in the face of rising incidence rates is testimony to the success of interventional strategies in the form of screening and adjuvant systemic therapy.

Breast cancer is a very heterogeneous disease that requires

the coordination of a multidisciplinary team for optimal treatment and outcomes. This team includes a breast radiologist, pathologist, breast surgeon, medical oncologist, radiation oncologist, plastic surgeon and genetic counselor. Evaluation of the tumor size, any multifocality or multicentricity, the surgical margins, histologic grade, exam of the sentinel node, immunohistochemical and gene-based assays are all critical to decision-making and treatment.²

Breast cancer is a unique disease that has sufficient prevalence in the population to make it feasible to screen that population. It also has a preclinical prior to the progression of micrometastases and “phenotypic drift” during which the disease can be detected by screening. Phenotypic drift is the natural evolution of the more aggressive cells in a heterogeneous tumor to be the dominant histologic type.

Randomized Clinical Trials

There are three cornerstones of any breast cancer screening program that lead to early detection. They are annual mammography, a yearly clinical breast exam and a monthly breast self-exam. The efficacy of screening mammography has been studied extensively. The current U.S. recommendations for screening mammography are based on evidence gathered in seven randomized controlled trials performed between 1963 and 1988 and several meta-analyses.³⁻¹⁰ These studies showed that screening mammography in women aged 40 years and older reduces cancer deaths by 29 to 45 percent.

In evaluating the results of the screening mammography trials, a few potential biases should be considered. One potential bias is lead-time bias, which refers to the interval between disease detection and the usual manifestations of the disease. The estimated lead time in cancer detection with mammography is 18 + 6 months. Another potential bias is length time bias, which refers to differences in the rate of growth of tumors. It is thought that interval cancers, those that present clinically during the interval between regularly scheduled screening mammograms, are the fastest-growing cancers and have a worse prognosis than cancers detected on regularly scheduled annual mammograms. The ability to discriminate between the less aggressive and the more aggressive disease is an important area of breast cancer research.¹¹ There is also the possibility of self-selection bias in clinical trials, which refers to the fact that patients who volunteer for studies tend to have better health awareness than the general population. The optimal method to screen for breast cancer is constantly being re-evaluated. Until there are further breakthroughs in research and treatment, mammography remains the only

proven screening technique to decrease breast cancer deaths in the general population.

Risk Factors

There are a number of established risk factors for breast cancer. The first and most obvious is being female. Just 1 percent of breast cancer is diagnosed in males.

Age is the next most important risk factor, with a steadily increasing risk as a woman ages. A woman in her 70s is three times more likely to develop breast cancer than a woman in her 40s.

A family history of breast cancer, particularly in a first-degree relative (mother, sister, daughter) is an important risk factor. If the relative had a premenopausal breast cancer or bilateral breast cancer, the risk increases even further. A family history of ovarian cancer and any history of breast cancer in a male relative also increase risk of an inherited mutation. Approximately 5 to 10 percent of breast cancer cases result from inherited mutations in breast cancer susceptibility genes BRCA1 and BRCA2. It is very important to identify these individuals as some families have as high as an 80 percent lifetime risk. Affected individuals have unique primary prevention and screening needs which will be detailed later.

Hormonal factors can increase a woman's risk of breast cancer. These include early menarche (before age 12), late menopause (after age 55), late age of first full term pregnancy (after age 35), nulliparity and hormone replacement therapy.

Mammographic density has been shown to be a powerful predictor of breast cancer risk. A woman with greater than 75 percent density on a mammogram has a five times greater risk of developing breast cancer than a woman with a fatty replaced parenchymal pattern.

Proliferative breast disease found on a prior biopsy is a risk factor. This includes atypical ductal hyperplasia (ADH), atypical lobular hyperplasia (ALH) and lobular carcinoma in situ (LCIS).

Irradiation of the breast region at an early age can increase risk of breast cancer by as much as 35 percent. This is usually for treatment of a cancer such as Hodgkin's disease.

Personal history of malignancy increases the risk of a subsequent breast cancer. In addition to a personal history of breast cancer, the other cancers that can increase breast cancer risk include a history of endometrial, ovarian or colon cancer.

While these factors can increase a patient's individual risk, approximately 75 percent of new breast cancer patients have no more risk than being a woman over 40 years of age.

Certification

In 1987, the American College of Radiology developed the Mammography Accreditation Program. This was incorporated into the 1992 Mammography Quality Standard Act (MQSA) and became mandatory through FDA regulation in 1994. The MQSA is a law that provides minimum training, interpretation and reporting standards and regulates all of the aspects which contribute to image quality and patient dose. All facilities in the United States are required to be MQSA-certified prior to providing mammographic services and must continue to pass a yearly inspection.

When Should Patients be Screened?

Annual screening mammography should begin at age 40. This recommendation is supported by major medical organizations, including the American Cancer Society, the National Cancer Institute, American College of Radiology (ACR), American College of Obstetricians and Gynecologists (ACOG) and the American Medical Association.¹²

In November 2009, the *Annals of Internal Medicine* published an article on screening mammography by the U.S. Preventive Services Task Force (USPSTF). They recommended screening women every other year from age 50 to 74 and recommended against breast self-exam and also questioned the usefulness of clinical breast exam. This created much furor among patient and advocacy groups. The task force was criticized for not having breast cancer or breast screening experts in its membership.

Soon after the article was published, the U.S. Secretary of the Department of Health and Human Services, Katherine Sebelius, issued a news release stating that "They (USPSTF) do not set federal policy... and I would be very surprised if any private insurance company changed its mammography coverage decisions... There is a great need for more evidence, more research and more scientific innovation... My message to women is simple. Mammograms have always been an important life-saving tool in the fight against breast cancer and they still are today. Keep doing what you have been doing for years..."

The American Cancer Society has reaffirmed its position that breast cancer screening should be annual and start at age 40. This position is supported and endorsed by numer-

ous additional medical groups including ACOG, ACR and the Society of Breast Imaging (SBI).

There is no established upper age limit to the beneficial use of screening mammography, because the age at which a woman would cease to benefit from screening mammography varies depending on the individual's overall health. The decision as to when to stop routine mammography should be made on an individual basis by each woman and her physician. As long as a woman is in reasonably good health and would be a candidate for treatment, she should continue to be screened with mammography.¹³

If a patient has a first-degree relative who has had breast cancer, screening should begin 10 years earlier than the age at which that relative was diagnosed or at 25, or whichever is older. For example, if the patient's mother was diagnosed at age 40, the daughter should begin screening at age 30.¹³ Patients who have received high-dose chest radiation (mantle therapy) should begin mammographic screening eight years after her radiation treatment or at 25 years, or whichever is older.¹³

Any patient with symptoms such as palpable mass, skin changes or pain is not a candidate for screening mammography and should have a diagnostic mammogram ordered where the breast radiologist can tailor the set of images to the particular patient's symptoms. This may involve getting a detailed history of the patient's symptoms and occasionally also using ultrasound to further evaluate any findings.

Technique

Mammography currently remains the only imaging modality that is recommended for routine screening for breast cancer in the general population because it has proven to decrease the death rate from breast cancer. A screening mammogram includes a craniocaudal and mediolateral oblique view of each breast. The technologist positions the patient to project as much of the tissue as possible on the images. Compression of the breast tissue to tolerance is obtained to eliminate motion artifact, separate the glandular densities, decrease scatter irradiation and even out the overall density of the breast. The quality of these images is of utmost importance for accurate interpretation.

The radiologist makes an assessment of the relative density of the breast using a quartile system, i.e. "almost entirely fat," 0 to 25 percent glandular density; "scattered glandular density," 25 to 50 percent glandular density; "heterogeneously dense," 50 to 75 percent dense; and "extremely dense," greater than 75 percent dense.

All mammograms are reported using the Breast Imaging-Reporting and Data System (BI-RADS). BI-RADS is a mammographic terminology which standardizes lexicon and facilitates reporting of the interpretation, communication, recommendations and outcome monitoring. This system uses category numbers of zero through six with each linked to a clear assessment and recommendation.

Findings

The most common mammographic findings of breast cancer include a mass or suspicious calcifications. There are many modifiers which the radiologist uses to separate the majority of masses and calcifications that are benign from the few that are indeterminate and need further workup. While there are many exceptions to the rule, malignant masses frequently have irregular shape, indistinct or spiculated margins and high radiographic density. Malignant calcifications can be found alone or in association with masses. Malignant calcifications are usually grouped or clustered, pleomorphic (varying in size and shape), fine, linear and branching. There are additional indirect signs that may indicate that a patient has breast cancer and these include evolving density, architectural distortion and asymmetric density.

Full Field Digital Mammography

Full Field digital mammography (FFDM) units have replaced screen/film mammography (SFM) in greater than 60 percent of the mammography facilities in the US. This percentage continues to increase. Digital mammography has a higher contrast resolution and higher signal-to-noise ratio and a lower radiation dose.

In a film-screen system, the film functions as the detector, storage and display device. With digital systems, these tasks are separated allowing for optimization of each function. Full field digital also allows for rapid throughput and electronic transmission of the image. There also is reduced cost of archiving. The final image can be manipulated to enhance interpretation with functions such as magnification, windowing and level adjustments and edge enhancement.¹⁴ Breast radiologists find these features to be very helpful in interpretation, despite that evaluating a digital mammogram takes considerably more time than for an analog mammogram.

The Digital Mammography in Screening Trial (DMIST) demonstrated that digital mammography was superior to film-screen mammography in detection of breast cancer in certain subgroups, which included women under age 49, women with dense breast tissue and pre- and peri-

menopausal women.¹⁵ A number of additional studies have been published comparing FFDM and SFM in large population-based screening trials. FFDM finds more cases of both invasive carcinoma and DCIS with similar positive predictive value and slightly increased recall rate. The most recently published trial in October 2009 was a review of 188,823 screening mammograms. It showed that FFDM found 21 percent more cancers than SFM.¹⁶ The Oslo II study revealed an even higher percent of additional cancers detected when comparing FFDM with SFM.¹⁷

There are a number of additional techniques amenable to digital mammography that are being investigated at this time. These techniques include tomosynthesis and dual energy mammography. Tomosynthesis is a cross-sectional technique which minimizes the effect of overlapping structures in the breast and should facilitate cancer detection. Clinical trials are underway to establish efficacy of tomosynthesis and define its role in future practice.

Computer-Aided Detection

Computer-aided detection (CAD) is becoming commonplace in U.S. screening programs. Mammographic CAD has proven to improve the rate of cancer detection in screening populations. In the case of screen-film mammography, the images are digitized and then subjected to a computer-based analysis. In the case of digital mammography CAD analysis is included in the display algorithm. The prompts, which are designed to detect calcifications, masses or asymmetry, are projected on the images with a keystroke. CAD offers the interpreter and ultimately the patient the advantage of increased sensitivity to detection of suspicious abnormalities.¹⁸ Studies indicate that readers using CAD detect 19.5 percent more cancers than without CAD.¹⁹ Detection is not diagnosis, and, therefore, it is still up to the interpreter to determine if a finding rises to the level of a suspicious lesion that would require additional evaluation.

Core Needle Biopsy

When a patient is screened and mammographic abnormalities are detected, the patient is called back and a diagnostic workup is performed frequently using special mammographic techniques such as magnification mammography or focal spot compression images. Ultrasound may also be used depending on the specific type of abnormality. If the lesion is still suspicious after the diagnostic evaluation, a core biopsy is frequently performed. A core biopsy is a tissue-sampling procedure guided by stereotactic technique in the case of calcifications or ultrasound if the lesion is a mass and visible with ultrasonic imaging.

In a recent multispecialty consensus conference² published in the *Journal of the American College of Surgery*, Silverstein, et al. stated that “percutaneous needle biopsy has demonstrated accuracy and is the optimal initial tissue-acquisition procedure for image-detected breast abnormalities. The use of percutaneous biopsy for diagnosis significantly reduces the overall cost of treatment and potential disfigurement of patients with breast lesions... In spite of the fact that there are few patients for whom needle biopsy is technically not feasible, an alarming 35 percent of initial diagnostic breast biopsies in the United States are still done using open surgical techniques. It was the Panel’s unanimous opinion that percutaneous needle biopsy represents ‘best practice’ and should be the new ‘gold standard’ for initial diagnosis. It should essentially replace open biopsy in this role.”

Core needle biopsy uses multiple devices. These range from 14G to 7G in size. Some of these devices have vacuum-assist and are superior in obtaining ample tissue for histologic analysis.

Ultrasound

Ultrasound should always be used as an adjunct and never as a primary screening tool. Results of ultrasound studies vary widely depending on the operator. There are at present no data to support whole-breast ultrasonic screening to decrease breast cancer death rates. A study by the American College of Radiology Imaging Network, ACRIN Study 6666, is underway to investigate this issue.

The goal of diagnostic breast ultrasonography should be to make the overall imaging assessment more specific, helping to guide further care. In the setting of a suspicious lesion, the ipsilateral breast should be scanned sufficiently to determine the extent of the index lesion and to assess for any satellite or synchronous lesions. Ultrasonography of the ipsilateral axilla should be performed for all suspicious or biopsy-proven invasive lesions to assess for morphologically abnormal nodes. If an abnormal node is detected, confirmation of malignant involvement by ultrasound-guided core biopsy will allow the surgeon to proceed directly to axillary dissection rather than sentinel node biopsy. Radiologic marker placement at the time of ultrasound-guided axillary node biopsy may facilitate subsequent confirmation of proper node recovery.²

Medical Audit

Under MQSA, all practices must strive to have 100 percent follow-up of all screened patients and any subsequent biopsy and staging information. Each individual interpreter

receives this information based on their cases. Each screening center also makes a combined report based on the accumulated data yearly. The Department of Health and Human Services has published desirable goals for the medical audit of screening outcomes. These include a less than 10 percent recall rate, sensitivity of greater than 85 percent and specificity of greater than 90 percent. The number of screen-detected cancers varies from two to 10 in 1,000 patients screened. This is usually six to 10 in 1,000 in those who have never been screened before and is usually two to four in 1,000 in those with yearly follow up screening. Greater than 50 percent of cancers detected by screening should be either Stage 0 or Stage 1. Greater than 75 percent of screen-detected invasive cancers should have negative nodes. Greater than 30 percent of screen-detected cancers should be “minimal” cancers, i.e. less than 1 cm in diameter.²⁰ These numbers should be obtainable with adequate experience of the interpreter and attention to all the details of imaging and diagnosis. Bassett at the University of California, Los Angeles published in the *American Journal of Radiology* that biopsy of palpable masses yielded a positive predictive value (PPV) for primary breast malignancy 34 percent of the time, and biopsy of mammographically detected abnormalities revealed malignancy in 31 percent of cases.

The American College of Radiology is launching a national mammographic database beginning October 2009. This is intended to be an aid to medical auditing where a practice will submit their data and have their outcomes analyzed and fed back in a meaningful way and thus create a large enough cumulative data warehouse from which to compare one’s practice and eventually to strengthen any weakness.

High-Risk Patients

Mammography alone is not adequate for surveillance of high-risk patients. Patients who have multiple family members with breast cancer may have an inherited high risk of developing breast cancer. High-risk clinics evaluate the actual level of risk in these patients and provide specialized services, such as genetic counseling/testing, risk reduction and screening breast MRI.

There have been tremendous advances in the field of genetics that allow for these patients to be tested for genetic predisposition. Potential high-risk patients are referred to a genetic counselor for risk assessment and possible genetic testing. If this testing proves to be positive, these patients then can pursue various risk reduction strategies and/or begin high-risk surveillance. Advances in MRI technology allow for rapid simultaneous bilateral acquisition of high-

resolution cross-sectional images of the breast.

Hereditary breast and ovarian cancer syndrome is associated with mutations of the BRCA1 and BRCA2 genes and is the most common form of inherited predisposition to breast cancer. Approximately 80 percent of cases of inherited breast cancer are due to mutations in either the BRCA1 gene (chromosome 17q12-21) or the BRCA2 gene (chromosome 13q12). Fifty percent of patients with the BRCA1 gene develop breast cancer by the time they reach 50 years old. Some of the 20 percent of inherited breast cancers not associated with mutations in BRCA1 or BRCA2 are associated with other genes, such as PTEN (Cowden disease), TP53 (Li-Fraumeni syndrome), STK11/LKB1 (Peutz-Jeghers syndrome), CDH1 (hereditary diffuse gastric carcinoma), and ATM (ataxia-telangiectasia). However, there are probably other susceptibility genes that have not yet been identified since BRCA1-2 and these other genes do not account for all cases of familial breast cancer.

Genetic Counseling

Genetic counseling has become very important to educate patients, their families and other health care providers about the role of genes in the development and transmission of cancer. Patients are referred for genetic counseling when they are suspected of having a hereditary cancer syndrome. (Figure 1) The genetic counselor performs a formal risk assessment based on the patient's personal and family history. They use various risk assessment models including the Gail, Claus or BRCAPRO models to determine relative risk of developing breast cancer and whether to do genetic testing based on this information. They discuss the benefits, risks, limitations and possible results of genetic testing and any recommended cancer screening and risk reduction strategies. We have found this to provide psychosocial support

to patients and their families throughout the genetic counseling and testing process. Genetic testing provides patients with information about themselves and their families that may affect their medical care and health. On the federal level, the Health Insurance Portability and Accountability Act (HIPAA) prohibits group health insurance plans from using genetic information as a basis for denying, canceling or limiting eligibility for coverage or increasing an individual's premium and also prohibits the use of genetic information as a pre-existing condition. Most states have enacted similar laws that prohibit the use of genetic information in decision-making regarding health insurance coverage, eligibility or employment.¹⁴

Risk Reduction

Breast cancer risk reduction strategies in those found to be at documented high risk include chemoprevention with selective estrogen receptor modulators such as tamoxifen or raloxifene, prophylactic mastectomy and prophylactic oophorectomy. A recent international study documented that prophylactic oophorectomy is generally accepted by women and their physicians. However, only a minority of women with BRCA1 or 2 mutation opt for prophylactic mastectomy or take tamoxifen for the prevention of hereditary breast cancer. Approximately one-half of these women at high risk for breast cancer rely on screening alone.²¹

Screening Breast MRI

Screening breast MRI has proven to be a powerful adjunct to mammography in patients with a BRCA mutation.²² The benefit of breast MRI is that it has markedly increased cancer detection compared to mammography with significantly more of these cancers being detected prior to nodal metastasis, i.e. MRI detects breast cancer at early stages. The invasive breast cancers detected by MRI had a node positive rate of seven percent compared to a node positive rate of 28 percent for those invasive cancers diagnosed by mammography. The call back rate for breast MRI screening compares favorably with mammography at 10 percent (range eight to 17 percent) The positive predictive value for biopsies is slightly higher for MRI than mammography at 43 percent (range 17 to 89 percent).²³

Screening MRI in high risk patients detects both mammographically and clinically occult breast cancers. Adding MRI to mammography gives an additional cancer yield of eight to 67 (mean=30) in 1,000 high-risk women screened. The consistent finding of numerous studies at numerous institutions of high-risk patients is that MRI has the highest sensitivity and cancer yield of any of our screening tools. The sensitivity of MRI in these studies ranges from

Figure 1. Genetic Counseling Referral of Patients at High Risk of Hereditary Breast Cancer

Indications for Referral for Cancer Risk and Genetic Evaluation

Any personal and/or family history of:

- Breast cancer diagnosed <50;
- Breast cancer in 2 or more close relatives;
- Bilateral breast cancer;
- Male breast cancer;
- Breast & ovarian cancer in the same woman or in close relatives;
- Ovarian cancer at any age; and/or
- Ashkenazi Jewish with breast or ovarian cancer at any age.

71 percent to 100 percent. The sensitivity of mammography at diagnosing cancers in these same patients is measured as only 13 percent to 40 percent.²⁴ One study by Lehman compared cancer yield of mammography, MRI and ultrasound in high-risk women. This revealed that mammography found only one-third as many cancers as MRI and that ultrasound was not useful to screen high-risk women. The PPV for biopsies performed as a result of MRI was 43 percent. This compares favorably with biopsies performed for palpable masses (34 percent) and for mammographically detected lesions (31 percent).

Patients with a sufficiently high risk undergo yearly mammograms and breast MRI. A number of international clinical trials support the use of yearly MRI and mammography to screen patients at high risk of developing breast cancer.²⁵⁻³⁰ The American Cancer Society has recently recommended that high risk patients pursue breast MRI due to its high sensitivity and proven ability to detect small curable cancers not seen on mammography.³¹ An expert panel endorsed the ACS guidelines regarding screening MRI.

Appropriate candidates include:

1. Women with a lifetime breast cancer risk of 20 percent or higher based on predictive models. This usually means those with two or more first-degree relatives with diagnosed breast cancer (mother, sisters or daughter);
2. Those with BRCA1 or 2 mutations or those having a first-degree relative with a BRCA 1 or 2 mutation who have not yet been tested themselves;
3. Those who have had radiation therapy to the chest between ages 10 and 30; and/or
4. Women with Li-Fraumeni, Cowden or Bannayan-Riley-Ruvalcaba syndromes and their first-degree relatives.

The ACS recommends that patients with less than 15 percent lifetime risk of breast cancer not be screened with MRI. They do, however, recommend further study on the group of patients with between 15 percent and 20 percent lifetime risk. This group includes women with a personal history of invasive breast cancer or DCIS, previous diagnosis of ADH, ALH or LCIS and women with mammographically dense breasts. A recent consensus panel² states that “the commonly used predictive models may not reliably identify all women at high risk. Many women who have significant risk may fail to meet the ACS threshold for screening. In the Panel’s view, screening MRI may be appropriate” for women with a 15 percent and 20 percent lifetime risk. (Figure 2)

MRI uses magnetic fields along with radiofrequency trans-

Figure 2. Risk Information

The American Cancer Society recommendations are as follows:

- Women at high risk, greater than 20 percent lifetime risk, should get an annual MRI and mammogram.
- Women at moderate risk, 15 percent to 20 percent lifetime risk, should visit with their physician about an MRI in addition to their annual mammogram.

Women at high risk include those who:

- Have a known BRCA1 or BRCA2 gene mutation;
- Have a first-degree relative (parent, brother, sister or child) with a BRCA1 or BRCA 2 gene mutation, and have not had genetic testing themselves;
- Have a lifetime risk of breast cancer of 20 percent or greater, according to risk assessment tools that are based mainly on family history;
- Had radiation therapy to the chest when they were between the ages of 10 and 30; and/or
- Have Li-Fraumeni syndrome, Cowden syndrome or Bannayan-Riley-Ruvalcaba syndrome, or have one of these syndrome in first-degree relatives.

Women at moderately increased risk include those who:

- Have a lifetime risk of breast cancer of 15 percent to 20 percent, according to risk assessment tools that are based mainly on family history;
- Have a personal history of breast cancer, ductal carcinoma in situ (DCIS), lobular carcinoma in situ (LCIS), atypical ductal hyperplasia (ADH) or atypical lobular hyperplasia (ALH); and/or
- Have extremely dense breasts or unevenly dense breasts when viewed by mammograms.

mitters and receivers to produce cross-sectional images. These images can be reconstructed in 3-D (sagittal, axial and coronal planes), particularly when high-field strength (3 Tesla) magnets are used. One advantage is that no ionizing radiation is used with MRI.

For cancer detection protocols, a paramagnetic contrast agent containing gadolinium is injected to evaluate enhancement. The patient lies prone on a padded table that contains the specialized imaging receivers, or coils. Scans are acquired rapidly, but image reconstruction and post-processing continue after the patient has left the scanner. Post-processing usually utilizes computer aided detection software to aid in interpretation. Pre and post-contrast images can be subtracted to emphasize enhancement. Breast MRI is interpreted in comparison with the mammogram. A complete breast MRI with CAD contains thousands of images.

Contraindications to MRI include implant expanders, cardiac pacemakers, neurostimulator devices, extreme claustrophobia and morbid obesity.

The sensitivity of MRI is high, and, therefore, a negative MRI is highly reassuring that there is no cancer in that patient. High sensitivity, however, means that there is a moderate false-positive rate and decreased specificity. Experts recommend that breast MRI only be done where MRI-guided core biopsy is also available.² Future improvements are expected with advanced pulse-sequences and incorporation of diffusion-weighted MR potentially being added to present protocols at 3 Tesla.³²

Remaining Challenges

Research is being done on many fronts to find “the cure.” Promising areas of cellular biology research include the PI3K enzyme, which is a central player in the pathway that controls cell growth and survival.

“Epigenetics” looks at how certain genes are used in the cell and how genes get turned on and off. There is also research into the molecular diversity of breast cancer and to define these various subtypes. The hope of these three promising areas of research is to find specific drugs to control each of these cell processes and disease subtypes. This in turn could improve the screening and treatment paradigm to discriminate minimal-risk disease from high-risk disease and therefore reduce treatment burden for patients and society.¹¹

The American Cancer Society has released data showing that the breast cancer mortality rate decreased by 2.2 percent per year between 1990 and 2004.³³ However, in African American women, the breast cancer death rate declined by only 1.6 percent per year and remained unchanged among Asian American and Native Americans. Reasons for the differences in mortality rates remain unclear.

Many challenges remain in order to realize the maximal benefit from earlier detection. There is a concerning decrease in the usage of screening mammography. Nearly one-third of American women are not undergoing mammographic screening at appropriate intervals. Thirty percent of American women who are 40 and older have had no mammograms in the last two years. Most women who are not having routine mammograms are not receiving a recommendation for mammography from their physician, among other reasons.³⁴ We must continue to communicate to our patients the importance of routine screening mammography and offer our high-risk patients genetic referral, risk reduction and breast MRI when appropriate.

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Diagnosis and Surgical Treatment of Breast Cancer

By Juliann Reiland-Smith, MD, FACS

Abstract:

Counseling a woman about surgical treatment of breast cancer is both challenging and rewarding. The layperson's view of breast cancer surgery is that it is disfiguring, if not mutilating. Today's newer approaches are neither, and informing the patient of these options can relieve anxiety, improve outlook and help maintain the patient's self image.

The surgical options for diagnosis and treatment of breast cancer are evolving. Minimally invasive biopsy techniques, (core needle biopsy) are becoming the standard for the diagnosis of breast cancer, replacing open surgical biopsy with its increased cost and large surgical scars. Sentinel lymph node biopsy is now considered the standard of care in evaluation of lymph nodes, compared to axillary lymph node clearance. Oncoplastic surgery improves cosmesis after breast conservation (lumpectomy). Skin sparing, areolar sparing, and nipple sparing mastectomies are becoming common approaches to mastectomy with reconstruction. Immediate reconstruction after mastectomy is now routinely performed with implants or autologous tissue. This article reviews these surgical approaches and will allow the primary care provider a better understanding and ability to counsel their patients in the options for surgical treatment of breast cancer.

Breast Biopsy

JP is a 67-year-old woman who had a breast abnormality found on both mammogram and ultrasound. She was referred to a surgeon for biopsy. She was informed about a needle localized breast biopsy and scheduled for surgery. Her

daughter searched the Internet and discovered a better option. The surgery was cancelled and the patient went to a radiologist for an ultrasound guided core biopsy.

Traditionally, breast biopsies involved localizing the lesion either with ultrasound or mammographically guided wires

placed within the suspicious area, then taking the patient to the operating room to surgically remove the wire and the tissue surrounding it. Since 2005, it has been recommended that minimally invasive biopsy techniques be used to sample tissue. In October 2009, a consensus report confirmed that minimally invasive breast biopsy is the optimal initial tissue-acquisition method and procedure of choice for image-detected breast abnormalities.¹

Minimally invasive breast biopsy or core needle biopsy is the acquisition of tissue through a percutaneous approach. These include large-core biopsy (12-14 gauge needle), or a vacuum assisted biopsy (7-11 gauge needle). Tissue obtained with this method allows for optimal workup and planning before the patient enters an operating room. The use of open surgical biopsy should be limited to those patients for whom technical reasons percutaneous biopsy is not indicated. With core needle biopsies so readily available and providing better tissue sampling, fine needle aspiration is being used less often to sample breast lesions.

Ultrasound guidance is the preferred method to obtain core biopsies. Because of the concern for missing a palpable lesion with a blind core biopsy, it is recommended that even palpable lesions have ultrasound guided core biopsy. Using ultrasound is less costly and less time-consuming than stereotactic breast biopsy. Stereotactic biopsy using mammography is best for smaller lesions, abnormalities seen on mammogram only, and those characterized by microcalcifications alone.

MRI-guided biopsy of an abnormality is also possible. Because MRI-guided biopsy is technically difficult, it is usually performed only if the lesion in question is not seen with any other modality.

NC is a 48-year-old woman who was found to have a clinically suspicious breast mass. She had a diagnostic mammogram which identified a 3-cm mass in her breast. This was considered suspicious and a biopsy was recommended. Her provider was assured that all was well with a negative pathology report. The patient returned for a repeat mammogram in six months. The 3 cm mass had become 9 cm. A biopsy was positive for invasive ductal carcinoma.

Of utmost importance with all methods of tissue evaluation is the correlating the histology with clinical and imaging findings. If pathology identifies a benign tissue sample and imaging indicates a suspicious lesion (BI-RADS 4 or 5), then reevaluation is needed to determine concordance. If a palpable abnormality is also seen on ultrasound and biopsied, yet pathology only identifies benign breast tissue, it

must be assumed the lesion was missed. Discussion with the surgeon, radiologist and pathologist may be necessary to come to a conclusion and plan for further evaluation of the abnormality. Depending on the findings this could mean re-evaluation with diagnostic imaging in three to six months, or repeat biopsy of the suspicious area.

Missing the diagnosis of a breast cancer is devastating to the patient, to her family and to the practitioners involved. There are many opportunities in the care of the female patient to miss this diagnosis, starting first with the patient who does not report the lump in her breast to her provider, or the provider who does not perform a breast exam with an annual physical exam. Every woman with a palpable mass needs further evaluation, usually starting with a clinical examination for correlation. In 2002, the Physicians Insurance Association of America reported that malignant neoplasms of the female breast continue to be the most prevalent and the second-most expensive condition resulting in malpractice claims against physicians.

Surgical Treatment of Breast Cancer

SH presented to a surgeon's office for a second opinion regarding treatment of a newly diagnosed invasive ductal carcinoma of the breast. Her first surgeon told her a mastectomy was her only choice for cure. The patient wanted to hear about any other options.

It's stunning that 30 years after the NSABP trials unequivocally proved that lumpectomy with radiation had the same survival benefit as mastectomy, patients are not aware of this fact. Ten-, 15- and 20-year data have been reported. The results continue to be the same. Comparing stage for stage, there is no survival benefit to having mastectomy compared to lumpectomy with radiation. Our patients need to understand that removing their breasts will not give them a better guarantee for survival. Recurrence rates differ, however. For a woman following mastectomy, the risk of local recurrence developing beneath the skin flap in the subcutaneous fat is 3 percent. For the woman with lumpectomy and radiation, most recently published data rates risk of recurrence at 7 to 10 percent. The risk of recurrence for women who have lumpectomy without radiation is as high as 39 percent.⁵

Once this information is presented in an unbiased fashion, it becomes clear to the patient that there are indeed choices that need to be made. Helping a woman navigate this decision is crucial. Most want to know their options, and when they realize both options are valid, many struggle to decide which is best for them.

For most women, their primary concern is surviving breast cancer. What needs to be addressed next is how that patient deals with illness, anxiety issues our medical system and all its fallibilities. Patients who choose mastectomy may decide this because they never want to deal with breast disease again, have anxiety about the possibility of a recurrence, are concerned about missed breast cancers or have had a personal experience with a close friend or relative who died of breast cancer.

On the other hand, women who choose lumpectomy with radiation decide that the difference in recurrence rates is minor, see no reason to remove an entire breast when only one portion is diseased, trust our medical technology's ability to monitor them in the future and accept that there are no guarantees and can live with that understanding.

There are situations where choosing lumpectomy with radiation is not advisable. When breast cancer is found in more than one quadrant of the breast (multifocal disease), breast conservation would be impossible because too much of the breast would have to be removed. If diagnostic studies originally missed the cancer, the patient and providers fear that the technologies' limitations may fail again to diagnose another future cancer or recurrence. This is also an issue when future follow-up would be difficult due to extremely dense breast tissue, or if there is concern regarding the patient's compliance with future follow-up, or when the breast cancer is too large or the breast is too small and good cosmesis is difficult to achieve. If the cancer presents as bloody nipple drainage and involves the ductal tissue leading to the nipple, nipple-sparing lumpectomy would be impossible, but a central lumpectomy with removal of the nipple areolar complex is acceptable.

Studies have shown a woman's satisfaction with her treatment is directly proportional to her participation in the decision-making process, rather than the specific procedure she eventually undergoes.

In the work-up of a new breast cancer on the right, MP underwent an MRI to evaluate the extent of her cancer. Another abnormality was also identified in the left, or contralateral, breast, and biopsy of the left breast lesion confirmed a breast cancer.

Once a patient is diagnosed with breast cancer, further workup is needed to determine extent of disease in the ipsilateral breast, whether disease is present in the axilla and if occult or suspicious lesions in the contralateral breast are present.

Evaluation of the tumor itself involves measuring for extent of disease and tumor size. The anatomical relationship of the tumor to the skin, the nipple and the chest wall may affect surgical planning, possibly identifying a situation where breast conservation would be contraindicated. Ultrasound gives fairly accurate information as to size of the tumor and may be all that is necessary. Breast MRI shows three-dimensional relationships of the tumor to the rest of the breast, and, in some instances, can be helpful in surgical planning.

Surgical treatment of breast cancer also requires evaluation of axillary lymph nodes to determine or rule out spread of disease. Preoperative evaluation of axillary lymph nodes is becoming more common and is considered best practice. The patient with metastatic spread to lymph nodes may be considered a candidate for chemotherapy before surgery (neo-adjuvant therapy). A cancerous lymph node identified before surgery would also require a total axillary node dissection during the surgical procedure instead of sampling the lymph nodes with sentinel lymph node biopsy (SLNB), which is explained in more detail later.

Mammograms can sometimes identify axillary lymph nodes that are suspicious. Ultrasound, breast MRI and breast-specific gamma imaging (BSGI) can also identify suspicious lymph nodes. Any axillary lymph nodes that are concerning for metastatic spread are then biopsied, usually under ultrasound guidance with either core biopsy or fine needle aspiration.

The incidence of a synchronous contralateral breast cancer is 3 percent to 8 percent. With a 99 percent negative predictive value, BSGI is a modality that can be used to evaluate and rule out occult disease in the contralateral breast. Suspicion about contralateral disease should be entertained when a patient presents with a missed breast cancer or has extremely dense breast tissue.

Breast MRI has been used extensively in the workup of a breast cancer. It was felt to improve surgical planning and reduce the number of re-excisions at lumpectomy because of positive margins. Recently, however, a study was published which found no benefit in MRI use for improving surgical margin status or breast conservation attempts. The use of MRI was also associated with treatment delay and increased mastectomy rate.⁶ Certainly, breast MRI has benefits in the work-up of breast cancer and there are situations where it is very helpful, but every woman with breast cancer does not need an MRI preoperatively.

Mastectomy

EL presented to a plastic surgeon to discuss reconstructive surgery. She had been diagnosed with breast cancer nine months earlier and had a modified radical mastectomy. At age 42, she was very self-conscious about her large scar from her surgery and wondered about reconstruction. She did not pursue reconstruction because she was afraid her insurance would not pay for it.

When mastectomy is the surgical option of choice, a patient needs to be informed about breast reconstruction. There is no age limit on reconstruction. Our Midwestern attitudes about women and vanity may make it difficult for women to admit they would like this option. Furthermore financial concerns may inhibit a patient from exploring reconstruction options. The Women's Health and Cancer Rights Act of 1998 (WHCRA) is a federal law that mandates insurance companies cannot deny coverage for their patients who choose to have reconstruction. If WHCRA applies, the insurance company must cover all stages of reconstruction on the ipsilateral side following mastectomy, reconstruction of the contralateral breast to produce a symmetrical appearance. Any physical complications of all stages of mastectomy, including lymphedema, are also covered under WHCRA.⁷

A simple mastectomy is the removal of the nipple areolar complex with an ellipse of skin and all the underlying breast tissue. A modified radical mastectomy is a simple mastectomy with a full axillary node dissection, which is defined as all nodes in the first and second levels of the axillary fossa.

Three newer terms used to describe mastectomy are skin-sparing, areolar-sparing and nipple-sparing. These are all used when performing immediate first-stage reconstruction. A skin-sparing approach removes the nipple-areolar complex only, with the rest of the skin intact. The breast is then removed through the small opening. This is performed in women who are smaller-breasted (bra cup A, B or C) in an effort to maintain as much natural skin as possible to facilitate creation of the breast envelope that will be made during immediate reconstruction. Contraindications to skin sparing mastectomy are a tumor that is too close (within 2 mm) or is involving the skin, or, if the patient chooses not to undergo reconstruction.

Nipple- and areolar- sparing mastectomy are more controversial. While both are being performed with increasing frequency, long-term data about recurrence rates in these procedures is unknown. Because of concerns about increased recurrence rates in the residual tissue of the

nipple-areolar complex, patient compliance and long term surveillance must be agreed to before these procedures are offered.

Immediate reconstruction is being performed more frequently and is recommended by the Consensus Conference III.³ This option needs to be discussed and investigated by the patient prior to her cancer surgery. Reconstruction is performed by a plastic surgeon immediately after the mastectomy.

The three most common approaches to reconstruction are: tissue expanders Trans Rectus Abdominus Muscle flap (TRAM flap) and Latissimus Dorsi flap (LD flap). Tissue expanders, thick plastic pouches with a port for instilling saline, are placed beneath the pectoralis major muscle. Through the port, saline is injected into the expander, usually in 60- to 100-cc increments at one- to two-week intervals. This fluid stretches the pectoralis major muscle outward beneath the skin. Once the desired breast mound size has been reached, usually several months later, the patient is taken back to the operating room, the tissue expander is removed and permanent silicone or saline filled implants are placed. TRAM flap reconstruction is where the rectus muscle and surrounding fatty tissue from the abdomen is rotated beneath the skin, up to the chest wall to form a mound of tissue beneath the skin flaps after mastectomy. LD flap reconstruction takes the muscle and surrounding fatty tissue from the back, swings it around and places it beneath the skin flaps, usually along with a silicone implant to simulate a breast mound.

The final stage of reconstruction is placing a nipple and areolar complex on the breast mound once the final reconstruction has been achieved and the incisions have healed. This may be six to eight months after the last surgery. There are two options for nipple reconstruction. The surgical option is to take a triangle of skin, usually from the groin or lower abdomen, or to take excess lateral chest wall skin from the mastectomy site. The skin is puckered and reshaped to form an areola and nipple. The other option is to have a tattoo placed in the appropriate area of the breast mound. Tattoo artists are capable of creating a three-dimensional nipple and areola to create the illusion of an erect nipple.

Breast-Conserving Surgery

RM is a 45-year-old patient who was diagnosed with a small, low-grade breast cancer. RM had always disliked her breasts because of their large size and felt that her breasts got in the way of her regular activities. When her surgeon

offered her bilateral breast reduction with her lumpectomy and radiation, she was thrilled.

Breast conserving surgery (BCS), lumpectomy, partial mastectomy and quadrantectomy all describe the surgical removal of the breast cancer with a rim of healthy, normal breast tissue surrounding the tumor. After the breast tissue has been removed, it is recommended that efforts are made to spatially orient the specimen to allow pathologists to identify the closest margins according to their location. While there is no definite consensus as to the exact margin size that is acceptable in a complete resection of the tumor, tumor at the margin is unacceptable. Multiple studies have been published discussing acceptable margins, and 2 mm is considered adequate in most of the literature. Failure to obtain adequate margins does require return to surgery for re-excision of margins.

The traditional technique of performing breast conserving surgery entailed making a skin incision, usually directly over the cancer, removing the cancer with a rim of breast tissue, (in a lump), then closing the incision. In the first few weeks after surgery, the defect will fill with fluid, forming a seroma and filling the defect and giving an initially good cosmetic result. However as the seroma resolves, the surrounding breast tissue and skin overlying the defect is pulled down into the defect, creating a divot. Sometimes, this will pull the nipple areolar complex toward the defect and deform the breast. Radiation is given around this time and is often blamed for the deformity, when, in fact, it more likely is a result of surgery.

In the surgical approach to breast conserving surgery, there are now techniques that will ensure a better cosmetic outcome. Oncoplastic surgery combines sound surgical principles of oncology with aesthetic and reconstructive surgery. It addresses the need of the patient to have complete resection of the cancer and to obtain the best cosmetic result from that surgery. Oncoplastic surgery may be as minor as placing an incision in a part of the breast where the scarring is minimal, for example, at the areolar edge in a curvilinear fashion or at the inframammary fold. More advanced approaches include the development of tissue flaps in the breast and rotation of those flaps to fill in the defect left at the lumpectomy site and supporting the skin to prevent deformity. Oncoplastic surgery could also involve reducing the breast size with the lumpectomy and performing a mastopexy or 'breast lift,' and it may involve contralateral breast reduction for symmetry. Formal courses are offered to surgeons interested in providing these options to their breast cancer patients. Obtaining a cosmetically

pleasing result after oncoplastic surgery can contribute to a woman's overall sense of well-being after treatment.

Lymph Node Evaluation

BK is an 84-year-old who was diagnosed with a 1.5 cm invasive lobular carcinoma of the left breast. She underwent lumpectomy with axillary node dissection. All of the 25 lymph nodes removed were negative for cancer. Three months later, she complained of left breast and left arm swelling. She had developed lymphedema.

Whichever surgery a patient chooses to remove the breast cancer, evaluation of the axillary lymph nodes is always part of the procedure. It is well-established that breast cancer most commonly spreads via the lymphatic system to the ipsilateral axillary basin. Traditionally, axillary lymph node dissection was performed in which the first two of three levels of axillary lymph nodes were removed. With improved diagnostic evaluation, breast cancers are often found when the tumor is very small. The chance of axillary involvement in a breast cancer under 2 cm is about 20 percent. The risk of lymphedema with axillary node dissection is 15-20 percent. Formal axillary dissection for breast cancer has no greater benefit when compared to the risks of the procedure. When sentinel lymph node biopsy (SLNB) was successfully used in the evaluation of melanoma, studies began to apply the technique to breast cancers. In 1999, the National Comprehensive Cancer Network (NCCN) recognized the procedure as a diagnostic tool in the surgical treatment of breast cancer. In 2003, the NCCN recommended that sentinel lymph node evaluation be the preferred method of axillary node staging for an invasive breast carcinoma.⁸ SLNB for management of DCIS is currently recommended only when a mastectomy is performed.

SLNB requires the injection of technetium, isosulfan blue or methylene blue into the area around the tumor or the nipple-areolar complex. Depending on the protocol, after 15 minutes to several hours, the patient is taken for her definitive surgery. Evaluation of the sentinel lymph nodes is performed with a gamma scanner to identify migration of technetium, or careful intraoperative evaluation of the axilla to identify the thin blue stained lymphatic channels leading to a blue stained node. The affected node or nodes are removed and sent to pathology for immediate evaluation.

The methods of immediate evaluation of the node include frozen section and imprint cytology (touch preparations). A substantial body of evidence shows that sentinel lymph node biopsy performed for initial pathologic axillary staging is accurate and causes significantly less morbidity than

axillary dissection. In the first published randomized trial comparing SLN biopsy to conventional level I and II axillary dissection, there was no difference in survival between the two arms.⁹ Sentinel lymph node biopsy should now be considered “best practice” and is recommended for pathologic axillary staging for most patients with invasive breast cancer. Surgeon experience improves results of SLN biopsy, and adequate training and case volumes are required for surgeons performing SLN biopsy.¹

Patients undergoing SLN biopsy also need to be aware of the small risk of a false negative biopsy. It is recommended that surgeons should perform 20 SLN biopsies under direct mentorship by an experienced colleague or perform immediate completion axillary lymph node dissection at least 20 times with a false negative rate of no more than 5 percent. “Best practice” indicates that any patient with a sentinel lymph node found to be positive intraoperatively go on to completion level I and II axillary node dissection at the original surgery. Any lymph node with cancerous cells measuring 2 mm or greater are also recommended for completion axillary node dissection. For those lymph nodes with cancerous cells measuring 2 mm or less, there continues to be controversy as to best practice. Depending on several factors, options may be completion axillary node dissection or radiation therapy to the axilla.

In the event that axillary lymph nodes are proven cancerous by tissue sampling before surgery, SLNB is not necessary, and axillary node dissection is performed.

Radiation Therapy

JL felt she had no alternatives than to undergo mastectomy for her breast cancer treatment. Because she was an off-road trucker, she would not be able to undergo the six weeks of radiation and keep her job. When she was offered MammoSite placement instead of whole breast radiation, her future grew brighter.

Radiation therapy following breast conservation surgery has diversified. The gold standard for treatment of the breast is the delivery of 45-50 gray with a boost to the resected tumor bed. This treatment usually begins four weeks after surgery. Whole-breast

radiation typically involves four to six weeks of therapy, five days per week. Newer treatments have aimed at decreasing the time a patient undergoes therapy.

Hypofractionated radiation therapy is the same dose as whole breast radiation but given in 16 days as compared to 30 to 35 days of standard radiation therapy. The downside

is the increased potential for long-term problems with cosmesis. Hypofractionated radiation is typically performed in women with smaller breast size (A, B or C cups).

Accelerated Partial breast irradiation (APBI) is the delivery of radiation to the tumor bed and the margin of tissue surrounding it. The advantages of APBI include decreased overall treatment time and decrease in the radiation dose given to the surrounding normal tissues outside of the involved breast.¹⁰ Several different approaches have been used to deliver this radiation. The MammoSite breast brachytherapy catheter, one of the more popular methods to deliver APBI, is a balloon placed in the lumpectomy cavity with a core tube that houses the radiation. The seeds of radiation are placed in the core tube then removed twice per day for five days. After completion, the catheter is deflated and removed. Other forms of APBI include interstitial radiation and 3-D conformal radiation.

Intra-operative Radiation Therapy (IORT) is a new radiation treatment for breast conservation therapy currently in clinical trials. In the operating room, after the cancer is removed radiation is delivered directly to the lumpectomy site, the incision is closed. The goal is that a single dose delivered at the time of surgery would eliminate the need for radiation after surgery. When access to care is an issue, this may be an excellent alternative.

The American Society of Clinical Oncology (ASCO) has developed guidelines for selecting patients who should be offered these forms of radiation therapy both within and outside of clinical trials.

Conclusion

Awareness of changes in the surgical care of breast cancer helps the primary care provider counsel and care for their patients.

After reviewing the information regarding the diagnosis and treatment of breast cancer, it is apparent that the options at every phase of this disease are complex and some are controversial. The treatment of breast cancer is not cookbook or one size fits all. New data changes recommendations fairly frequently and navigating these changes at the provider level is challenging. To help address these complexities, breast care centers have begun implementing a multidisciplinary conference comprising the physicians and other caregivers involved in the treatment of breast cancer. In Sioux Falls, both Avera McKennan Hospital & University Medical Center and Sanford USD Medical Center hold weekly, one-hour conferences. Regular attendees include primary care providers, radiologists, sur-

geons, plastic surgeons, oncologists, radiation oncologists, pathologists, nuclear medicine physicians, geneticists, social workers, nurse navigators, researchers and physical therapists. Each patient presented has different issues regarding their care, which are discussed, and a specific plan is offered. One patient may be presented several times during the course of their treatment as issues arise. Discussing and planning the patients' care can illuminate issues that one provider may not have anticipated but may seem obvious to another due to their frame of reference. The result is more seamless care. Even though the patient may go to several offices and have many providers caring for them during their treatments, they understand that those providers sat down together and discussed their particular case.

The treatment of patients with breast cancer has many rewards. The greatest reward of all is watching the patient as she begins her journey, afraid and anxious about her future and even her survival, then to see her grow in strength and perseverance as she faces this disease and fights it. Being a part of that process is one of the many privileges of being a physician.

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The Role of Radiation Therapy in the Management of Breast Cancer in South Dakota

By Michael J. Swartz, MD; Daniel G. Petereit, MD

Abstract:

Radiation therapy has a pivotal role in the management of lung, breast, prostate, and colorectal cancer. It is frequently used with curative intent as a single treatment modality or, more frequently, combined with chemotherapy and/or surgery. Radiotherapy also provides effective palliation of symptoms caused by locally advanced or metastatic disease. In this article, we review the role of radiation in the treatment of breast cancer.

Introduction

Curative treatment options for women with early-stage breast cancer include either mastectomy or a breast-preserving approach, consisting of lumpectomy followed by adjuvant radiation therapy. In multiple prospective randomized trials, lumpectomy followed by whole breast irradiation (WBI) was found to yield equivalent results to a mastectomy, not only in terms of overall survival, but also in terms of local control and development of second primary cancers in the contralateral breast.¹⁻³ Because of these excellent results, as well as the overall superiority of the cosmetic results, the NIH released a consensus statement in 1990 recommending breast-conserving

treatment as a preferable option for women with early-stage breast cancer.⁴

Despite these endorsements, many women continue to choose a mastectomy.⁵ A 1992-93 Medicare survey reported that only 1.4 percent of Medicare patients underwent breast conservation in Rapid City.^{6,7} Although the reasons are many, distance from the cancer center is presumed to be a major impediment to breast conservation. Standard WBI requires a six-week course of radiation, which may be an impediment to breast conservation – particularly for women who do not live in close proximity to a cancer center. The inverse relation-

ship between breast conservation rates and the distance from the cancer center is supported by the observation of lower rates of breast preservation in rural areas.^{6,8}

Initial studies of breast preserving therapy also included treatment arms in which women underwent a lumpectomy only, with no WBI. These women experienced local failure rates three times higher than their counterparts who received WBI.^{1,2} Interestingly, the most common site of recurrence was near the lumpectomy cavity, and not in other quadrants within the affected breast. Furthermore, the rates of local failure in these uninvolved quadrants of the treated breast were similar to the rates of failure in the contralateral breast.² Taken together, these facts lead to a hypothesis that perhaps the benefit of post-lumpectomy radiation therapy is in the treatment of the lumpectomy cavity and adjacent tissue. Thus, perhaps WBI could be replaced with radiation of only the region around the lumpectomy cavity while preserving excellent local control rates.

Accelerated partial breast irradiation (APBI) is an umbrella term describing a radiation technique in which only the lumpectomy cavity and a rim of adjacent breast tissue are treated. Since only a portion of the breast is irradiated, larger fraction sizes are prescribed and can be administered twice daily. This results in overall treatment duration of five days rather than six to seven weeks, thus accelerating the treatment. Multiple techniques have been developed to deliver APBI, including external beam radiation and brachytherapy techniques. These strategies are all designed to minimize the amount of normal tissue exposed to radiation in order to deliver effective treatment to the lumpectomy cavity with minimal toxicity.

The data supporting APBI has been generated from single institutional phase I/II studies and a recently reported phase III study. The National Institute of Oncology in Budapest performed a randomized trial comparing whole breast radiotherapy (50 Gy in 25 fractions) to breast brachytherapy (5.2 Gy daily over seven days) targeting just the lumpectomy cavity. In this study, there was no difference in local failure or cosmesis at five years (N=258). Local control rates from single institutional series with up to eight to 10 years of follow-up are excellent and are consistent with historical control rates from WBI series.^{9,10} In series in which cosmetic results are reported, the rates of good to excellent results range from 75 to 100 percent.^{9,10} A large phase III trial in the U.S. is nearly finished accruing patients and is comparing six weeks of external beam radiotherapy to breast brachytherapy via a variety of techniques (anticipated accrual 3,000 women). Selection criteria for APBI include patients with tumors < 3 cm with negative margins and negative lymph nodes.

Techniques

APBI can be delivered using conformal EBRT targeting the lumpectomy cavity plus a small margin of normal breast tissue while sparing most of the normal breast. Breast brachytherapy, however, is the more widely utilized and long-established technique. There are two methods of brachytherapy to deliver APBI: intracavitary brachytherapy using a balloon-type-device inserted in the lumpectomy cavity; and multi-plane interstitial brachytherapy using multiple catheters placed directly through the cavity (see Figures 1 and 2). The interstitial approach is the only technique with long-term supporting data, and until recently, was most commonly used; however, only a few select institutions have maintained the expertise to perform interstitial brachytherapy.¹¹

MammoSite is a specialized catheter developed by Proxima

Figure 1: MammoSite Method of APBI

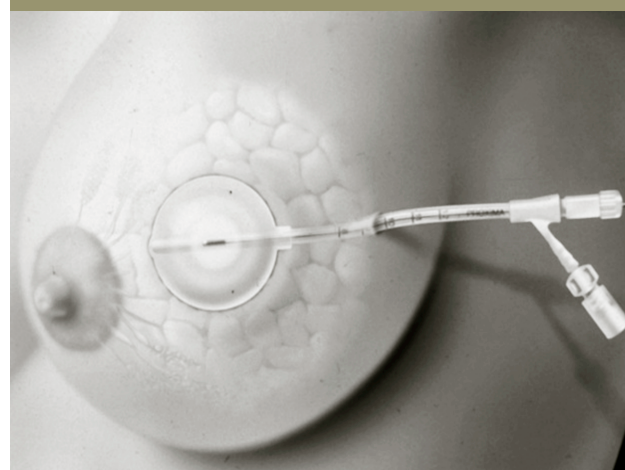
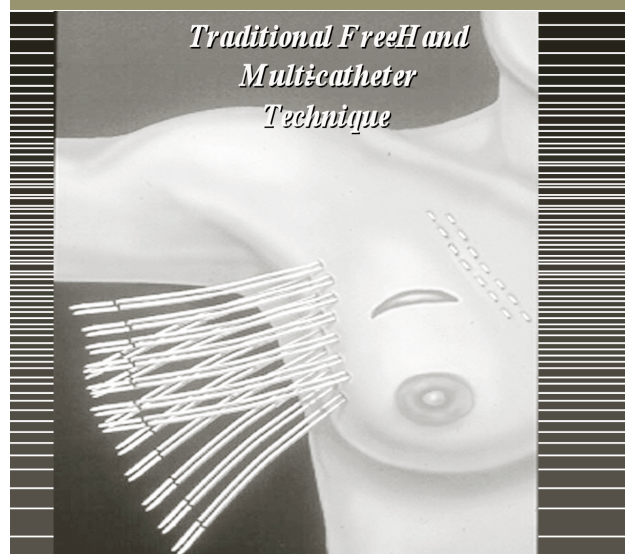


Figure 2: Interstitial Method of APBI



Therapeutics for delivery of APBI.¹² This device consists of a single catheter with an inflatable balloon at the closed end. The catheter is placed in the lumpectomy cavity, either at the time of lumpectomy, or more commonly in a separate outpatient procedure in the weeks following the lumpectomy. The balloon is then inflated to conform to the volume of the lumpectomy cavity. A radioactive HDR (high-dose-rate) source is then remotely placed at the center of the balloon to deliver appropriate dose to the surrounding lumpectomy cavity. The dose is prescribed to a volume 1 cm deep to the lumpectomy, leading to an inherent inhomogeneity not seen with multiple catheter interstitial implants. Like interstitial brachytherapy, the fractionation schedule is typically 3.4 Gy X 10 fractions over five days on an outpatient basis. Each treatment session is less than 15 minutes. The initial MammoSite data has demonstrated acceptable toxicity rates with cosmetic results comparable to the interstitial approach.¹² In early follow-up, there have been no local recurrences among 43 patients treated in the initial pilot study using the MammoSite technology.¹³ In the U.S., approximately 50,000 MammoSite devices have been placed – the majority off-study.

At the cancer center in Rapid City, the majority of patients undergoing APBI are treated on a phase II, NCI sponsored clinical trial, using either the intracavitary or interstitial technique.^{7,14,15} We have enrolled 32 patients on this study, many of whom lived a significant distance from Rapid City and would have chosen a mastectomy due to the inconvenience of six weeks of conventional external beam radiation if the brachytherapy option had not been available.

APBI is an emerging technique that can shorten the duration of treatment for women with early-stage breast cancer. The 10-year results for patients treated with interstitial brachytherapy are excellent, with local control rates comparable to external beam radiation. The first phase III trial using interstitial APBI demonstrated equivalent results to WBI at five years. While thousands of patients have been treated with the MammoSite device with encouraging preliminary data, close monitoring will be necessary to determine local control and toxicity rates. The implementation of these techniques may translate to increased rates of breast preservation while maintaining excellent local control and cosmesis. Given the geographic challenges faced by many South Dakotans, APBI is an especially important treatment option for women with early-stage breast cancer in South Dakota. All women with early stage disease should be referred for consideration of breast conservation with or without APBI before undergoing mastectomy.

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Prostate Cancer Screening: What's a Fellow to Do?

By Fredric H. Thanel, MD, MPH; Mark K. Huntington, MD, PhD

Abstract:

Prostate cancer is responsible for more than 27,000 deaths annually and is the most common non-skin cancer of men in North America. Over the years, a variety of screening approaches have been recommended. Despite increased sensitivity of the tests and effective public awareness campaigns, screening for this cancer remains surprisingly controversial. In this article, we review what makes a good screening test. We also review the evidence behind screening for prostate cancer and the current screening recommendations by a variety of reputable organizations.

Introduction

Few diseases alarm men more than the specter of prostate cancer. In addition to the implications of cancer in general, the perceived affects of prostate cancer and its treatment on sexual function and “manliness” are significant. It is not surprising that there is great interest in prevention of this condition. Yet, few conditions can match prostate cancer when it comes to controversy surrounding its screening. The focus of this article is to summarize the epidemiology of the condition, review the definition of a good preventative screen-

ing test, catalog current prostate cancer screening recommendations, evaluate the current evidence and attempt to generate a synthesis of all this. Four case scenarios, drawn from the authors' practice, illustrate the importance of this topic.

Case 1

A 63-year-old male smoker with untreated hypertension and a family history of prostate surgery in his father at age 92, complains of urinary frequency, especially at

night. His rectal exam shows a very large, smooth prostate. Although you discuss smoking cessation, he is reluctant to quit or even to treat his hypertension and declines colon screening. You convince him to take hydrochlorothiazide for his hypertension and an alpha blocker for his benign prostate hypertrophy symptoms. On subsequent visit, he reports improvement in his urinary frequency and has a fasting lipid panel done. When other screening tests are discussed, he declines.

Seven months later he is seen for flu-like symptoms and is found to have microscopic hematuria. CT scan shows enlarged periaortic lymph nodes, and his serum prostate-specific antigen (PSA) is 429. Prostate biopsy shows cancer with a Gleason score of 9. In less than one year from the diagnosis, he dies from complications of metastatic prostate cancer.

Would PSA screening have been a benefit to this patient?

Case 2

A 58-year-old with well-controlled diabetes mellitus and hypertension has PSA screening. His level returns at 7.8, and he is referred to urology for transrectal ultrasound-directed biopsies. Biopsies are benign, and subsequent PSA tests are the same or slightly lower than the initial value. He subsequently develops anxiety manifested by cancer phobias, persistent chest pains despite normal coronary angiogram and has lost his job.

Did PSA screening benefit him?

Case 3

A 67-year-old man has a slightly elevated screening PSA of 4.8. Subsequent biopsies are positive for low-grade prostate cancer, (Gleason class 6), confined to the gland. Of the many treatment options, he chooses radiation administered by seed implants. His PSA remains nearly undetectable, but he has intermittent constipation and diarrhea with rectal urgency, diagnosed as irritable bowel syndrome. He has erectile dysfunction that responds poorly to medications.

Did he benefit from screening and early detection of his disease?

Case 4

A 47-year-old man with previous gastric bypass surgery and a family history of prostate cancer in his father and maternal uncle had a PSA test done as part of a health care maintenance exam. His rectal exam revealed a possible nodule on the right. PSA is 5.9, repeated of 4.9, with a free fraction of 8 percent. He underwent trans-rectal biopsies (12 pattern), which showed Gleason 3+3 (6) grade adenocarcinoma involving 25

percent of the left lobe samples. There was no evidence of spread beyond the capsule. After being given multiple therapy options, he chose radical retro-pubic prostatectomy.

Will he benefit from the screening ?

Epidemiology and Risk Factors

Prostate cancer is the most common non-skin malignancy in men. Prevalence varies by age and method of detection: autopsy studies showing approximately 15 percent in age group 51-60 years, 25 percent in 61-70, and 40 percent or more in groups over age 70. Lifetime cumulative incidence is 18 percent in the post-PSA era.¹ It is estimated that more than 27,000 deaths in the U.S. are due to prostate cancer.² Despite the high prevalence of disease, most men die from vascular disease or other cancers.³ The lifetime proportional mortality for prostate cancer is 3 percent, (as compared to approximately 40 percent for cardiovascular disease). Symptoms are most commonly absent, but 5 percent present as overwhelming aggressive malignancy as described in Case 1.

The advent of PSA screening in the 1990s allowed detection of asymptomatic disease and resulted in a rapid rise in incidence of diagnosed prostate cancer.⁴ The incidence increase was paralleled by a jump in prostate cancer specific mortality.^{1,5} Health beliefs and financial incentives may influence some to describe an "epidemic" of cancer, rather than detection bias. Regardless, the incidence has reached a new, if somewhat higher plateau, and mortality has subsequently gone down.^{6,7}

Age is perhaps the most significant risk factor for developing prostate cancer. As described above, the disease tends to be nearly nonexistent in the fourth decade, increasing with the physiologic decrease in testosterone and other androgens.⁵

Hypogonadism is associated with higher risk, as well. Despite androgen sensitivity of prostate cancer and androgen deprivation as a treatment, men with low testosterone have an increased risk.⁵

African-American men appear to have a relative risk of 1.6 to as high as 3.0, and higher-grade disease; therefore, a higher mortality.⁸ Access to care may also play a role in the mortality gap. Asian men have a lower incidence and mortality than Caucasian.^{7,8} Whether these differences are genetic or environmental is uncertain, but race and ethnicity represent additional risk factors.

A family history of prostate cancer doubles the risk. Relative risk if one's father has prostate cancer is approximately 1.6; with a brother, it is approximately 2.5.⁸

There are other, less well-defined risks. High consumption of animal fat, especially red meat, may increase risk.⁹ One

prospective study showed no increased risk with red meat but with high processed meat consumption.⁸ Obesity seems to increase the risk of more aggressive high grade disease.⁷ Tallness is associated with higher risk and earlier onset.^{10, 11} Increased risk has been reported with high intake of alcohol, defined as >4 drinks per day, 5 days per week;^{1,12} decreased frequency of ejaculation, seven times per month, compared to >20;^{1,8} and military service, compared to age-matched non-military men.¹³ There appears to be no increased risk post-vasectomy, with benign prostate hypertrophy (BPH) or with prior history of prostatitis.

Controversy exists regarding the role of dairy intake, especially a possible increased risk with low-fat milk consumption and low dietary and serum calcium, and decreased risk with higher vitamin D intake and long-term sun exposure.¹⁴⁻²⁰ Results from large prospective cohort studies including Prostate, Lung, Colorectal, and Ovarian cancer screening (PLCO) study,²¹ National Institutes of Health –American Association of Retired Persons (NIH-AARP) study,^{22,23} the Health Professions Follow-up (HPF) study, 8 National Health and Nutrition Examination Survey (NHANES) data²⁴ and large European databases²⁵ are inconsistent in this regard. Despite these uncertainties, some epidemiologists have suggested that increasing vitamin D intake would prevent 100,000 cases of breast, colon and prostate cancer in the U.S. alone; preventing 75 percent of the deaths from these diseases. Case fatality rates for various cancers would be cut in half worldwide. These predictions seem grandiose, given the inconsistency of the data, and were likely projected from selected studies.²⁶ Nevertheless, sun exposure seems to have a consistent benefit. Whether supplemental vitamin D confers the same is controversial.^{27,28}

Possible protective factors include a diet high in phytoestrogens and isoflavones (soy),²⁹ lycopenes (processed tomatoes), selenium and vitamin E.⁸ In the Prostate Cancer Prevention Trial (PCPT), finasteride was shown to reduce the incidence of biopsy detected disease by 25 percent but doubled the number of men with high-grade disease.^{12,30}

A Web-based risk scoring system is available using PLCO data.³¹ Unfortunately, race or ethnicity was not uniformly identified in the PLCO trial, so risks are calculated for white men and must be adjusted for African-Americans or Asians.

Current Recommendations

A number of tests have been employed for prostate cancer detection. These include digital rectal exam (DRE), PSA, PSA velocity, free PSA levels and trans-rectal ultrasound directed biopsy (TRUS). Positive biomarker tests are defined, respectively, as PSA >4ng/mL, PSA rise of 0.75ng/mL/year over three years, and <25 percent free

fraction with a total PSA of 4-10ng/mL. Future tests might include MRI, biomarkers such as endothelin and semaphorin 3A, or genetic markers such as urinary gene PCA3, and others yet to be identified.³²

Befitting the poor performance of available tests and the lack of strong evidence of benefit (discussed below), there is little consistency in screening recommendations. These are summarized on Table 1. Whom and when to screen varies dramatically between guidelines issued by different groups.

The Evidence

Historically, screening for prostate cancer meant the DRE. As all clinicians and patients know, “digital” does not refer to computer technology in this application. Because of the discomfort as well as the lack of sensitivity, other modes of detection have been developed.³³⁻³⁵ Of these, only PSA has been implemented clinically on any scale, and virtually any discussion of laboratory screening for prostate cancer implies the use of PSA. In addition to its elevation in cancer, PSA can be slightly elevated in BPH and transiently elevated shortly after ejaculation and in prostate trauma or infection.^{1,36,37}

Hopes that laboratory detection might replace detection on physical exam have not been realized. Studies of men diagnosed with prostate cancer have found that despite having PSA levels well below the cut-off levels recommended by several guidelines, a considerable proportion had aggressive pathological features at the time of surgery. A number of potential explanations for this exist.³⁸ As a result, many guidelines that favor prostate cancer screening continue to include the DRE as an important component of early prostate cancer detection.³⁹⁻⁴¹

As seen above, the availability of a screening intervention capable of detecting a pre-symptomatic condition is only part of the framework for determining screening policy. The detection must result in improved outcomes. It is quite challenging to design a clinical trial to evaluate the effectiveness of prostate cancer screening. It has been estimated that substantially more than 200,000 participants would be required to demonstrate differences in both cancer-related and all-cause mortality. Studies of more manageable size require lengthy durations, and even then sacrifice discriminatory power.⁴² Intermediate endpoints, while useful surrogates for cancer-related mortality,⁴³ don't factor in screening-related morbidity and mortality. Despite these challenges, such investigations proceed. Recently, two important ones released their reports.^{6,36,44}

The long awaited PLCO trial, which enrolled nearly 80,000 participants, compared annual PSA/DRE to “usual care.” No mortality differences were found at seven to 10 years.⁶ Limitations of this study included a low overall mortality rate, making differences between subgroups difficult to

Table 1. Comparison of recommendations by several expert groups. NR indicates “no recommendation for or against”

Organization	Screen?	Age	Comments:
American Academy of Family Physicians ⁵⁸	NR No	<75 >75	The current evidence is insufficient to assess the balance of benefits and harms of prostate cancer screening in men younger than age 75. The AAFP recommends against screening for prostate cancer in men age 75 years or older.
American Cancer Society ⁵⁹	Ambiguous: No, officially, but offer DRE and PSA annually; default is test	50 (40-45 in high risk men)	ACS does not support routine testing for prostate cancer at this time. ACS does believe that health care professionals should discuss the potential benefits and limitations of prostate cancer early detection testing with men before any testing begins. This discussion should include an offer for testing with the prostate-specific antigen (PSA) blood test and digital rectal exam (DRE) yearly, beginning at age 50, to men who are at average risk of prostate cancer and have at least a 10-year life expectancy. This discussion should take place starting at age 45 for men at high risk of developing prostate cancer. This includes African American men and men who have a first-degree relative (father, brother, or son) diagnosed with prostate cancer at an early age (younger than age 65). This discussion should take place at age 40 for men at even higher risk (those with several first-degree relatives who had prostate cancer at an early age). If, after this discussion, a man asks his health care professional to make the decision for him, he should be tested (unless there is a specific reason not to test).
American College of Physicians ⁶⁰	No		Rather than screening all men for prostate cancer as a matter of routine, physicians should describe the potential benefits and known harms of screening, diagnosis, and treatment; listen to the patient's concerns; and then individualize the decision to screen. Indirect evidence based on decision models suggests that if screening and treatment prove beneficial, men who are 50 to 69 years of age will enjoy most of the benefit from screening. Men older than 69 years of age will gain little from screening. It is important to note that because additional information is obtained from digital rectal examination (for example, information on occult blood in the stool, masses, rectal fissures, fistulas, and hemorrhoids), digital rectal examination is valuable for evaluating conditions other than prostate cancer. In issuing a general recommendation against the routine use of such tests, the College acknowledges that it may be reasonable for a physician to recommend that an individual patient be screened for prostate cancer. The area of greatest controversy is screening for men who are between 50 and 69 years of age. For men in this age group, the physician should be particularly guided by the patient's preference and by the physician's and the patient's interpretation of the risk-benefit equation. Clinicians should be prepared to discuss this issue with their patients, to provide counseling on an individual basis, and to document these discussions. Potential benefits must be balanced against the potential morbidity and mortality related to treatment by radical prostatectomy or radiation therapy. Black men and men with a family history of prostate cancer should be made aware of their higher lifetime risk. However, available evidence does not suggest that they should be cared for differently from men at average risk.
American College of Preventive Medicine ⁶¹	No DRE Yes PSA in high risk men	40-45 in high risk	Pending resolution of ongoing controversies, screening for prostate cancer among African-American men and those with a family history of prostate cancer has the potential to detect treatable forms of disease that are more likely to occur in these groups than in the general population. While the usual age for prostate cancer screening is between 50 to 70 years in average risk men, it has been suggested that those who are at high risk may benefit from earlier screening beginning at age 45, while higher-risk men (those with two or more first-degree relatives with prostate cancer before age 65) be screened at age 40.
American Urological Association ⁶²	Yes DRE and PSA in well-informed men	40	The decision to use PSA for the early detection of prostate cancer should be individualized. Men should be informed of the known risks and the potential benefits of early screening. Early detection and risk assessment of prostate cancer should be offered to men 40 years of age or older who wish to be screened. Men who wish to be screened for prostate cancer should have both a PSA test and a DRE.
Cochrane Collaboration ⁶³	NR		There is insufficient evidence to either support or refute the routine use of mass, selective or opportunistic screening compared to no screening for reducing prostate cancer mortality. Currently, no robust evidence from randomised controlled trials is available regarding the impact of screening on quality of life, harms of screening, or its economic value.
European Urological Association ⁶⁴	No		Current published data are insufficient to recommend the adoption of population screening for prostate cancer as a public health policy due to the large overtreatment effect. Before screening is considered by national health authorities, the level of current opportunistic screening, overdiagnosis, overtreatment, quality of life, costs, and cost-effectiveness should be taken into account.
Institute for Clinical Systems Improvement ⁶⁵	NR		Evidence is currently incomplete and/or high burden and low cost, therefore left to the judgment of individual medical groups, clinicians and their patients: Prostate-specific antigen (PSA) screening and digital rectal exam of the prostate.
University of Michigan Health System ⁶⁶	Yes PSA, annually	>50 (40 in high risk men)	Clinicians who screen for prostate cancer should share decision making with patients, giving objective information about the potential risks and benefits of screening. For men > age 50, consider initiating PSA screen. For men with positive family history and for African Americans, consider starting PSA screening at age 40. Stop when life expectancy is less than 10 to 15 years
US Preventive Services Task Force ⁶⁷	No DRE NR PSA	<75 only	Given the uncertainties and controversy surrounding prostate cancer screening in men younger than age 75 years, a clinician should not order the PSA test without first discussing with the patient the potential but uncertain benefits and the known harms of prostate cancer screening and treatment. Men should be informed of the gaps in the evidence and should be assisted in considering their personal preferences before deciding whether to be tested. If treatment for prostate cancer detected by screening improves health outcomes, the population most likely to benefit from screening will be men age 50 to 74 years. Even if prostate cancer screening is determined to be effective, the length of time required to experience a mortality benefit is greater than 10 years. Because a 75-year-old man has an average life expectancy of about 10 years, very few men age 75 years or older would experience a mortality benefit. Similarly, men younger than age 75 years who have chronic medical problems and a life expectancy of fewer than 10 years are also unlikely to benefit from screening and treatment.

detect, and the fact that a fair number of “usual care” participants also received screening on an individualized basis.

PLCO found poor interobserver agreement in DRE, even among urologists. Abnormal DRE, defined as any asymmetry, nodule, stony-hard gland or loss of lateral sulcus, occurred in 7.5 percent with a positive predictive value (PPV) for cancer on biopsy of 34 percent. Eleven percent of tumors found on DRE had a normal PSA, and 30 percent had spread beyond the capsule at the time of exam. PSA, using the usual cutoff of 4.0 ng/dl, showed a sensitivity of 40 percent for Gleason class 7 or higher tumors, using histological diagnosis on 12 core transrectal biopsy as the reference standard. Sensitivity for lower grade disease was

even worse, at 20 percent. Specificity was likewise poor, at 85 percent. Even the gold standard for the PLCO study, TRUS, has a relatively low sensitivity. Most urologists recommend a grid of 10 to 12 biopsies, sampling multiple areas of the gland in addition to sonographically suspect areas. As noted in Case 4, it is common for positive biopsies to occur in areas opposite an abnormal DRE or a suspicious hypoechoic area.

Across the pond, the European Randomized Study of Screening for Prostate Cancer (ERSPC) found a somewhat different result. In a study involving 182,000 men aged 50 to 74, they found that PSA-based screening reduced the rate of death from prostate cancer by 20 percent but was

associated with a high risk of overdiagnosis.³⁶ In their hands, the NNS was 1410, with 48 being the NNT. It is interesting to note that this 20 percent reduction is less than the 25 percent the study was designed to show or exclude.⁴⁴

PSA screening is associated with psychological harms, and its potential benefits remain uncertain.⁴⁵ Treatment, which is pursued by most Americans with an elevated PSA46, has adverse effects.^{47,48} An accurate assessment of the comparative effectiveness and harms of treatments for localized prostate cancer is difficult because of limitations in the evidence.⁴⁹ There is no robust evidence from randomized controlled trials for the impact of screening on quality of life, harms of screening or its economic value.^{50,51}

In an effort to minimize overtreatment, ERSPC investigators developed a nomogram for the identification of indolent disease.⁴⁴ The application of this nomogram allows “active observation” in place of therapeutic intervention for about 30 percent of screen-positive patients. Still, they point out that “many pending problems still have to be resolved prior to the introduction of population-based screening as a worldwide healthcare policy.”⁴⁴ Among these include selection of the appropriate risk calculator. Application of such nomograms requires comparison of the risk factors known, and those unavailable, of the study population to those of the patient. When this is not done, dissimilarities result in grossly inaccurate predictions for individual patients.⁵²

Thus, we have two large, well-designed studies, PLCO and ERSPC, which came up with disparate answers concerning

the effect of prostate cancer screening on cancer-related morbidity and mortality. Neither effectively evaluated all-cause morbidity and mortality between the screened and non-screened groups, so offer no information on net benefit or harm of screening. Needless to say, these studies have not ended the debate over prostate cancer screening!⁵³

A variety of patient education modalities have been employed to aid in informed consent, including written, video- and Internet-based. Studies have demonstrated that the various methods are essentially equivalent.⁵⁴ Prostate cancer screening decision tools can enhance patient knowledge, decrease decisional conflict and promote greater involvement in decision-making. However, in the absence of good outcome measures, truly “informed” consent in the decision to screen or not screen remains elusive.⁵⁵

Conclusion

We encourage residents in our program to follow the U.S. Preventative Services Task Force recommendations (Table 1): prostate cancer screening is optional and should be considered only after educating the patient to the controversial nature of the tests, treatments and the disease. This will likely decrease the screening rate in a given practice. In one study patient education resulted in a decrease in those opting for screening from 55 to 34 percent.^{56,57} As part of these guidelines, PSA screening is not offered to men over 75 or those with a life expectancy less than 10 years, as it is likely harmful. Universal prostate cancer screening cannot be recommended based upon currently available evidence, though with medical advances, an effective screening test and strategy may someday emerge.

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Please note: Due to limited space, we are unable to list all 64 references. You may contact South Dakota Medicine at 605.336.1965 for a complete listing.



Surgical Treatment of Prostate Cancer: What to Do?

By Paul Eckrich, MD

Abstract:

Although there is a paucity of prospective studies comparing surgical treatment of prostate cancer to other treatments, surgical treatment is usually recommended for men with a good chance for cure who have ten or more years life expectancy. Proper selection of men undergoing surgery is critical to achieve cures and minimize side effects. Laparoscopic and robotic prostatectomy have become the predominant approach for surgery despite a very slow learning curve, greater expense, and higher dissatisfaction rates compared to more traditional approaches. Outcomes using a laparoscopic or robotic approach are equivalent to open methods only after 250 to 1000 procedures. In this era of increasing medical costs, utilization of robotic and laparoscopic approaches to prostatic cancer surgery needs to be critically examined.

Discussion

The American Cancer Society estimates there will be 192,280 newly diagnosed prostate cancers and 27,360 prostate cancer deaths in the United States in 2009. This makes prostate cancer the most common non-skin cancer and the second-highest cause of cancer deaths in men in the United States. More than one in six men will develop prostate cancer in their lifetime, and one in 35 will die from it.¹

The main goal of radical prostatectomy (RP) is to cure the cancer and prevent death and morbidity from the disease. The fact that many more men will die from concurrent disease than from prostate cancer is well understood, so selection of men who will benefit from surgery is paramount. Preservation of quality of life with regards to side effects is critical, as quality of life can be seriously affected by RP.

All treatments for prostate cancer adversely affect sexual function. Nerve-sparing RP has been shown in age-adjusted studies to have no statistical difference compared to external beam radiation (ERB) or brachytherapy. Sexual function tends to remain stable after RP but can continue to deteriorate after ERB over time.² It remains controversial whether nerve-sparing RP is associated with increased cancer at the surgical margins compared to non-nerve-sparing RP. Some studies show no statistical increased margin rates while others do. In my own personal experience, I have had many individuals who were found to have tumor in the neurovascular bundle without any other evidence of capsular penetration or local spread. Nerve-sparing procedures tend to be most successful in young men with good sexual function prior to the surgery. Preservation of erectile function in older men or in men who have poor pre-operative erections has had limited success at best.

Urinary incontinence has been reported in 14 percent to 18 percent of men undergoing RP, though there is no uniform definition of incontinence.³ Incontinence is worst immediately after surgery and will improve up to one year after the procedure, with severe incontinence commonly reported at less than 5 percent for RP.

RP provides more accurate staging than needle biopsy with the latter understaging up to 30 percent of the time. Patients on active surveillance have a 52 percent to 60 percent chance of initiating treatment within five years and have the risk of disease progression, consequently increasing the potential risk of poorer outcomes. Improved staging with RP identifies patients at higher risk with more advanced disease who will need more aggressive treatment.

There are no prospective studies that definitively show a difference in active treatments. However, at least one study shows survival benefit of RP over watchful waiting.⁴ Retrospective studies have shown radical prostatectomy to have superior ten-year cancer specific survival and superior overall mortality when compared to EBR and hormone deprivation therapy (HDT). Data from the Prostate Strategic Urologic Research Endeavor (CaPSURE) looked at 8,321 men with localized prostate cancer. Survival analysis was adjusted for age, comorbidities and Cancer of the Prostate Risk Assessment score. In the study, 1,466 men died during follow-up, with 261 from prostate cancer with mean time to death at 6.8 years. Compared to RP, the risk of cancer-specific mortality for EBR was almost two times higher and more than three times higher for HDT. These differences were more pronounced with high-risk men. Outcomes for all-cause mortality showed the RP group superior to ERB and HDT.⁵

There is no specific age cut-off for performing RP. Life expectancy of eight years or less shows no advantage with

RP, EBR or brachytherapy. Urologists traditionally have recommended RP when life expectancy is greater than ten years, due to the theoretical risk of recurrence with EBT or brachytherapy. However, long term data is lacking.

Although there is a paucity of long-term prospective studies comparing different treatment modalities, most urologists believe that surgical removal of the prostate affords the best survival in men who have ten or more years of life expectancy. Recent trends have shifted toward "minimally invasive" laparoscopic or robotic methods (LP) from the traditional radical retropubic prostatectomy (RRP) and lesser performed radical perineal prostatectomy (RPP). Up to 85 percent of radical prostatectomies are estimated to be done using minimally invasive approaches.

One assumes that with such a significant shift in surgical approaches, there must be significant benefits in survival, side effects or cost. Data comparing the three approaches shows that in experienced hands, LP is at best equivalent and does not provide improved outcomes in cures or complications and does so at increased cost.⁶⁻⁹ There is also a steep learning curve, requiring at least 250 and up to 1,000 cases before the curve levels off.^{10,11} Intuitive Surgical, who markets robotic systems, requires a physician to have done only 20 cases in order to proctor other physicians learning this approach. It has been suggested that this is far from ideal for ensuring trainee competency.¹²

The radical perineal prostatectomy was first described by Hugh Hampton Young in 1905. It is also currently the least performed approach, having fallen out of favor with the utilization of pelvic lymph node dissection, which favors the retropubic or LP approach.

Pelvic lymphadenectomy should be performed in men at high risk for nodal disease and has been shown to offer a survival benefit.¹³ Whether pelvic lymph node dissection in men with low risk has benefit remains controversial. Lymph node dissection is associated with increased cost and risks of lymphocele formation, deep venous thrombosis, scrotal and distal extremity edema. Omitting pelvic lymphadenectomy had been suggested in patients with a 3 percent to 5 percent chance of nodal disease.¹⁴ With the trend toward lower stage/grade cancers, the majority of men presenting with prostate cancer would not need pelvic lymph node dissection, eliminating that disadvantage of the RPP.

RPP has equivalent outcomes and complications to RRP and LP. RPP has the advantages of a minimally invasive procedure with respect to blood loss, complications, hospitalization and time to full activity. It does it at substantially less cost than LP.^{9,15-18} This difference is even more pronounced if one factors in the cost of pelvic lymphadenectomy.

In this era of increasing costs and the need for cost containment, utilization of limited resources must be critically examined. Assuming equivalence in outcomes and complications of the various surgical approaches, we must be sure we are getting the most for our health care dollar. LP has at best equivalent outcomes to RRP and RPP at significantly higher costs and has 4.4 times the dissatisfaction rate of RRP.¹⁹ LP also has a very steep learning curve. LP

still does not have improved outcomes when the learning curve has been met. Can we financially justify LP over the more traditional approaches?

In determining who will benefit from any surgical approach and which approach to use, one must consider the plethora of incomplete and conflicting data. Until better served, we must practice the art more so than the science of medicine.

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Screening for Colorectal Cancer

By Gail Waldbly, MD; John J. Ryan, MD, FACS

Abstract:

Screening for cancer is performed in order to detect unsuspected cancers in an asymptomatic population. Screening is justified for the detection of precancer and cancer when the screening test is safe and the disease has a prevalence that justifies the cost and also when testing has low rates of false positive results. Screening can lead to the early diagnosis of specific cancers which, when treated, can result in a prolonged life span. Colorectal cancer is the third-most common form of cancer in the Western world. Many of these cancers are thought to arise from precancerous lesions in the colon, such as adenomatous polyps. The specific advantage of colorectal cancer screening include the earlier detection of such cancers, the detection of benign conditions such as polyps that can predispose the cancer and the potential for earlier and curative therapy in these patients. Screening for colorectal cancer is indicated where life expectancy is greater than five years and, in general, for people under 75 years of age.

Introduction

Screening for colorectal cancer (CRC) saves lives, by preventing cancer, and by detecting cancer at earlier, more curable stages. Ninety percent of patients survive if their CRC has not spread beyond the bowel wall.¹ Unfortunately, only 60 percent of CRC in the United States is detected before it spreads outside the bowel wall.²

Compliance with CRC screening is less than optimal, both in South Dakota and nationwide. Only 20 percent of adults over age 50 reported that they had fecal occult blood testing (FOBT) between 2006 and 2008. Only 62 percent of adults over 50 reported that they had ever had a flexible

sigmoidoscopy or colonoscopy by 2008.³

CRC Prevalence

Approximately 147,000 individuals develop CRC each year in the U.S. One-fourth develop rectal cancer; the other three-fourths develop colon cancer.⁴ Most CRC occurs in individuals over age 50; the median age at diagnosis is 71.⁵ South Dakota expected 430 new CRC cases in 2008.⁶ Approximately 50,000 individuals die from CRC each year in the U.S.,⁷ with 160 CRC deaths expected in South Dakota in 2008.⁶ (Note: Actual South Dakota data had not yet been released at the time of publication, hence use of the word “expected.”) In the U.S., CRC incidence⁸ and death rates are declining,⁹ most likely due to CRC screening.

History of CRC screening

In 1926, Dukes reported that carcinomas of the colon and rectum arise in adenomas.¹⁰ In 1951, Jackman and Mayo coined the term adenoma-carcinoma sequence.¹¹ Both reports set the stage for CRC prevention by removing precancerous polyps. In 1948, the University of Minnesota Cancer Detection Center instituted rigid sigmoidoscopic screening for rectal cancer. They discovered rectal cancer in 0.16 percent of 12,000 patients they screened,¹² a very low yield.

In 1963, Overholt performed the first flexible sigmoidoscopy in the U.S.,¹³ and In 1965 Olympus produced the first prototype forward-viewing fiberoptic colonoscope.¹⁴ In 1970, Smith Kline and French Laboratories launched the Hemocult™ guaiac fecal occult blood test (gFOBT).¹⁵

The American Cancer Society published their first formal CRC screening guidelines for average-risk adults in 1980, recommending digital rectal exam (DRE), fecal occult blood testing (FOBT) and proctosigmoidoscopy.¹⁶ In 1981, Eddy reported that one-sixth of all colorectal cancers were within reach of a digital rectal exam.¹⁷ By the 1980s, the flexible sigmoidoscope had replaced the rigid proctoscope.¹⁷

The next advancement was the videocoloscope, which displayed an image on a video monitor,¹⁸ first produced by Welch Allyn in 1983. Then, in 1993, David J. Vining, MD, performed the first virtual colonoscopy, or CT colonography, at the Wake Forest University Health Sciences Center in Winston-Salem, NC.¹⁹

In 1997, the American Cancer Society added CRC screening recommendations for high-risk individuals, based on an interdisciplinary panel study by the American College of Gastroenterology, American Society for Gastrointestinal Endoscopy, American Gastroenterological Association, American Society of Colon and Rectal Surgeons and Society of American Gastrointestinal Endoscopic Surgeons.

Screening Recommendations for Average Risk Individuals over 50

The American Cancer Society, the U.S. Multi-Society Task Force on CRC, and the American College of Radiology recommend:

Tests to detect adenomatous precancerous polyps and CRC:

- Flexible sigmoidoscopy every 5 years, or
- Colonoscopy every 10 years, or
- Double-contrast barium enema (DCBE) every 5 years, or
- CT colonography (CTC), or virtual colonoscopy, every 5 years

Tests to detect CRC:

- Guaiac-based fecal occult blood testing, high

sensitivity, yearly, or

- Fecal immunochemical testing (FIT), high sensitivity, yearly, or
- Stool DNA testing, at an undetermined interval

The U.S. Preventive Services Task Force (USPSTF) recommends screening for CRC, with fecal occult blood testing, sigmoidoscopy, or colonoscopy, beginning at age 50 years, and continuing until age 75 years. The USPSTF does not recommend routine CRC screening after age 75, if the patient has had negative CRC screening since age 50. The USPSTF does not recommend any CRC screening over age 85.

In 2009, Norwegian researchers reported that in over 55,000 individuals followed over seven years, flexible sigmoidoscopy screening did not reduce the incidence of CRC. These results may decrease use of this procedure for CRC screening.

Inherited Risk Factors, Exceptions Which Change Screening Recommendations

- African Americans: Start screening at age 45.
- First degree relative <60, with CRC or advanced adenomas*: Start screening at age 40, or 10 years earlier than the age at which the youngest affected relative was diagnosed, and repeat every five years.¹¹
- Two first degree relatives, any age, with CRC or advanced adenomas*: Start screening at age 40, or 10 years earlier than the age at which the youngest affected relative was diagnosed, and repeat every five years.¹¹
- Hereditary Non-Polyposis (HNPCC) gene carrier: Colonoscopy every two years from age 20 to 25 until age 40, then yearly.¹¹
- Familial Adenomatous Polyposis (FAP): Start flexible sigmoidoscopy or colonoscopy in the early teens. Repeat yearly, until has colectomy.¹¹

*Advanced adenomas are ≥ 1 cm or contain high grade dysplasia or villous elements.

Personal Risk Factors, Which Require More Frequent Colonoscopy

- Ulcerative colitis and Crohn's colitis: Start colonoscopy eight to 10 years after onset of colitis symptoms.
- Personal history of advanced adenomas: Repeat colonoscopy interval depends on polyp details.
- Personal history of CRC: If no colonoscopy to cecum before surgery, colonoscopy within six months; otherwise, colonoscopy one year after surgery. If normal, repeat in three years. If again normal, repeat every five years.
- History of rectal cancer, after anterior resection: Consider adding flexible or rigid proctoscopy every six months for first five years.

Colonoscopy

Colonoscopy prevents CRC by finding and removing most precancerous polyps and by detecting those at higher risk. Screening colonoscopy should find precancerous polyps in ≥ 15 percent of women and ≥ 25 percent of men over 50. Polyp detection rates correlate with time spent examining the colon during scope withdrawal. Poor bowel preparation decreases polyp detection. Split-dose bowel preparation, with one-half the prep the night before colonoscopy and the second half four to five hours before colonoscopy, improves visualization, especially during colonoscopies later in the day.¹¹

Flexible Sigmoidoscopy

The flexible sigmoidoscope is 60 cm in length and usually reaches the distal descending colon during the procedure. Approximately half of CRC in the U.S. arises distal to the descending colon, within reach of a flexible sigmoidoscope.

Virtual Colonoscopy (CT Colonography)

CT colonography creates three-dimensional, fly-through images. CT colonography detects 90 percent of polyps ≥ 1 cm and may detect disease outside colon. CT colonography misses most polyps ≤ 5 mm.¹¹

Disadvantages of CT colonography include that it exposes the patient to radiation, polyps can't be removed during the procedure and CT colonography is recommended every five years, twice as often as colonoscopy.^{8,11}

Fecal Tests

Fecal tests detect CRC; they cannot prevent CRC.¹¹

Double-Contrast Barium Enema

Double-contrast barium enema CRC screening is declining. The American Cancer Society, the U.S. Multi-Society Task Force on CRC and the American College of Radiology include double contrast barium enema as a screening option.⁸ The American College of Gastroenterology does not recommend double contrast barium enema,¹¹ nor does the USPSTF include it among its recommendations.²³ Screening double contrast barium enema should be performed every five years, twice as often as colonoscopy.⁸

Conclusion

Colorectal cancer is a common cancer, and when detected early, appropriate treatment can result in long-term survival. Understanding the nature of this cancer has elucidated the polyp-cancer neoplasia sequence. Technological advances such as the forward viewing fiberoptic colonoscope have allowed cost-effective screening in appropriate age groups at risk, thus facilitating early and potentially curative intervention. Although recommended, compliance with population screening programs has remained suboptimal. Newer imaging techniques potentially offer alternative

techniques, which may increase compliance but, as yet, do not match colonoscopy for the detection sensitivity of small polyps. Tissue diagnosis is not available with virtual imaging. Recent evidence has all but eliminated flexible sigmoidoscopy alone as an appropriate screening tool. Fecal occult blood testing should be regarded as a technique for detecting colorectal cancer, not as a screening technique to identify those patients at higher risk for cancer (i.e., patients with colonic polyps). Major efforts are needed to increase compliance rate with screening. Screening has been a major advance in the early detection of this common and curable cancer which, if untreated, remains uniformly fatal.

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Please note: Due to limited space, we are unable to list all 21 references. You may contact South Dakota Medicine at 605.336.1965 for a complete listing.



Increasing Colorectal Cancer Screening in South Dakota

By Laura Seeff MD; Norma Schmidt, MA

Colorectal cancer is the second-leading cause of cancer deaths among U.S. adults among cancers that affect both men and women, and primarily affects persons age 50 and older.¹ In 2005, more than 141,000 new cases of colorectal cancer were diagnosed across the U.S., and 53,000 people died from the disease.¹

Screening for colorectal cancer has a tremendous potential to save lives. It is estimated that 76 to 90 percent of new colorectal cancer cases would be reduced, and 70 to 90 percent of colorectal cancer deaths reduced if all precancerous colorectal polyps were identified and removed.^{2,3} Most colorectal cancers develop from precancerous polyps, or growths inside the colon, which slowly develop into colorectal cancer. Screening tests can identify and remove polyps, preventing the development of colorectal cancer altogether, and can also detect early cancers, which can be treated more effectively and at a lesser cost. Unrealized financial savings are also possible through the prevention and earlier detection of colorectal cancer.

Although regular screening has been shown to reduce incidence and mortality from this disease, only approximately half of U.S. adults have been screened for colorectal cancer as recommended, and disparities in the use of screening tests exist.⁴ Screening for colorectal cancer is complex, since multiple screening tests are acceptable, each with a different recommended interval and each performed by different types of health care specialists. In an effort to better understand how to structure and implement population-level colorectal cancer screening and to explore the most viable and cost-effective models, the U.S. Centers for Disease Control and Prevention (CDC) initiated a four-year colorectal cancer screening demonstration program in 2005 in five sites across the U.S. designed to reach low-income persons aged 50 to 64 who are under or uninsured for colorectal cancer screening.^{5,6}

In 2009, CDC substantially expanded this effort and recently awarded \$600,000 to the South Dakota Department of Health for FY 2009 to develop a statewide

colorectal screening program, as part of a 26 state/tribal program in 22 states and four tribal organizations (Figure 1). The new South Dakota program is building on the infrastructure developed through the "All Women Count!" breast and cervical cancer screening program but will include both men and women over age 50.

The five-year, 26-site CDC Colorectal Cancer Control Program has two primary goals: 1) The provision of direct screening services to populations at greatest need; and 2) Attention to increasing colorectal screening rates among the U.S. population age and older nationwide. CDC plans to substantially increase the program focus on population-based activities in order to achieve a screening rate for the U.S. population age 50 and older of 80 percent by 2014. This means that in addition to providing financial support for screening uninsured and underinsured individuals, non-screening components will be required to increase public awareness of the importance of colorectal screening, increase physician recommendation and referral for colorectal screening and increase coverage of colorectal cancer screening by health coverage systems to work to increase screening rates in both the insured and uninsured population.

The focus of the program in South Dakota is on average-risk persons age 50 and older, regardless of income and insurance status and regardless of who is paying for the services delivered. For those persons for whom screening and diagnostic follow-up reimbursement is provided with federal funds, eligibility criteria are based on income, age and indication.

For screening, average-risk persons are those with no symptoms suggestive of gastrointestinal disease, no personal or family history of colorectal polyps or cancer, no inflammatory bowel disease (Crohn's disease or ulcerative colitis) and no evidence of genetic syndromes associated with colorectal cancer.

For surveillance, persons are those with a personal history of polyps or colorectal cancer and can receive services beginning at age 40. The USPSTF recommendations do apply to those with first-degree relatives who have had colorectal adenomas or cancer, although for those with first-degree relatives who developed cancer at a younger age or those with multiple affected first-degree relatives, an earlier start to screening may be reasonable.

The South Dakota program and its medical advisory boards (MABs), will make general program eligibility determinations for clients with family history of colorectal cancer, but

they are eligible for services from CDC's perspective.

By June 30, 2014, we anticipate that 80 percent of South Dakota adults over age 50 will have been screened for colorectal cancer. Current Behavioral Risk Factor Surveillance Survey (BRFSS) data indicate that in 2008, 79.3 percent of adults age 50 and older have not had a blood stool test with the past two years. In addition 37.6 percent of adults age 50 and older have never had a sigmoidoscopy or colonoscopy.⁷ Of particular interest to program planners is 2006 BRFSS data that indicate 33.7 percent of people over age 50 had health care providers who did not recommend colorectal screening.⁷ However, of those whose provider recommended screening, 78 percent had the colorectal test. Individual health care providers will be critical to achieving our program goals.

Clinical guidelines developed for the South Dakota Colorectal Cancer Control Program will be developed by a medical advisory board comprised of specialists, internists, family doctors, midlevel practitioners and health systems representatives. The final guidelines will be consistent with the Screening for Colorectal Cancer Recommendation Statement of the U.S. Preventive Services Task Force (USPSTF), October, 2008.⁸ The USPSTF recommends screening for colorectal cancer using fecal occult blood testing, sigmoidoscopy, or colonoscopy in adults, beginning at age 50 and continuing until age 75.

The USPSTF recommends against routine screening for colorectal cancer in adults aged 76 to 85 if previous screening tests have been normal. Certain considerations support colorectal cancer screening in an individual patient older than age 75. The specific considerations to be considered for screening these individuals will be described by the Program's MAB.

The USPSTF concludes that the current evidence is insufficient to assess the benefits and harms of computed tomographic (CT) colonography and fecal DNA testing as screening modalities for colorectal cancer.

If we are to be successful in reaching the goal of 80 percent screened for colorectal cancer by 2014, it will take a concerted effort that includes all the partners who are involved in the prevention and early detection of cancer. The new colorectal cancer control initiative offers a unique opportunity to design a comprehensive program with consistent and streamlined screening messages, built on a solid clinical service base with strong partnerships, quality screening and surveillance, timely and appropriate diagnostic follow up, effective treatment options and supportive

patient navigation systems. Finally, this will need to be a program that collects and reports on the clinical and cost-effectiveness of CRC screening tests at the population level.

Partners in the health care provider community, voluntary health organizations, the South Dakota Comprehensive Cancer Control Consortium, the Northern Plains Comprehensive Cancer Control Program and cancer centers in South Dakota are beginning work to build a cost-effective and efficient colorectal cancer screening program that will benefit South Dakotans wherever they live, regardless of who pays for their health care. For more information about the program and how you can become involved, contact the Department of Health at 1-800-738-2301. The South Dakota cancer community will also have the opportunity to interface with the other programs funded under the CDC's colorectal cancer control program and with national organizations such as the National Colorectal Cancer Roundtable (www.NCCRT.org), which will help to further strengthen the overall impact that this important effort will be able to achieve.

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Surgical Treatment of Non-Small Cell Lung Cancer

By Verlyn Nykamp, MD

Abstract:

Surgical resection remains the best treatment option for patients with limited stage non-small cell lung cancer (NSCLC). Stage I and Stage II lung cancer, where there is no lymph node involvement or the involvement is limited to the peribronchial and hilar lymph nodes (N1), can be completely resected with good five-year survival rates (50 to 90 percent). Controversy remains regarding surgery's role in treating more regionally advanced lung cancers involving mediastinal or subcarinal nodes (N2). These tumors (Stage IIIA) have poor survival with surgery, and there has been an advancing role for chemotherapy and/or radiation in their treatment. Surgery is rarely indicated in Stage IIIB or IV lung cancer.

Stages of Lung Cancer

Lung cancer is staged based on the TNM system, which was updated based on new survival rate data in 2009 (See Tables 1 and 2). Few changes in the surgical approach to lung cancer will result from this update. Large tumors (>7 cm) with local lymph node involvement (N1) were upstaged to IIIA, secondary to poor survival rates. Many of these tumors appear clinically NO on positive emission tomography (PET) and will still be approached surgically. T4 disease, based on same-lobe nodules, was downstaged. These historically have been operated on, based on the hope that that they represented synchronous primary lung cancers. All

other major groups of surgical patients had no stage changes.

Present day staging involves the routine use of computed tomography (CT) and PET scanning. These studies are very accurate and have significantly decreased the number of patients who will have a disparity between clinical and pathological stages. A recent study shows that only 3 percent of patients were upstaged by mediastinoscopy from the PET/CT stage.¹

Resectable Lung Cancer

Stage I and Stage II lung cancers are limited to the lung, adjacent resectable structures (T3) and hilar lymph nodes

(NI). The majority of these tumors get excellent local control with lobectomy. Mediastinal lymphodectomy should be a routine part of lobectomy for cancer to provide accurate staging and possibly provide some survival benefit.² Lesser resections (wedge excision and segmentectomy) have been studied on multiple occasions, but in general should not be used on a patient with adequate pulmonary reserve, as they provide inferior local control.³

More difficult localized tumors are represented in the T3 group. These tumors invade the chest wall, diaphragm or mediastinum but remain Stage II due to no lymph node involvement. Prognosis in these patients is related to completeness of resection, which should be performed in an en bloc fashion. Unfortunately, five-year survival falls significantly to the 30 percent range when adjunct structures are involved, even with clean lymph nodes.⁴ T3 also includes tumors in a main stem bronchus but less than 2 cm from the carina. This group requires pneumonectomy or sleeve lobectomy for complete tumor removal. These more complex procedures involve higher morbidity/mortality rates but are justified when compared with the very poor non-surgical outcomes. It is important to note that even N1 involvement in a T3 tumor classifies the patient as a Stage IIIA, and any advantage to surgery is probably lost.⁵

Potentially Resectable Lung Cancer

Stage IIIA lung cancer represents involvement of ipsilateral mediastinal and/or subcarinal lymph nodes (N2). The majority of Stage IIIA patients will have preoperatively recognized (via CT or PET scan) advanced nodal involvement. At present, a multidisciplinary approach, using neoadjuvant chemotherapy or chemoradiation is the first line of therapy.⁶ Depending on the location and extent of disease, subsets of the patients may be considered for restaging and surgery following initial treatment. Unfortunately, clear-cut data to show improved survival, regardless of treatment strategy, is lacking and prognosis remains poor with five-year survivals less than 30 percent.⁷

Patients with “minimal” N2 disease, which is not found by CT or PET scan preoperatively but discovered in the lymph node samples, fare only slightly better. Five-year survival of single-station N2 patients approaches 40 percent, but multi-station N2 patients follow the usual Stage IIIA course.⁸

Patient Selection

After proper staging, less than 30 percent of lung cancer patients will be considered for surgical resection. Assessment of cardiopulmonary reserve is the final step in

the preoperative evaluation. Before proceeding with lung resection, patients with good performance status need a forced expiratory volume in one second (FEV1) of >60 percent of predicted with or without a cardiac stress test (depending on age and risk factors for coronary artery disease). In general, patients who tolerate normal daily activities will tolerate resection well and, by six months after surgery, most will show little if any change from preoperative pulmonary function tests.⁹ Patients whose postoperative predicted FEV1 is less than 30 percent of normal, should undergo additional testing to determine their carbon monoxide diffusion capacity (DLCO) and arterial blood gases (ABG). For patients with very borderline pulmonary function, oxygen consumption studies and quantitative ventilation-perfusion scans will usually give the information needed to determine suitability for lobectomy or pneumonectomy.

Table 1: American Joint Committee on Cancer (AJCC) Stage Groupings

Occult Carcinoma	TX, N0, M0
Stage 0	Tis, N0, M0
Stage IA	T1a, N0, M0 T1b, N0, M0
Stage IB	T2a, N0, M0
Stage IIA	T2b, N0, M0 T1a, N1, M0 T1b, N1, M0 T2a, N1, M0
Stage IIB	T2b, N1, M0 T3, N0, M0
Stage IIIA	T1a, N2, M0 T1b, N2, M0 T2a, N2, M0 T2b, N2, M0 T3, N1, M0 T3, N2, M0 T4, N0, M0 T4, N1, M0
Stage IIIB	T1a, N3, M0 T1b, N3, M0 T2a, N3, M0 T2b, N3, M0 T3, N3, M0 T4, N2, M0 T4, N3, M0
Stage IV	Any T, Any N, M1a Any T, Any N, M1b

Source: American Joint Committee on Cancer

Table 2: TNM DEFINITIONS

Tumor (T)

TX	Primary tumor cannot be assessed, or tumor proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor 3 cm or less in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus)
T1a	Tumor more than 2 cm but 3 cm or less in greatest dimension
T1b	Tumor more than 2 cm but 3 cm or less in greatest dimension
T2	Tumor more than 3 cm but 7 cm or less or tumor with any of the following features (T2 tumors with these features are classified T2a if 5 cm or less); Involves main bronchus, 2 cm or more distal to the carina; invades visceral pleura (PL1 or PL2); Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung
T2a	Tumor more than 3 cm but 5 cm or less in greatest dimension
T2b	Tumor more than 5 cm but 7 cm or less in greatest dimension
T3	Tumor more than 7 cm or one that directly invades any of the following: parietal pleural (PL3) chest wall (including superior sulcus tumors), diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium; or tumor in the main bronchus (less than 2 cm distal to the carina but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung or separate tumor nodule(s) in the same lobe.

T4	Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina, separate tumor nodule(s) in a different ipsilateral lobe
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Regional Lymph Nodes (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
N2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph nodes(s)
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph nodes(s)

Distant Metastasis (M)

M0	No distant metastasis
M1	Distant metastasis
M1a	Separate tumor nodule(s) in a contralateral lobe tumor with pleural nodules or malignant pleural (or pericardial) effusion
M1b	Distant metastasis

Source: American Joint Committee on Cancer

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The Role of Radiation Therapy in the Management of the Lung, Prostate and Colorectal Cancer in South Dakota

By Michael J. Swartz, MD; Daniel G. Petereit, MD

Abstract:

Radiation therapy has a pivotal role in the management of lung, breast, prostate, and colorectal cancer. It is frequently used with curative intent as a single treatment modality or, more frequently, combined with chemotherapy and/or surgery. Radiotherapy also provides effective palliation of symptoms caused by locally advanced or metastatic disease. In this article, we review the role of radiation in the treatment of lung, colon, and prostate cancer. We also discuss ongoing clinical trials and a unique cancer disparity program, “Walking Forward”, that investigates methods of improving access to cancer care, with the ultimate goal of improving cancer cure rates.

Introduction

Radiation therapy involves the use of ionizing radiation to eliminate or control the growth of malignant cells. Approximately 70 percent of cancer patients are treated with this modality during their disease course, whether for curative or palliative intent. Radiation is most commonly delivered using external beams of ionizing radiation generated by a linear accelerator. The shape, intensity, direction

and orientation of these beams can be modulated in order to deliver highly precise and conformal radiation dose to targets of all sizes anywhere in the body. Brachytherapy is one of the oldest forms of radiation and involves placing radioactive isotopes within the body, often directly in the tumor. The isotope emits gamma rays that transmit very high doses of radiation to the tumor and very little to the surrounding normal tissues. With either form of radiation,

the goal is to deliver tumoricidal doses with relative sparing of the adjacent tissues. The use of one form of radiation over the other depends upon the clinical scenario with the goal of achieving the optimal therapeutic ratio.

Radiation therapy plays a critical role in the management of the four most common malignancies affecting cancer patients in South Dakota. Radiation therapy can be curative when used either alone or in combination with other treatment modalities, such as surgery or chemotherapy in the initial management of lung, breast, prostate and colorectal cancers. For early stages of laryngeal and prostate cancer, radiotherapy alone yields high cure rates. For advanced stages of lung and rectal cancer (non-metastatic), radiation is combined with chemotherapy and/or surgery with curative intent. Radiotherapy also provides very effective palliation for locally advanced and metastatic cancers. The precise treatment strategy and its intent depend on the overall health of the patient, and on the tumor site, stage and location. In this article we will review the role of radiation in the management of each of the four most common cancers in South Dakota and will discuss some of the unique challenges these treatments may pose to patients living in our state.

Colorectal Cancer

Surgical resection and staging is critical in the potentially curative management of colorectal cancer. These malignancies are associated with a high risk for regional and microscopic spread. The risks of spread beyond the tumor depend upon the stage, tumor size and location. For colon cancer patients, there is a significant risk for occult liver disease. Adjuvant chemotherapy is administered in order to reduce the risk of relapse at distant sites, including the liver. Chemotherapy improves survival for these patients as demonstrated in numerous randomized trials.¹⁻³ Chemotherapy is recommended for Stage 3 and 4 as well as some Stage 2 colon cancer patients.

Tumors arising in the rectum have a unique recurrence pattern among colorectal cancers and represent the largest subgroup of these tumors requiring adjuvant radiation therapy. In contrast to tumors arising in the colon, which predominantly recur at distant metastases, the failure pattern associated with rectal cancers is characterized by a significant risk of local and nodal recurrence within the pelvis.^{4,5} Once this pattern of failure was recognized, numerous trials incorporated radiation with surgery to reduce the risk of regional disease.

Early trials evaluated the use of radiation alone after surgery.

Patients with Stage 2-3 disease have the highest risk of locoregional recurrence after surgery. Numerous trials have demonstrated decreased rates of local or regional disease recurrence in such patients receiving adjuvant radiation therapy.^{6,7} Radiation alone, however, has not been associated with improved overall survival after surgery.⁸ This observation led to the incorporation of chemotherapy with radiation therapy in the adjuvant setting. Chemotherapy works as a radiosensitizer in the pelvis and also addresses micrometastases above the pelvis. Randomized trials have demonstrated both improved locoregional disease control and survival with the use of adjuvant chemoradiation therapy for Stage 2-3 rectal cancer.^{9,10}

There is now evidence that chemoradiotherapy before surgery (neoadjuvant) is more effective for certain patient subsets, compared to treatment after surgery (adjuvant).¹¹ Treatment before surgery can result in pathologic downstaging, improved local disease control and a higher probability of performing sphincter-preserving surgery.¹¹⁻¹³ Preoperative chemoradiation therapy was compared to postoperative chemoradiation therapy, with modern surgical techniques, in a landmark clinical trial that established preoperative therapy as the current standard treatment approach for patients with T3, T4, or node-positive rectal cancer.¹¹ This trial demonstrated improved local disease control, toxicity rates and sphincter preservation with preoperative chemotherapy and radiation therapy compared to postoperative treatment. All patients with rectal cancer should undergo careful preoperative staging, including transrectal ultrasound staging of the primary tumor, and should be referred to medical and radiation oncology before surgery to determine if they meet the above criteria.

Radiation therapy is also appropriate as adjuvant local treatment for patients with advanced colon cancers that extend into adjacent organs or structures, especially if the margins are positive. Radiation can also be used to treat metastatic tumor deposits in a variety of anatomic locations. Stereotactic body radiation therapy is emerging as an effective treatment option for certain liver and lung metastases.^{14,15} Radiation also provides effective palliation for patients with advanced, symptomatic tumors arising in the colon or rectum.

Lung Cancer

Lung cancer is the most common cause of cancer death in the United States, with approximately 214,000 new cases diagnosed each year and 160,000 deaths.¹⁶ Eighty percent

of lung cancers are classified as non-small cell lung cancer (NSCLC,) and 20 percent are small cell lung cancer (SCLC). While both types of lung cancer are associated with exposure to tobacco smoke, they are managed quite differently due to different patterns of spread and biologic behavior. Radiation therapy plays an important role in the management of both major subtypes of lung cancer and is used for a number of disease presentations.

Non-small cell lung cancer is managed surgically when diagnosed early. Ideal surgical candidates are those with relatively small tumors confined to one lung without obvious mediastinal nodal extension (Stage 1 or 2 disease). Surgery for such patients yields high local control rates and is considered the treatment of choice when feasible.^{17,18} Patients must have adequate pulmonary reserve in order to undergo a successful surgical resection. Lobectomy is the preferred surgical approach and has been associated with improved local control, compared to less extensive surgery such as wedge resection or segmentectomy.¹⁹ Even after complete resection, rates of metastatic disease recurrence are significant. Therefore, adjuvant chemotherapy has been studied and has been shown to improve survival by five to 10 percent by reducing the risk of metastatic disease.²⁰ Patients with Stage 2 and higher disease experience the most benefit from adjuvant chemotherapy.

Patients with inadequate pulmonary reserve or severe medical comorbidities are considered poor surgical candidates, even when presenting with early stage disease. These patients can be treated effectively with definitive radiotherapy. Using conventional radiation treatment planning and dose fractionation, results are generally considered inferior to those potentially achieved with surgery.²¹ Radiation therapy, however, is still a curative treatment option for medically inoperable, early-stage lung cancer. The results achieved with primary radiation therapy correlate with the dose of radiation utilized and with the size and extent of the disease.

Over the last several years, stereotactic body radiation therapy (SBRT) has been developed as a more effective method to deliver radiation for medically inoperable early stage disease. Conventional radiation treatment for lung cancer requires six to seven weeks of daily treatments, each delivering a relatively low dose to the tumor. SBRT delivers a similar total dose of radiation, but compresses the treatment to between three and five very large fractions delivered over approximately two weeks. SBRT requires sophisticated equipment capable of ensuring accurate, precise delivery of the high dose radiation. South Dakota

native Dr. Robert Timmerman has performed much of the pioneering work in developing SBRT as a viable treatment option for medically inoperable NSCLC. Dr. Timmerman and others have published results from studies evaluating SBRT that compare favorably with results from surgical series, with local control approaching 90 percent at three years.²²⁻²⁴ Long-term experience with SBRT is developing, but this approach is rapidly becoming an important treatment option for patients with medically inoperable early stage disease, and has been incorporated in our own practice.

The management of Stage 3 disease requires a combination of treatment modalities and depends on the extent of disease and on the health of the patient. While chemotherapy and radiation are essential components of therapy for Stage 3 disease, patients without clinical mediastinal lymph node involvement may also undergo surgical resection. Surgery is appropriate for such patients who are healthy enough to undergo an extensive pulmonary resection. When surgery is performed as initial management of Stage 3 disease, it is followed by adjuvant chemotherapy. Radiation therapy is also considered after surgery for patients found to have positive surgical margins or mediastinal lymph node involvement, and has been associated with improved survival in several studies.^{25,26}

The combination of chemotherapy and radiation therapy followed by surgery (trimodality therapy) has also been studied in patients with Stage 3 disease with mediastinal lymph node involvement. The early results from the study of this treatment approach suggest improved progression-free survival with trimodality therapy compared with chemotherapy and radiation alone, but no improvement in overall survival.²⁷ The study demonstrated higher-than-expected rates of early mortality after surgery, especially for patients requiring a pneumonectomy. The risks associated with surgery in this study demonstrate the importance of a multidisciplinary approach in the management of patients with Stage 3 disease.

Chemoradiation therapy alone is the treatment of choice for patients with unresectable Stage 3 disease. Radiation plays a critical role in this combination of treatments, serving as the primary means of achieving local disease control. Radiation dose escalation has been associated with improved local disease control which, in turn improves overall survival.²⁸ Modern radiation treatment techniques allow for relatively higher, more effective radiation doses to be delivered with better sparing of the surrounding normal tissues. Definitive high-dose radiation therapy can now be

delivered for primary lung cancer with reduced risk of treatment-related morbidity. A number of current studies are evaluating the use of modern radiation techniques to increase dose beyond what is currently considered standard in order to continue to improve local control.

While radiation therapy alone can provide local disease control, metastatic failure is common. Chemotherapy combined with definitive radiation therapy can improve both local disease control and metastatic recurrence, thereby enhancing overall survival.^{29,30} The timing of combined chemotherapy and radiation therapy affects the outcome of treatment. Sequential chemotherapy and radiation therapy improves overall survival compared to radiation therapy alone.³¹ Concurrent administration of chemotherapy and radiation therapy aims to exploit the potential synergistic effect of chemotherapy when given with radiation. This approach has now become the standard of care and has been associated with better overall survival compared to sequential therapy for advanced disease.^{32,33}

Small cell lung cancer (SCLC) is managed quite differently and is distinguished from NSCLC by its rapid doubling time, high growth fraction and propensity to metastasize early in the course of the disease. Because of the biology and clinical behavior of SCLC, surgery has a limited role in its management. Chemotherapy and radiation will typically provide very high response rates, but recurrence is frequent both locally and at distant sites. Staging of SCLC is straightforward and relates to the feasibility of delivering definitive radiation treatment. Patients with disease confined to one side of the chest that can be safely treated with radiation therapy have limited stage disease. Those with tumors on both sides of the chest or with metastatic disease have extensive stage disease.

The mainstay of treatment for SCLC is chemotherapy because of its proclivity to metastasize early. Radiation therapy also plays a crucial role in the management of limited-stage disease. With chemotherapy treatment alone such patients experience very high rates of local disease progression. Numerous randomized studies and meta-analyses have suggested that thoracic radiotherapy, combined with chemotherapy, results not only in improved local disease control but also in improved overall survival.³⁴⁻³⁶ The timing of radiation therapy also appears important, as several analyses suggest that early initiation of thoracic radiation given with concurrent chemotherapy improves survival.^{37,38} Because of the rapid proliferation and high growth fraction of SCLC, accelerated radiation fractionation (shorter treatment duration) has been proposed as a

potentially more effective treatment approach. One large study comparing twice-daily radiation treatments over three weeks to once-daily radiation treatments over five weeks suggested an improvement in overall survival with the accelerated, twice-daily treatment approach.³⁹ The study has been criticized for the relatively low dose used in the once-daily arm but highlights the importance of aggressive radiation dosing for limited-stage SCLC.

Extensive stage disease is considered a systemic disease process and is treated primarily with chemotherapy. In spite of the widespread nature of extensive stage disease, response rates with chemotherapy are reasonable. Distant relapse remains a common occurrence, however. Patients with both limited- and extensive-stage disease develop brain metastases frequently, in part because of the limited penetration of chemotherapy within the brain. Reported rates of brain metastases are as high as 40 percent at one year, even after a complete or near complete response to treatment elsewhere in the body.^{40,41} Given the morbidity and mortality risks associated with brain metastases, prophylactic cranial irradiation (PCI) has been studied as a means to reduce their occurrence for patients with both limited and extensive stage disease. In separate studies, PCI has been shown to both reduce the risk of brain metastases and to improve overall survival in patients with either limited or extensive stage disease who respond to initial chemotherapy and/or chemoradiation therapy.^{40,41} PCI is now a standard consideration for those with both limited and extensive stage disease who respond to initial therapy. Radiation plays a key role in the management of SCLC and should be a part of the treatment strategy for patients with both limited and extensive stage disease.

In spite of the numerous advances in the management of both types of lung cancer, mortality rates remain high. Improved survival for both types of lung cancer will continue to occur only through continued basic and clinical research. It is, therefore, very important for oncologists to participate in clinical trials in order to improve the cure rates for these patients.

PROSTATE CANCER

Prostate cancer is the most commonly diagnosed non-cutaneous cancer, and is the second leading cause of cancer death among American men. Approximately 192,000 men will be diagnosed with prostate cancer in the United States in 2009, and 26,000 men will die of the disease. American men have a one in six lifetime probability of developing prostate cancer.⁵⁸ Given the prevalence of prostate cancer, understanding the evaluation, risk stratification and

potential treatment options associated with the disease is critical. In this section on prostate cancer, we review these issues and discuss a number of potential treatment strategies. We also review ongoing clinical trials including those available in conjunction with our own community-based research program, which is sponsored by the National Cancer Institute (NCI).

Due to the widespread availability of serum prostate-specific antigen (PSA) screening, the incidence rates of prostate cancer have changed substantially over the last 20 years, rapidly increasing from 1988-1992 and leveling off since 1995. Approximately 50 to 60 percent of patients are now diagnosed with organ-confined disease. Risk stratification schemes using the clinical stage, PSA and Gleason scores (GS) are used to predict the likelihood of a patient having organ confined disease which guides therapy. The Gleason score is a measure of the aggressiveness of the cancer, is based upon the architectural pattern, and is assigned a number between 4 and 10. The higher the number, the more aggressive the cancer. Risk stratification is also commonly used to predict biochemical and clinical outcome after treatment with either a radical prostatectomy (RP) or radiation.⁵⁹ The D'Amico stratification is most commonly used and describes favorable prostate cancer associated with PSA levels <10 ng/ml, Gleason score <7 and stage <T2A disease. Patients with favorable prostate cancer are considered to have a relatively low risk for extraprostatic disease, seminal vesicle involvement and pelvic lymph node metastasis with 10-year biochemical control rates as high as 80 to 90 percent with surgery or radiation. High-risk disease is characterized by >T2C disease, GS 8-10, or PSA >20; whereas, intermediate risk disease includes T2B, GS 7 and a PSA 10-20. Other emerging prognostic criteria include PSA velocity (PSA rise per year), percent positive cores and perineural invasion. Risk stratification is a critical first step in determining the optimal management of prostate cancer.

Active surveillance may be an appropriate option for low-risk patients who are agreeable to close follow-up and do not show any clinical or biochemical evidence of disease progression. It is also considered appropriate for elderly patients with significant medical co-morbidities who have a relatively short life expectancy. Patients undergoing active surveillance should undergo regular PSA testing and should have biopsies of the prostate repeated at some point. Treatment should be considered if a repeat biopsy demonstrates a GS of 7 or above, or if the PSA doubling time is less than three years. For a more thorough discussion, please see reference No. 4.⁶⁰ There is now compelling evidence

that definitive treatment for prostate cancer improves survival. A recent randomized Swedish study demonstrated that a radical prostatectomy (RP) improved survival by 5 percent over observation alone and was associated with a 50 percent reduction in prostate cancer mortality.⁶¹ While this study calls into question the appropriateness of active surveillance, a large randomized phase III trial is planned in the United States to randomize 2,100 men with prostate cancer to observation or definitive treatment. This study aims to determine whether some men with prostate cancer may safely avoid definitive treatment.

Excellent control rates are achieved for low-risk patients using single modality therapy. RP, permanent seed implant (PSI) or external beam radiotherapy (EBRT) are considered appropriate treatment options for low-risk disease.⁶² There have been no randomized trials comparing these three treatment options directly. The rates of disease control achieved with surgery or with definitive radiotherapy – whether a PSI or EBRT – are similar. There are no compelling data supporting the superiority of one treatment option over another. Selection of treatment is typically based on patient preference, convenience or potential short- or long-term toxicities, which differ with each treatment option.

For low-risk disease, external beam radiation will achieve high cure rates with minimal toxicities. The typical radiation doses delivered with contemporary techniques are significantly higher than they were several years ago. Radiation dose escalation has been associated with significant improvements in biochemical disease control (PSA stability) as demonstrated in four randomized trials.⁶³⁻⁶⁶ Prior to the last decade, it was not safe to treat prostate cancer patients above 70 Gy (35 treatments, Monday through Friday, at 2 Gy per day), due to high rates of bladder and rectal complications. With computerized treatment planning and increasingly complex radiation delivery systems, it is now possible to deliver 76 to 80 Gy with acceptable toxicities. Most radiation oncology centers use intensity modulated radiotherapy (IMRT) to dose escalate by using either a modified linear accelerator or a TomoTherapy unit. In 2004, the TomoTherapy program was implemented in Rapid City.⁶⁷ TomoTherapy delivers IMRT treatments through a process very similar to a CT scan.⁶⁸ The linear accelerator rotates around the patient while 64 multi-leaf collimators sculpt or “paint” the radiation dose. Radiation is passed through a binary collimating system, creating precise pencil-like beams of differing intensity to deliver radiation dose which conforms to the targeted area. External beam radiation is frequently used to treat prostate cancer since the acute toxicities are usually mild and well-controlled

with medications, and there is long term clinical data supporting its safety and efficacy.⁶⁹ The disadvantages of EBRT include the inconvenience of daily treatments for eight weeks and the cost.

The distance from the cancer center is often a burden and a barrier for patients to undergo cancer treatment, and in particular for low-risk prostate cancer patients considering EBRT. A phase II multi-institutional IMRT trial is open at our institution. In this study the number of treatments are decreased from 22 (2.94 Gy per fraction) to 16 (3.63 Gy) to 12 (4.3 Gy) by increasing the daily dose of radiation. These schedules were designed to give an equivalent dose of 76 Gy in 38 treatments. This trial has accrued 320 patients nationwide with 50 accrued in Rapid City. The current dose level is 3.63 Gy x 16 over four weeks. No significant toxicities have been encountered to date with excellent biochemical control rates at three years.^{70,71}

Permanent seed implant or brachytherapy is appropriate as monotherapy for low-risk patients with a prostate less than 50 to 60 grams, normal to near normal bladder function and no contraindications to general anesthesia. A transrectal, prostate ultrasound volume study is performed two to four weeks before the implant for radiation planning and to determine the anatomic feasibility of the procedure. The brachytherapy procedure is outpatient, takes 60 to 90 minutes, and is performed jointly by a radiation oncologist and an urologist. Radioactive iodine seeds are most commonly used and remain in the prostate permanently, but decay by six months to deliver an eventual dose of 145 Gy. The acute toxicities are higher compared to external beam radiation and include urinary irritative symptoms and changes in bowel habits. These usually resolve by four to six months. The Seattle Prostate Institute has performed 10,000 implants with 15 years of follow-up, demonstrating cure rates as high or higher than any other approach reported to date for low-risk disease.⁷² PSI is considered the most cost-effective treatment for low-risk disease and is more convenient. For patients who live a significant distance from a cancer center, this is often the most desired radiation treatment option. Technical expertise performing PSI is important, as improved biochemical control rates are clearly associated with the quality of seed implants.^{73,74} Thus, it is critical that patients who undergo permanent seed implants are treated at facilities that have adequate patient volume and expertise to maximize cure rates.⁵³

For patients with intermediate- and high-risk disease (non-metastatic), combination therapy is generally preferred. Surgery alone is often considered suboptimal for patients

with a high risk of extraprostatic disease extension. Radiation in combination with androgen deprivation is the standard of care. Five randomized trials have demonstrated the superiority of the combination approach compared to radiation alone.⁷⁵ An LHRH (luteinizing hormone-releasing hormone) agonist such as leuprolide or goserlin is most commonly used. On a molecular level it has been shown to promote apoptosis and may act synergistically with radiation-induced cell killing. There is emerging clinical data that a prolonged course of treatment may eradicate microscopic metastatic disease as well. The ideal length of androgen deprivation continues to be defined, but is often prescribed for six months in patients with intermediate-risk disease and for two to three years in high-risk disease.

Patients with intermediate- and high-risk disease may also be treated with IMRT combined with a brachytherapy boost. Several retrospective series have suggested higher and more durable biochemical control rates when patients undergo a PSI boost compared to EBRT alone.⁷⁶ Two phase II clinical trials are currently open for intermediate- and high-risk prostate cancer patients at our institution. For intermediate patients, treatment on study includes a short course of IMRT (2.2 Gy x 16), followed by a permanent seed implant boost (110 Gy). For eligible high-risk patients, the pelvic lymph nodes are treated on study to 56 Gy and the prostate to 70 Gy in 28 fractions with IMRT in order to decrease the overall treatment time from eight weeks to six weeks. The theme of these trials is to reduce the barrier of distance and time away from home, while maintaining or improving the therapeutic window.⁴⁸ In addition, higher daily doses of external beam radiation may enhance cell killing due to the radiobiology of prostate cancer cells.

The complications from radiation can be temporary or long term. The acute side effects are typically mild to moderate, transient and well controlled with medications. These include some degree of bowel, bladder and/or rectal irritation. The acute toxicities are enhanced when brachytherapy is the sole method of treatment or if used in combination with EBRT. With brachytherapy, there is a 20 to 30 percent risk of urinary retention requiring a Foley catheter for two to three days, in addition to the risk of bleeding, infection and anesthesia. More worrisome are the late or permanent complications that can take months or even years to develop. These include a 30 to 50 percent risk of erectile dysfunction (often reversed with medications) [all forms of radiation], 5 to 10 percent risk of a urethral stricture [brachytherapy], 1 to 5 percent risk of rectal bleeding [all forms of radiation], and <5 percent risk of bladder dysfunction, including a 1 percent risk of urinary incontinence [all forms of radiation].

Fistulas and bowel obstructions are rare with modern radiation delivery systems and techniques.^{69,76,77}

Currently, there are many effective treatment options for patients with prostate cancer. Although early detection is critical for successful treatment, even patients with more advanced stages of disease (non-metastatic) can be cured as described above. In order to improve cure rates, further characterization of the biology of prostate cancer, as well as participation in clinical trials will be essential.

"Walking Forward", a Community-Based Research Program

"Walking Forward" is a community-based participatory research program in western South Dakota funded by the National Cancer Institute. The primary goal of this initiative is to address the high cancer mortality rates among American Indians by facilitating access to innovative

clinical trials, behavioral and genetic research and tailored patient navigation (program detailed in a recent *South Dakota Medicine* article by Kanekar and Petereit).^{48,56} The barrier of distance from the reservation to the cancer center has been partially addressed through patient navigation programs and participation in clinical trials for common disease sites such as prostate and breast cancer using brachytherapy and tomotherapy. These same studies also benefit the rest of the population in western South Dakota, as the entire region is considered medically underserved. <http://bhpr.hrsa.gov/shortage/muaguide.htm> "Walking Forward" was just funded for another five years by the NCI and will further focus on cancer prevention, education and screening, in addition to clinical trials and radiogenomics for both the American Indian and non-American Indian populations.

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Please note: Due to limited space, we are unable to list all 77 references. You may contact South Dakota Medicine at 605.336.1965 for a complete listing.



Pathways to Personalized Medicine for Breast and Prostate Cancers: Emerging Diagnostic Methods and Prognostic Biomarkers

By Allison P. Watson and Kristi A. Egland, PhD?

Abstract:

Early and personalized diagnosis for breast and prostate cancer is crucial for optimizing treatments leading to long-term patient survival. Once cancer metastasizes from the breast or prostate to other tissues of the body, therapies are limited, and there is no cure for the diseases. Currently used screening modalities for breast and prostate cancers have limitations. Routine screening for breast cancer includes clinical breast exams and mammograms. Improvements in imaging techniques, such as magnetic resonance, ultrasound, digital breast tomosynthesis and ductography are being explored as adjuncts to mammography. A new approach to breast cancer screening involves the detection of abnormalities at the cellular level and uses various means to collect cellular material from the ductal system, including nipple aspirate fluid, breast ductal lavage, fiber optic ductoscopy and random periareolar fine needle aspiration. Current screening methods for prostate cancer include digital rectal exam and serum PSA levels. However, these methods offer low sensitivity and specificity and do not allow differentiation between significant- and minimal-risk cancers. New approaches to prostate cancer screening involve different calculations using PSA, as well as molecular urine tests. With the recent advances in microarray technologies and whole-genome sequencing of tumors, the identification of specific biomarkers for diagnosis and prognosis, as well as new therapeutic targets, is quickly paving the way for personalized medicine. In the future, routine patient care will include using the molecular signature of a patient's disease to guide treatment.

Introduction

Rising health care costs have become a major issue facing Americans, and one of the main concerns is always cancer. Cancer is one of the leading causes of death in the United States, second only to heart disease. Presently,

over one quarter of deaths in the United States are attributed to cancer, compared to 12.5 percent of deaths worldwide.¹ In addition to the loss of human life due to cancer, the financial burden is substantial. Direct costs (such as costs of treatment, care and rehabilitation), and

indirect costs (such as loss of economic output due to days missed from work) are mounting due to the growth and aging of the population. Now, more than ever, we as a global population are in need of new and improved methods of prevention, early detection and treatment.

Breast Cancer (BrCa)

BrCa is the most commonly diagnosed cancer in women and is the leading cause of cancer death among women worldwide.¹ The South Dakota State Department of Health predicts that there will be approximately 530 new cases of female BrCa and 100 deaths due to this cancer in 2009. BrCa represents the second-leading cause of cancer death for South Dakota women and is the second-most commonly diagnosed cancer, after cancers of the skin. Two important factors in BrCa prognosis are the size of the tumor and how far it has spread. Since women who present with BrCa in Stage 1 have a greater likelihood of remaining disease free after five years than those that are diagnosed with Stages 2-4, the greatest hope for cure is early detection.² In November 2009, the U.S. Preventive Services Task Force (USPSTF) released new recommendations for breast cancer screening in the general population.³ Briefly, the USPSTF does not recommend routine screening mammography in women 40 to 49 years of age. Biennial mammography screening is recommended for women 50 to 74 years of age, while the benefits and harms of mammography screening in women older than age 75 is currently unknown. The USPSTF does not recommend that clinicians teach women how to perform breast self-examinations, and the additional benefits and harms of clinical breast examination (CBE) in women 40 years or older are unknown.³ These new guidelines have caused a great deal of controversy among cancer organizations. The American Cancer Society (ACS) issued a statement in response to the USPSTF new guidelines stating that the ACS will continue to recommend annual screening for all women beginning at age 40 using mammography and CBE. Otis W. Brawley, MD, the chief medical officer of the ACS, stated, "With its new recommendations, the USPSTF is essentially telling women that mammography at age 40 to 49 saves lives; just not enough of them."⁴

Imaging Techniques for Breast Cancer Detection

Mammography, MRI and Ultrasound

Mammography remains the most reliable and widely used method to detect BrCa. This method provides radiographic images of the breasts using a very low dose of ionizing radiation and without the need for contrast material. Image quality is optimized by compression of the breast tissue. Mammography is best when at least two sets of images are collected – one in the mediolateral oblique view and one in cranial-caudal view. This allows for more

accurate spatial orientation.

A recent advancement in mammographic techniques involves the use of digital mammography and software that can highlight suspicious areas or lesions in the breast tissue that might not initially be recognized by a radiologist. However, there are always trade-offs with improved sensitivity in screening techniques. Improved sensitivity without the accompanying increased specificity brings the risk of more false positives and increased potential for further imaging and biopsies. About one in 10 women who get a mammogram will need additional imaging, but the overwhelming majority of these women will not have BrCa, as only two to four of every 1,000 mammograms leads to a cancer diagnosis. Much research is being done to determine the best balance between a higher number of false positives and improved BrCa detection.

Women with an increased lifetime risk of BrCa may be counseled to receive additional screening on top of annual CBE and mammogram. This may include magnetic resonance imaging (MRI) possibly as early as age 30. MRI has higher sensitivity than mammography and allows detection of smaller tumors.⁵ For women without significantly increased lifetime risk of developing BrCa, MRI is not currently recommended for screening.⁵ Another technique becoming more commonly used in BrCa detection is ultrasound. This method is generally only used after CBE and/or mammography detect the presence of a lesion. Ultrasound uses sound waves that pass through a gel-covered skin probe to determine whether the nodules or densities are solid or cystic. Breast MRI and ultrasound should not be considered replacements for mammography, but rather additional diagnostics to further define previously detected abnormalities.

CBEs and mammography remain the gold standard in BrCa screening, but as incidence rates remain high, there is an ever-growing need for new and improved techniques to detect the cancer in its earliest stages, when it is most curable. Mammography and CBEs are limited in their sensitivity by the size of the tumor. Most experts agree that is difficult to detect tumors smaller than 1 centimeter by either of these methods, and as many as one in four breast tumors in high-risk women may be missed by currently used screening modalities.⁶

Digital Breast Tomosynthesis

DBT is a new technique that is currently only available for research purposes. This method produces a 3-dimensional picture of the breasts using a combination of tomography and 3-D reconstruction with breast X-ray imaging.⁷ While conventional mammography takes only two X-rays of each breast from different angles, tomosynthesis takes multiple X-rays of each breast from many angles. This

produces highly focused 3-D images of the whole breast. Another advantage includes the ability to take images of the breast without the degree of compression required for mammography. Compression of breast tissues is not only uncomfortable for patients, but it also causes overlapping of the breast tissue, possibly obscuring a breast cancer from view. Although DBT improves the visualization of lesions, blood vessels, microcalcifications and dilated ducts,⁷ this method provides no advantage over mammography for lesions that are well-demonstrated by conventional mammography.^{8,9} The most appropriate use of DBT may be for patients referred with an abnormal screening mammogram or with clinical symptoms.¹⁰

Ductography

A ductographic study allows identification and localization of an intraductal lesion and is performed by retrograde filling of the lactiferous ducts with contrast material and imaging using a special type of X-ray. However, conventional ductography is invasive, has inherent complications and contraindications, produces only a 2-D image and cannot distinguish between benign and malignant lesions.¹¹ With advancements in imaging techniques, a variation of the ductogram using magnetic resonance (MR) instead of conventional X-rays may prove helpful. This method can non-invasively detect fluid-filled tubular structures within the breast using T₂ weighted images to accentuate the visibility of structures.¹² MR ductography requires no contrast material to be instilled directly or injected intravenously, and produces a 3-D image. However, the image produced may only represent a small portion of the actual lesion, as it is only able to detect the portion existing within the duct. With the addition of contrast material injected intravenously and traditional MR mammography, this method has the potential for high sensitivity in detection of intraductal lesions.¹¹ Both conventional and MR ductography are limited in their usefulness, as these methods are costly and may be contraindicated in many patients. In general, conventional ductography is not routinely used, and MR ductography is only recommended in cases with pathologic nipple discharge.

Cytologic Detection Methods for Breast Cancer

It is believed that at least 85 percent of BrCas arise in the epithelial lining of mammary ducts, within the terminal-duct-lobular unit as a morphologically identifiable precursor lesion.¹³ It is hypothesized that the earliest possible detection methods for BrCa involve detecting these abnormalities at a cellular level. The development of a procedure to easily, reliably and reproducibly retrieve breast duct cells could substantially alter currently used methods of BrCa detection. Identification and characterization of early cellular and genetic changes may allow for detection of BrCas before

standard screening by CBE and mammogram would detect the lesion. Several methods are being developed to obtain the ductal epithelial cells, including nipple aspirate fluid, breast ductal lavage, fiber optic ductoscopy and random periareolar fine needle aspiration of breast parenchyma (RPFNA).

Nipple Aspirate Fluid (NAF)

Discharge from the nipple is a relatively common symptom, but most discharge is not associated with neoplasms, benign or malignant.¹⁴ However, the most clinically significant cause of nipple discharge is an underlying breast malignancy, which is reported in 5-21 percent of cases.¹¹ Fluid obtained from the nipple contains breast epithelial cells, free DNA and proteins and can often be obtained by means of aspiration.¹⁵ In a procedure called "nipple aspiration," fluid containing epithelial cells is obtained from ducts and analyzed for cytologic abnormalities. Small cups are placed on the breasts, and the device warms the breasts and gently massages them while applying light suction to bring nipple fluid to the breast surface. The procedure can yield up to 50 ml of fluid containing approximately 200 epithelial cells. However, nipple aspiration is limited in its effectiveness in certain populations due to factors that influence fluid production within the breast ducts. Factors that are associated with higher NAF yield include younger age (30 to 50 years), previous lactation, early onset of menarche, high dietary fat intake and consumption of soy protein.¹⁶ Prior chemotherapy and/or radiation therapy to the chest significantly decrease production of NAF. However promising this procedure sounds, nipple aspiration alone has not been shown to detect cancer early in a large number of cases.

Breast Ductal Lavage (BDL)

BDL is a variation of the nipple aspiration procedure, which is applied principally to NAF-producing ducts.¹⁷ This method results in a greater percentage of adequate cellular material for evaluation than nipple aspiration alone. The difference between NAF and BDL is that BDL utilizes a fine microcatheter for the purpose of lavage. An anesthetic cream is used to numb the surface of the nipple, and gentle suction is used to draw fluid from the ducts to the nipple surface. The catheter is then guided to the fluid-producing ducts and saline is slowly inserted through the catheter to rinse the duct and collect the cells. The collected fluid is then analyzed for cytologic abnormalities. Despite the higher cellular yield, this method only allows for examination of one or two of the 15 to 20 ducts that open at the nipple, perhaps entirely missing focal abnormalities in the remaining ducts not visualized.¹⁸

Fiber optic Ductoscopy

Fiber optic ductoscopy involves the use of a silica fiber-scope with cannulation of a duct identified by the presence

of discharge. This method allows for direct visualization of the major ducts and at the same time permits the use of a saline lavage to retrieve cells from the ductal system.¹⁹ Lesions within the duct appear elevated and white, while the surface of normal duct epithelium appears lustrous and smooth.²⁰ However, like BDL, fiber optic ductoscopy allows examination of only one or two ducts. In addition, this method has limited ability to visualize smaller-caliber and peripheral ducts, due to the size of the scope and complex branching pattern of the ductal system.¹⁸ Fiber optic ductoscopy appears to be most useful in determining appropriate margins of resection for *in situ* or invasive BrCa at the time of surgery.²¹

Random Periareolar Fine Needle Aspiration (RPFNA)

For RPFNA, no specific duct or lesion is targeted, but a large area of breast tissue is evaluated to detect a field effect in the breast due to an underlying malignancy. Studies have shown that multifocal and multicentric patterns of proliferative changes can be observed in the breast when there is a focal lesion.²² For this technique, two different quadrants are selected adjacent to the edge of the areola, and emphasis is placed on sampling areas of dense breast tissue, where proliferative glandular tissue is often present.²³ A needle with an attached syringe is pre-wetted with tissue culture medium, inserted through the skin and used to aspirate material from the breast. The goal of this method is to sample cells from the terminal-duct-lobular unit. Studies show that RPFNA is more likely than NAF and BDL to produce an adequate cellular specimen for evaluation, but morphology of cells obtained by all methods is generally similar.¹³ The advantage RPFNA has over NAF and BDL is that it does not require NAF production, and the success rate for obtaining adequate samples is highest with RPFNA.²³

Breast Cancer Prognostic Markers

Single Tissue Markers: Estrogen Receptor, Progesterone Receptor and Amplification of HER-2

Tumor markers are materials of genetic origin that are produced by tumors themselves or by the host in response to the tumor.^{24,25} Tumor markers provide information for assessing disease risk, prognosis, metastatic potential and evaluation of response to therapy. Several prognostic tumor markers for BrCa are currently used in clinical practice, including Estrogen Receptor (ER), Progesterone Receptor (PR) and amplification of *HER-2* (26). One of the first evaluative tests performed on newly diagnosed breast tumors is to determine the status of the ER and PR. Many studies indicate that a higher expression level of the ER correlates positively with increased responsiveness to anti-estrogen therapy (e.g., tamoxifen).²⁴ In addition, the presence or absence of the PR in breast tumors can provide prognostic information. Clinical studies indicate that

ER(-)/PR(+) patients have an increased disease-free and overall survival rate compared to ER(-)/PR(-) (27). *HER-2* amplification occurs in about 25 to 30 percent of patients with breast cancer, and it is often associated with a poor prognosis.^{26,28,29} However, the anti-HER2 monoclonal antibody (mAb), Trastuzumab (or Herceptin), has shown clinical efficacy for the treatment of metastatic BrCas with *HER-2* overexpression,^{30,31} and in combination with standard adjuvant chemotherapy, the risk of recurrence has decreased by more than 50 percent.^{32,33} The development of targeting the *HER-2* oncoprotein with a mAb has transformed a very aggressive tumor phenotype (*HER-2* positive) into one with a favorable outcome.

Genome Profiling Approach to Breast Cancer Treatment

Over the past 10 years, whole-genome profiling technologies have greatly expanded our knowledge about genetic pathways associated with tumorigenesis. For BrCa, gene-expression profiling has led to the molecular classification of tumors into three main subtypes: luminal (ER+), *HER-2*-like (mainly ER- and *HER-2*+) and basal-like (triple negative, i.e. ER-, PR-, *HER-2*-). These findings reinforce the biological importance of the well-studied tumor markers, ER, PR and amplification of *HER-2* as well as the heterogeneous nature of the disease.³⁴ The future of prognostic markers is their use for personalized medicine, in which a patient's molecular signature of their disease will guide treatment.

Oncotype DX

The Oncotype DX assay (Genomic Health, CA, USA) determines the risk of distant recurrence in patients with early-stage (Stage 1 and 2), lymph node negative, ER+ invasive breast cancer that are being treated with tamoxifen.³⁵ The assay is based on measuring the expression levels of 16 outcome-related genes, associated with proliferation and endocrine response, and five reference genes by using reverse transcription-PCR on formalin-fixed, paraffin-embedded tissues. For each patient, a mathematical algorithm is used to determine a recurrence score between 1 and 100, which correlates with metastatic disease within 10 years.³⁶ The recurrence score is categorized into three groups: low risk (<18), intermediate (18 to 30) or high (>31). Studies have shown that patients with a low recurrence score have derived little benefit from chemotherapy, and these patients may be successfully treated using hormone therapy alone. However, if a tumor has a recurrence score over 31, the patient will substantially benefit from chemotherapy (37-39). Currently, the National Cancer Institute is sponsoring the TAILORx (Trial Assigning Individualized Options for Treatment (Rx) individualized treatment trial through the Eastern Cooperative Oncology Group (ECOG) to evaluate the effect of chemotherapy in women with an Oncotype DX midrange recurrence score.⁴⁰

MammaPrint

The MammaPrint assay (Agendia BV, The Netherlands) was developed in 2001 at the Netherlands Cancer Institute in Amsterdam to distinguish patients with a high risk of metastatic recurrence from those that could be spared chemotherapy because the risk of long-term distant metastasis is so low.⁴¹ The MammaPrint assay is a prognostic test for women under the age of 61 with either ER+ or ER-, lymph node-negative BrCa.³⁶ Unlike the Oncotype DX, this assay requires freshly prepared, unfixed biopsy tissue. The assay focuses on 70 genes that are involved in proliferation, invasion, metastasis, stromal integrity and angiogenesis. The MammaPrint assay uses a microarray-based multi-gene assay to determine the risk of relapse for BrCa patients.

Prostate Cancer (PrCa)

PrCa is the second most common malignancy worldwide and accounts for 20 percent of all male cancers. Some estimate that nearly one half of all men will have evidence of prostatic carcinoma at autopsy. Nearly three quarters of the newly diagnosed cases of PrCa occur in economically developed countries.¹ In the United States, PrCa remains the most common malignancy among men and the second-leading cause of cancer death of men. The South Dakota State Department of Health predicts that there will be approximately 580 new PrCa cases and 100 deaths due to this cancer in 2009 in South Dakota. The age-adjusted incidence rate for PrCa in South Dakota is somewhat higher than that of the United States population as a whole.

Prostate Specific Antigen (PSA) is the most commonly used serum marker for cancer detection. PSA is used to screen for PrCa in men and to monitor the response to treatment. In the last 20 years, incidence rates of PrCa in the United States have changed significantly, due, in part to changes in screening with PSA. In general, PrCa incidence rates peaked in 2001 and have since been on a steady decline. Mortality rates from PrCa have also been declining in recent years. In the United States, deaths from PrCa decreased by 4.1 percent per year from 1994 to 2005.⁴² Both normal prostate epithelial cells and PrCa produce PSA. In PrCa the loss of the normal glandular architecture is thought to increase the access of PSA to the peripheral circulation, resulting in elevated PSA in the serum.⁴³ Therefore, the levels of PSA can be measured by a simple blood test for PrCa detection. PSA is not cancer-specific but rather organ-specific, which limits its clinical utility. Although cancer cells produce an abundant amount of PSA, any condition that disrupts the normal architecture of the prostate, such as benign prostatic hyperplasia (BPH) and prostatitis, may also cause elevation of serum PSA. Conversely, serum PSA levels will not be elevated in tumors confined to the prostate or

a large portion of early-stage tumors, such as prostate intraepithelial neoplasia (PIN).

Two studies published in March 2009 examined the effect of PSA screening on prevention of PrCa mortality.^{43,44} Both studies showed that after seven and 10 years of PrCa screening by PSA tests and digital rectal exams, the death rate from PrCa did not differ significantly from the unscreened control group. In fact, the studies show that PSA screening leads to overdiagnosis, such that 48 men were treated unnecessarily for PrCa for every one death that was prevented.⁴⁴ Because PrCa is a heterogeneous disease, the challenge is to distinguish between clinically indolent types that do not pose threat to life versus aggressive tumors that require aggressive treatment. A man has a one in six chance of being diagnosed with PrCa in his lifetime, and a one in 33 chance of dying from the disease. Despite the high incidence rates, the majority of PrCa cases never develop symptoms. Many tumors are very slow growing – it is estimated that one in 10 prostate tumors will never progress. Since PrCa can be a very indolent disease, many men will develop other co-morbidities, and most men will die with their PrCa rather than from it.

There are a number of curative treatment options for patients with localized disease, including radical prostatectomy, radiotherapy, chemotherapy and androgen deprivation. Although primary tumors are commonly cured by surgery combined with adjuvant treatment, side effects of treatment can have a negative impact on sexual and urinary function.⁴⁵ An attractive concept is delaying treatment to rigorously monitor men until evidence of disease progression is detected and then perform curative therapy or active surveillance.⁴⁶ When PrCa progresses, it generally spreads through the lymphatic system or by hematologic spread to distant sites, particularly bone. PrCa is considered to have progressed beyond the localized state when there is extension of the cancer into or through the prostatic capsule, the base of the bladder or the seminal vesicles. PrCa can present a challenge to physicians and patients, as it is usually a silent disease until an advanced stage. Unfortunately, there is no cure for metastatic PrCa, and the treatment remains palliative. The goal of future diagnostic and prognostic tests is to detect PrCa at an early stage and discern indolent types from aggressive for proper treatment of the individual.

Serum-Based Methods for Detection of Prostate Cancer

In the recent past, methods of detecting PrCa generally included a combination of the digital rectal exam (DRE) and serum testing for PSA in all men over the age of 50. However, these methods lack both sensitivity and specificity, and no studies have shown that screening with PSA reduces mortality from PrCa.⁴⁷ On DRE, PrCa may feel like an area of increased firmness within the prostate

gland, loss of the median sulcus or an irregularly enlarged prostate. Given the current evidence about the value of these screening methods, the ACS no longer recommends that average-risk men undergo regular screening. Instead, it is recommended that the decision to screen be made after discussing the potential benefits, limitations and harms associated with testing.

An issue with the current screening methods for PrCa is that there is no consensus on what can be considered a "normal" PSA level. Recent studies have shown that screening by PSA level may be more appropriate for men of younger age, when the serum level of PSA is less influenced by benign prostatic hypertrophy and prostatitis.⁴⁸ Another limitation of PSA screening is that it offers no prediction of the severity or aggressiveness of the cancer and cannot be used alone to guide treatment options. Methods to validate PSA as an appropriate screening technique have defined different ways of utilizing PSA derivatives.

Free PSA

Multiple molecular forms of PSA have been discovered. Some PSA that is secreted from the prostate cannot form complexes with serum antiproteases.⁴⁹ This form is termed unbound or "free PSA." A lower percentage of free PSA has been shown to have independent positive predictive value for the risk of developing PrCa. A free PSA level of 25 percent or higher confers a lower risk for PrCa, and has also been shown to have 95 percent sensitivity.^{50,51} Despite the promise of free PSA levels and its diagnostic capabilities, it does have some limitations. As patients age and their prostate volume increases, so does the percentage of free PSA.⁵² Also, manipulation of the prostate (DRE, biopsy and the like.) increase the proportion of free PSA to total PSA.⁵³ Currently, the only two assays approved by the FDA for PrCa screening are total PSA and free PSA.

PSA Density

PSA density takes into account the differences in serum PSA levels and varying sizes of prostate glands. The PSA level is divided by the volume of the prostate, which is determined sonographically. As PSA density increases, so does the risk of PrCa compared to BPH.⁵² Studies have also correlated PSA density with the aggressiveness of the cancer, showing that very high PSA density is associated with a greater risk of high Gleason grading, larger tumors and distant spread of the cancer.⁵⁴

PSA Velocity

PSA velocity involves recording annual trends in serum PSA levels for individual patients. Studies have correlated high PSA velocity with not only an increased risk of PrCa, but also with the aggressiveness of the cancer.⁵⁵ However, the sensitivity and specificity of PSA velocity

for PrCa are not enough to justify the use of PSA velocity in men who do not have elevated PSA levels.^{56,57} The most effective use of PSA velocity may be in prognostics. Having a high PSA velocity as much as 10 to 15 years before the diagnosis of PrCa has been correlated with more aggressive tumors and an increased likelihood of recurrence after treatment.^{58,59}

Early Prostate Cancer Antigens (EPCAs)

Like PSA, EPCAs are proteins in serum that can be measured by a simple blood test. EPCAs are essential elements of the nuclear matrix of cells, the structure of which changes with the development of PrCa.⁶⁰ One study using immunohistochemical analysis showed that anti-EPCA antibodies positively stained noncancerous prostate biopsies of men who, as much as five years later, were diagnosed with PrCa.⁶¹ A subsequent study demonstrated that antibodies to EPCA can be used for enzyme-linked immunosorbent assays (ELISA) that are both sensitive and specific for PrCa.⁶² Another, unrelated nuclear structural protein, EPCA-2, may offer even higher specificity and sensitivity, in addition to the ability to differentiate localized PrCa from PrCa that has spread beyond the prostate itself.⁶³

Molecular Urine Markers for Early Detection of Prostate Cancer

Given the high incidence rate of PrCa and the limitations of DRE and PSA screening, advances in early diagnosis and detection methods are needed. While tissue sampling of the prostate can provide a definitive diagnosis, less-invasive tests that are easily performed and reliably reproduced are essential. One of the more promising techniques for early detection of PrCa involves the use of molecular urine tests. These tests utilize recently identified PrCa biomarkers that are more specific or highly overexpressed in PrCa cells compared with normal prostate cells, unlike PSA, which is expressed similarly in both normal and cancer cells.⁴⁸ Molecular urine tests are based on the identification of these biomarkers in the urine obtained after applying mild digital pressure over the palpable surface of the prostate gland.

Prostate Cancer Antigen 3 (PCA3)

PCA3 (also known as DD3) mRNA has been shown to be highly overexpressed in PrCa, with low expression in normal tissue,⁶⁴ and is not correlated with prostate volume.⁶⁵ Analysis of post-DRE urine samples for the expression of PCA3 by Reverse Transcription-PCR analysis offers both high sensitivity and specificity for PrCa.⁶⁶ A recent study also reported a direct correlation of PCA3 score with tumor volume and Gleason score.⁶⁷ Given this correlation, a molecular urine test for PCA3 mRNA may prove most useful for determining which patients require aggressive treatment versus active surveillance. Recently, this method has been used for the development of a commer-

cially available PCA3 diagnostic test. Although not yet FDA-approved, many research labs in the United States offer this test.⁵²

Alpha-Methylacyl Coenzyme A Racemase (AMACR)

The AMACR gene encodes an enzyme that regulates the peroxisomal beta-oxidation of phytol-derived branched-chain fatty acids. It has been reported to be a highly sensitive and specific marker for immunostaining of PrCa tissue, and is currently a standard tool used in the diagnosis of PrCa in needle biopsies of ambiguous lesions.⁶⁸ A more recent study has also shown that AMACR mRNA can be detected in the urine sediments obtained after DRE. Taken alone, this study showed that urinary AMACR has a sensitivity of 70 percent and a specificity of 71 percent.⁶⁹ Combined with other tests such as PCA3, both sensitivity and specificity are much improved.

Application of Functional Genomics and Next-Generation Sequencing to Cancer

Over the last 10 years, microarray technologies have had a tremendous impact on science and medicine. Expression microarray analysis has led to classification of tumors and early prediction of drug response in patients. Currently, we are in the midst of the next technological revolution in biological sciences, namely the next-generation, cost-effective sequencing technologies. Within the next three to four years, entire human genome sequences at the single nucleotide resolution are predicted to cost around \$1,000 and require a few days to perform.⁷⁰ To put that into perspective, for twice the cost of a FISH-based HER-2 amplification assay, it would be possible to sequence the entire genome of the patient's tumor at the

single-nucleotide level. One goal of full-genome sequencing is to tailor drugs to the genetic makeup of a patient's tumor. Scientists are currently cataloging the spectrum of genes that are somatically mutated in cancer and linking the changes to outcome data. This information will be used to search for new predictive tumor markers and therapeutic strategies. Such approaches will have high clinical impact when the predictive relationship between mutations and tumor response is linked. For PrCa, the answer to which patients have indolent versus aggressive tumors may simply be found in the tumor's genomic sequence. Additionally, targeted therapies currently are not available for triple-negative BrCa patients. Functional genomics may provide insight into understanding these cancers, allowing for new therapeutic targets to emerge for personalized treatment.

Conclusion

It is estimated that nine million people worldwide will die from cancer in 2015, and 11.4 million in 2030.⁷¹ In the United States alone, approximately \$20 billion is spent annually to screen for BrCa and PrCa.⁷² The identification of novel non-invasive screening modalities, prognostic biomarkers and targeted therapies is urgently needed. Many cancers, such as BrCa and PrCa, are very heterogeneous diseases, and the utilization of a combination of biomarkers and multiple therapeutic targets may improve detection and treatment of patients.⁷³ With the recent advancements in microarray technology, functional genomics and next-generation sequencing, identifying multifactorial biomarkers, discovering new drug targets and tailoring therapy to the genomic makeup of a tumor will be a reality in the near future.

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Please note: Due to limited space, we are unable to list all 73 references. You may contact South Dakota Medicine at 605.336.1965 for a complete listing.

Quality Focus:

Colorectal Cancer Awareness

The month of March is Colorectal Cancer Awareness Month, and the South Dakota Council on Colorectal Cancer is providing you with opportunities to learn more about how you can help with this effort to increase colorectal cancer screening rates in your practice.

Why Screen for Colorectal Cancer?

- Screening not only can prevent colorectal cancer, but it also reduces mortality.
- Patients are more aware of and motivated toward colorectal cancer screening than ever before.
- Providers are increasingly asked to raise colorectal cancer screening rates as health plans, the Centers for Medicare & Medicaid Services (CMS), and other third-party payers are looking at colorectal cancer screening rates as a quality measure.

Dale Bachwich, MD, gastroenterologist with Rapid City Regional Medical Center, will be presenting two webinars:

March 11, 2010, noon-1 pm (CT)
Colorectal Cancer Screening Update

March 30, 2010, noon-1 pm (CT)
Colorectal Cancer Screening Toolkit for Office-Based Practices

Accreditation Statement: This activity has been planned and implemented in accordance with the Essentials and Standards of the Accreditation Council for Continuing Medical Education. Rapid City Regional Hospital is accredited by the South Dakota State Medical Association to provide continuing medical education for physicians.

Credit Designation: Rapid City Regional Hospital designates this education activity for a maximum of 1 *AMA PRA Category I Credit™*. Physicians should claim credit commensurate with the extent of their participation in the activity.

How to Increase Colorectal Cancer Screening Rates in Practice: A Primary Care Clinician's Evidence-Based Toolbox and Guide

In addition to other helpful items, the toolbox and guide include the following:

- Checklist for increased screening, office policies, reminder systems, and communication aids
- Template telephone scripts for patient follow-up
- Sample reminder letters to patients at average and increased risk
- Descriptions of electronic reminder systems

The guide can be found online at the following sites: www.nccrt.org and www.cancer.org/colonmd.

The Toolbox is sponsored by the American Cancer Society, the National Colorectal Cancer Roundtable, and Thomas Jefferson University.

To register for these webinars, please contact Denise Kolba: denise.kolba@cancer.org or 605-323-3548, or visit www.cancer.org/mwcoloncancerwebinars



American Cancer Society / Avera Health Plans / Avera McKennan / Community HealthCare Association of the Dakotas / DAKOTACARE / Rapid City Regional Medical Center / Sanford USD Medical Center / South Dakota Foundation for Medical Care / South Dakota State Medical Association / South Dakota Department of Health / Wellmark Blue Cross Blue Shield of South Dakota

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South Dakota Cancer Registry

South Dakota's Cancer Surveillance System

SOUTH DAKOTA
DEPARTMENT OF HEALTH

The South Dakota Cancer Registry (SDCR) is South Dakota's statewide cancer surveillance system. The SDCR is housed within the South Dakota Department of Health. The data collected by the SDCR are used to monitor cancer trends, target cancer control and prevention programs, provide a research base for studies into cancer causes, and to ultimately reduce death and illness due to cancer.

In 2001, the SDCR came into existence and is obligated to collect cancer cases diagnosed from that year forward, regardless of the vital status of the cancer patient. SDCL 1-43-11 through 1-43-18 requires all licensed hospitals, physicians, physician assistants, nurse practitioners, nurse midwives, pathology laboratories and free-standing radiology centers that detect, diagnose, or treat cancer in South Dakota to report required cases to the SDCR.

Malignant cancers diagnosed and/or treated in South Dakota must be reported to the SDCR, as well as benign brain and central nervous system tumors. The following cancers are NOT reportable: carcinoma *in situ* of the cervix (CIS), intraepithelial neoplasia of the cervix (CIN) and prostate (PIN) and basal or squamous cell carcinoma of the non-mucoepidermoid sites of the skin. The SDCR acknowledges and applauds the reporting efforts of the South Dakota medical community.

For each cancer patient diagnosed or treated within South Dakota, the registry collects patient demographics, disease specific details, and all treatment information. Adherence to national standards and guidelines assures quality and consistency in case reporting. The SDCR is certified by the North American Association of Central Cancer Registries, which establishes measures for excellence in the areas of completeness, quality and timeliness.

The majority of cancer cases in South Dakota are abstracted by a certified tumor registrar (CTR) who is specially trained and nationally certified in cancer surveillance. Cancer data collection standards continually evolve to support technological advances in cancer diagnostics and treatments. To keep abreast of the ever-changing standards, the SDCR partners with hospital-based cancer registries for continued cancer surveillance educational and training opportunities.

Strict security measures assure confidentiality of patient and institutional records. The SDCR complies with all applicable federal and state laws related to access of protected health information.

SDCR data are used by health planners, epidemiologists, physicians, hospitals, legislators, researchers, and others to:

1. Monitor the incidence and mortality of cancer to detect potential public health problems;
2. Inform and educate by providing descriptive data on cancer incidence and mortality about risks, prevention, and early detection of cancers known to be elevated in their communities;
3. Guide decisions about how to use public-funded cancer control resources by more accurately targeting intervention resources for communities and patients and their families; and
4. Respond to public concerns.

Released publications are available at the SDCR website <http://doh.sd.gov/SDCR/>. For additional information, contact the South Dakota Department of Health at 605-773-3361. The SDCR is funded with a grant from the Centers for Disease Control and Prevention.

