The Journal
OF THE SOUTH CAROLINA MEDICAL ASSOCIATION

Breast Cancer Disparities in South Carolina: Early Detection, Special Programs, and Descriptive Epidemiology

Swann Arp Adams, PhD [1,2,3]
James R. Hebert, MSPH, ScD [1,2,3,4]
Susan Bolick-Aldrich, MSPH, CTR [5]
Virginie G. Daguise, PhD [6,7]
Catishia M. Mosley, MSPH [5]
Mary V. Modayil, MSc [1,2,3]
Sondra H. Berger, PhD [8]
Jane Teas, PhD [2]
Michael Mitas, PhD [10]
Joan E. Cunningham, PhD [2,11]
Susan E. Steck, PhD [1,2,3]
James Burch, PhD [1,2,3]
William M. Butler, MD [2,12]
Marie-Josephe D. Horner, MSPH [13]
Heather M. Brandt, PhD [2,3,9]

Breast cancer is the most commonly diagnosed cancer among women,[1] and risk increases substantially with age.[2] It is the second leading cause of cancer death among women in South Carolina and in the United States (U.S.). In South Carolina, European-American women are more likely to be diagnosed with breast cancer than are African-American women (see Figure 1);[3] however, African-American women are more likely to die from breast cancer than are European-American women (see Figure 2).[4] Although breast cancer can occur in men, women are at a much (≈ 100-fold) higher risk of developing breast cancer.

Address correspondence to: Dr. Adams, Cancer Prevention and Control Program, The University of South Carolina, 2221 Devine Street, Columbia, SC, 29208. Email: swann.adams@sc.edu.

Etiology and Pathogenesis

It is clear from cross-country comparisons[5-11] and migrant studies[6,9,10] that non-genetic (i.e., primarily lifestyle-related) causes of breast cancer dominate as plausible explanations of inter-population rate differences in incidence as well as rates of change over time. Although somewhat controversial, some studies have found that conventional risk factors (including those related to reproduction, family history, and socioeconomic status) explain less than 50% of breast cancer incidence.[12-14] Other studies have found that lifestyle-related factors such as obesity, decreased physical activity, and hormone therapy use may explain a larger proportion of breast cancer incidence.[15-17] However, these documented factors do not easily explain the ethnic disparities seen in breast cancer. Further, although the role of diet continues to be the focus of most primary prevention efforts, the evidence from analytic epidemiologic studies is equivocal in its support.[18-29] One of the few randomized clinical trials of a low-fat, high-fruit and vegetable diet suggests that long-term consumption of this type of diet may lower the risk of invasive breast cancer; however, further research is needed.[30] Low-penetrance genetic traits, environmental agents, or hormones also may contribute to uncharacterized risk.[31]

Long-term exposure of breast tissue to estrogen plays a major role in breast tumor formation.[31] Consequently, reproductive factors such as total numbers of pregnancies, age at first pregnancy, breastfeeding, age at first menstruation, and age at menopause, which affect a woman's lifetime exposure to estrogen, have been shown to be strongly associated with breast cancer risk.[32-35] Previous studies have shown that an earlier age at first pregnancy, a greater number of total pregnancies, and breastfeeding function to lower a woman's risk of breast cancer in the long term. It is estimated that each of these factors may reduce the risk up to 30%.[33] Additionally, a later age at first menstruation and an earlier age at menopause also decrease a woman's risk of breast cancer.

In efforts to determine exactly how these reproductive factors may influence breast cancer risk, researchers have examined the relationship between blood estrogen levels and breast cancer.[36-38] Most breast cancers occur among post-menopausal women, and several large prospective studies have identified an association between elevated post-menopausal estrogen levels and breast cancer risk.[36-38] The relationship between pre-menopausal estrogen levels and subsequent breast cancer development is more difficult to ascertain, but is supported by some studies.[38-40] Increased mammographic breast density is another risk factor for breast cancer.[41-43]

Several studies show an effect of obesity and adult weight gain on breast cancer.[44-48] Interestingly, substantial adult weight gain is associated with a decreased risk of breast cancer pre-menopausally and increased risk post-menopausally.[15] However, the role of overall and regional adiposity and stature has been a matter of discussion for decades.[49-51] Various mechanisms can explain the effect of overweight, including increased extra-ovarian conversion of androstenedione to estrone in adipose tissue,[52] the potential for carcinogen storage

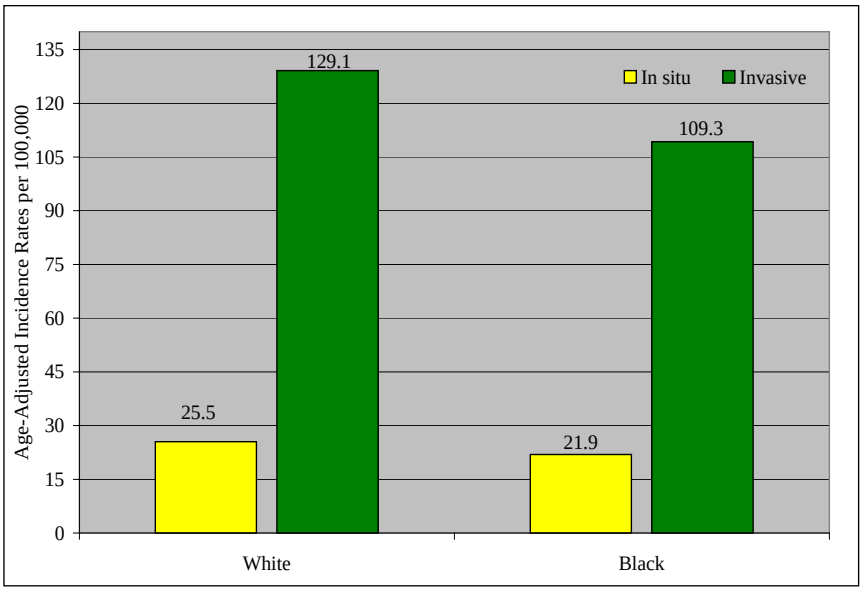

Figure 1. In-situ vs. Invasive Female Breast Cancer Age-Adjusted Incidence (1998-2002) Rates per 100,000 in SC by Race

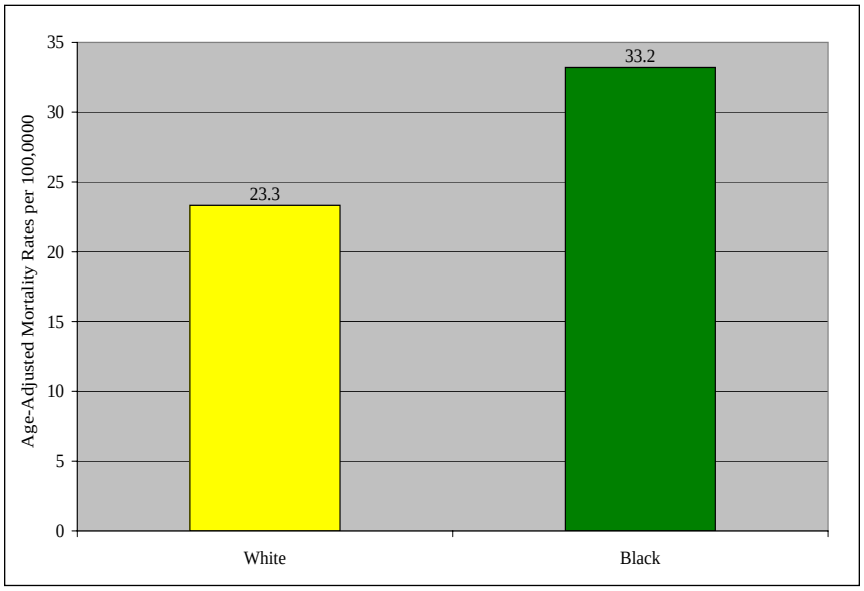

Figure 2. Female Breast Cancer Age-Adjusted Mortality (2000-2004) Rates per 100,000 in SC by Race

in adipose tissue,[53] and the contribution of hyperinsulinemia.[16] Physical activity, which is related to dietary behavior,[54] can also influence risk and its impact is independent of diet and body mass index,[55-57] but it is subject to measurement problems.[58-60] While there are inconsistencies in the breast cancer literature related to physical activity, Friedenreich found that 24 of 36 studies reported a reduced risk for breast cancer (average risk reduction ~ 30 to 40%).[61] The International Agency for Research on Cancer concluded that the evidence was convincing for a protective effect of physical activity on breast cancer risk.[15]

A recent review of the literature reveals that between 30 to 60 minutes of moderate or vigorous activity per day is needed to significantly reduce breast cancer risk.[61] The possible biological mechanisms by which physical activity influences breast cancer risk are reductions in hormone levels (causing anovulatory menstrual cycles with moderate activity or secondary amenorrhea with more strenuous activity during a woman's reproductive years), achieving energy balance (thereby contributing to weight maintenance or weight reduction), improving insulin sensitivity, modulating growth factors such as insulin-like growth factor I, or influencing inflammation and immune response.[62-64] Lifestyle factors represent categories of effect modifiers and potential confounders of one another. For example, exercise/physical activity[65-67] or smoking[68,69] could modify the effect of diet in determining overall health status.

Still other important and potentially modifiable risk factors for breast cancer are alcohol consumption and smoking.[32-34] Some of the most recent estimates indicate that breast cancer risk increases roughly 10% for every 10g of alcohol consumed per day.[33] Of interest, there seems to be a threshold above which risk does not increase (i.e., women who consume large amounts of alcohol are not at particularly high risk).[33] The evidence for smoking is more complex. Earlier studies indicated no association between smoking and breast cancer risk; however, more recent research has shown that the role of passive smoke was not assessed accurately in these earlier studies.[32] Once this additional information was considered in the research, investigators found that women who have been exposed to passive smoke for two hours a day for 25 years or who were actively smoking were at an elevated risk for breast cancer in comparison to women who were never exposed to smoke.[70]

A useful tool for clinicians to use in determining a woman's risk for breast cancer is the Gail model. The Gail model combines several known risk factors including: age, age at first menstrual period, age at first live birth, number of first-degree relatives with breast cancer (mother, sister[s], and/or daughters), number of previous breast biopsies (either positive or negative), and whether at least one biopsy had atypical

hyperplasia, together in a multiple variable statistical computation to estimate a woman's five-year cumulative risk of a breast cancer diagnosis.[71,72] The U.S. Preventive Services Task Force recommends that the Gail model be used to identify women for enrollment into breast cancer chemoprevention trials,[73] and the U.S. Food and Drug Administration guidelines state that women 35 years or older with Gail model risks >1.67% are eligible for tamoxifen chemoprophylaxis.[74] While the Gail model can be useful in the clinical practice, it does not take into account other lifestyle-related risk factors previously discussed.[75]

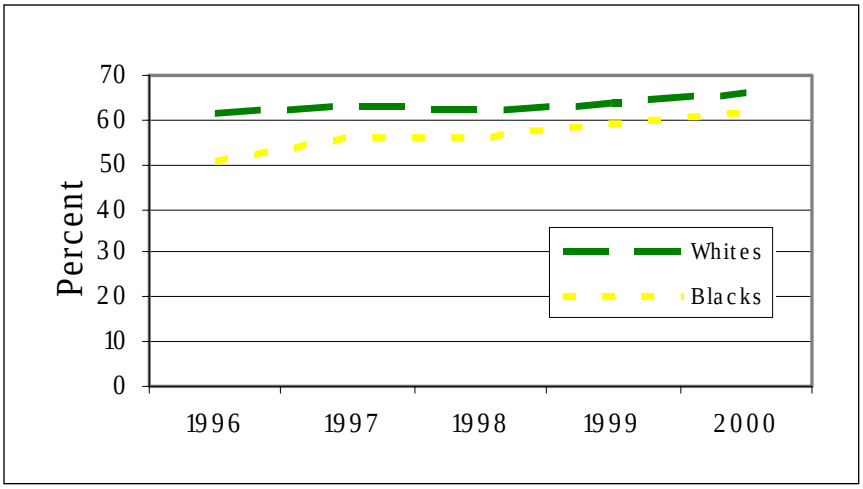

Figure 3. Prevalence of Mammography in SC (1996-2000, BRFSS)

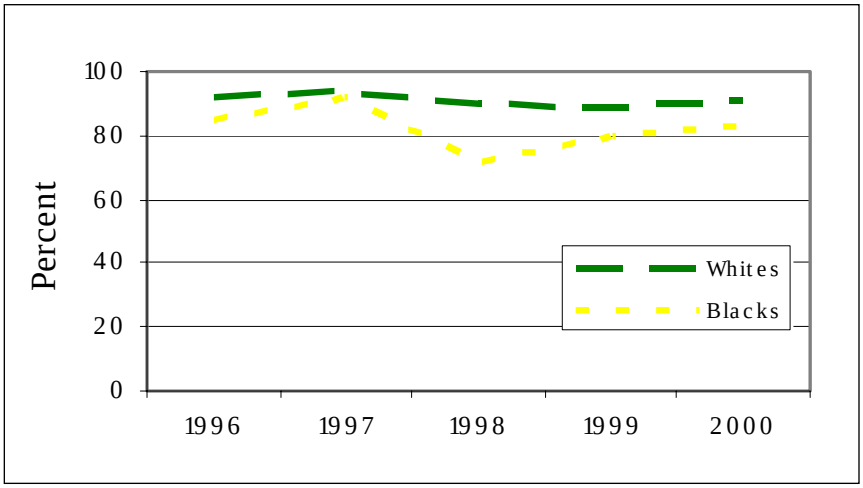

Figure 4. Prevalence of Clinical Breast Exam in SC (1996-2000, BRFSS)

Ethnic differences in cancer incidence and mortality within the U.S. can also provide important etiologic clues that may be inapparent when focusing on studies conducted within homogeneous populations. Breast tumors in African-American women tend to be more aggressive even within the same size category, leading to a poorer stage-for-stage prognosis than in their European-American counterparts.[76] Two distinct hypotheses have been proposed for these differences: 1) socio-economic disparities in the African-American community adversely affect access to care and disease screening; or 2) the biological nature of breast cancer and its disease manifestation are inherently worse for African-American women.[76,77] Although a body of literature has addressed these hypotheses over the last few years, no clear answer has emerged.[78-91] It certainly is possible that the observed differences result from a combination of the two hypotheses. In a prospective investigation of 156,570 postmenopausal women participating in the Women's Health Initiative, the increased mortality observed in African-American women was associated with unfavorable biological characteristics of breast tumors and was independent of socio-economic factors and other established risk factors (e.g., body mass index).[92]

Recommendations for Early Detection

Survival rates for breast cancer have greatly increased over the past half-century, most likely due to continuous improvements in medical technology that have enabled early detection and treatment. Given that many of the known risk factors for breast cancer (i.e., reproductive choices) are not amenable to conventional public health messages, one strategy for reducing mortality is early detection through self-examination, clinical examination, and mammography.[93] Still other strategies might include modification of lifestyle factors such as exercise, weight maintenance, adolescent smoking, and limiting alcohol intake.

The American Cancer Society (ACS) has recommended that women in the 40-49 year age group have mammograms every one – two years and that those women aged 50 years and older have mammograms every year.[94] Women who have a family history of breast cancer or a previous breast cancer diagnosis should talk to their physician about the need to begin screening or diagnostic tests at an earlier age. Although not common, it is possible for women under 40 years of age to develop breast cancer and indeed certain minority populations appear to have greater numbers of breast cancer cases in this age group than other ethnicities.[94] The ACS recommends that women between 29 – 39 years of age have clinical breast examinations every three years and do monthly breast self-examinations.[94] Although not as controversial as prostate cancer screening in men, there is debate

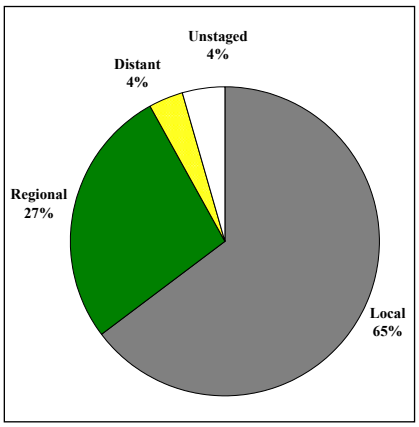

Figure 5. Female Breast Cancer Stage at Diagnosis in SC among White Women, 1998-2002

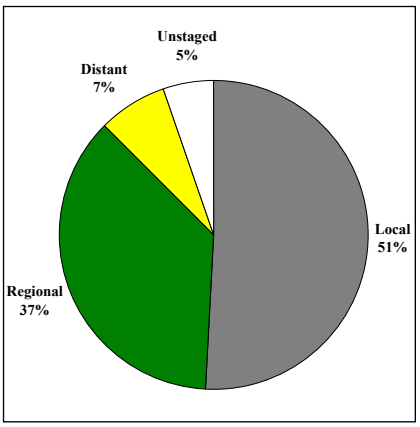

Figure 6. Female Breast Cancer Stage at Diagnosis in SC among Black Women, 1998-2002

on the utility and frequency of some screening tools and it should be noted that longer intervals between mammograms are recommended in Europe.[95-99]

Special Programs in South Carolina

The National Breast and Cervical Cancer Early Detection Program (NBCCEDP) began in 1991 in response to the Breast and Cervical Cancer Mortality Prevention Act of 1990. Through this act, $64 million was appropriated to 12 states to provide screening and follow-up services to low-income women. Special emphasis was placed on serving racial minorities and the underserved. South Carolina was one of the eight states to apply and receive NBCCEDP funding. From these funds, the South Carolina Department of Health and Environmental Control (DHEC) created "The Best Chance Network" (BCN). The BCN program contracts with health care providers including private practices, hospitals, federally funded primary care centers, surgeons, laboratories, and radiology facilities to provide funding for screening and diagnostic follow-up services which include clinical breast examinations, mammograms, pelvic examinations, and Pap (Papanicolaou) smears. Diagnostic follow-up services also are provided under this program. These include surgical consultation, fine-needle aspirations, biopsies, diagnostic mammograms, and ultrasounds, which ensure that women with abnormal screening results receive timely and appropriate diagnostic evaluation and treatment referrals. Since it began screening in 1992, the BCN program has provided over 96,000 clinical breast exams, over 91,000 Pap smear tests, and more than 64,000 mammograms to 55,246 women.

South Carolina is a relatively rural state, with very high African-American representation in rural areas (> 40% of all rural residents are African-American). It is also a poor state, where the average personal income is about 81% of the national average.[100] These factors make access to educational and health care resources and to research programs difficult. Speaking to the success of the BCN at reaching minority communities, approximately 60% of enrollees are African-American and an estimated 60% reside in a county classified as rural by the U.S. Census Bureau. Consequently, this program offers the ideal environment to examine ethnic differences in breast cancer among economically disadvantaged women, especially those residing in rural settings.

With the passage of the Breast & Cervical Cancer Treatment Act in 2000, South Carolina has now been able to provide treatment for BCN participants who are diagnosed with breast cancer. Since 2001, South Carolina has offered treatment coverage under Medicaid through an agreement with the Department of Health and Human Services (DHHS). The availability of treatment for the women of the BCN was a significant milestone.

Most recently, the DHHS, in partnership with DHEC and community advocates, worked successfully to obtain one million dollars in state funds towards cervical and breast cancer treatment. These funds, which became available beginning on July 1, 2005, have been earmarked for breast and cervical cancer treatment under the Breast & Cervical Cancer Treatment Act. With this new funding, women with breast cancer or pre-cancerous conditions such as atypical hyperplasia, will qualify for Medicaid to pay for their treatment if they are younger than 65 years of age; do not have insurance coverage that covers breast cancer treatment; and have a family income that is at or below 200% of the federal poverty level. Furthermore, by receiving treatment for breast cancer under Medicaid, women receive full Medicaid benefits for the duration of the cancer treatment.

One example of a medical system-based program is Palmetto Health's Certificate of Public Advantage (COPA). This hospital-funded program, which was developed to initiate community health outreach within the immediate service area, has generated several other programs, including the Cancer Health Initiative. One component of Palmetto Health's COPA Cancer Health Initiative is to provide breast cancer screenings to women 35 years of age and above who are uninsured or underinsured and live in Richland, Lexington, and Fairfield counties. Women who qualify receive screening mammograms and clinical breast examinations. If abnormal test results occur, women are notified by mail or phone and referred to Palmetto Health's Breast Center for additional follow-up. The Cancer Health Initiative makes financial arrangements with the Breast Center to ensure that the patient is not billed at the time of follow up.

Descriptive Epidemiology

Nationally, African-Americans have an overall lower incidence (12%) of breast cancer than do European-Americans, African-American women are more likely to die of invasive breast cancer than are European-American women (34.5 vs. 25.4 per 100,000 women).[1] Additionally, trends in breast cancer incidence and mortality over time evince patterns that vary markedly by ethnicity. From 1975 to 2002, Surveillance, Epidemiology, & End Results (SEER) data indicate that European-American women had a 29% increase in breast cancer incidence and a 22% decrease in mortality.[4] While African-American women experienced an identical 29% increase in incidence, they had a 16% increase in mortality during that time.[4]

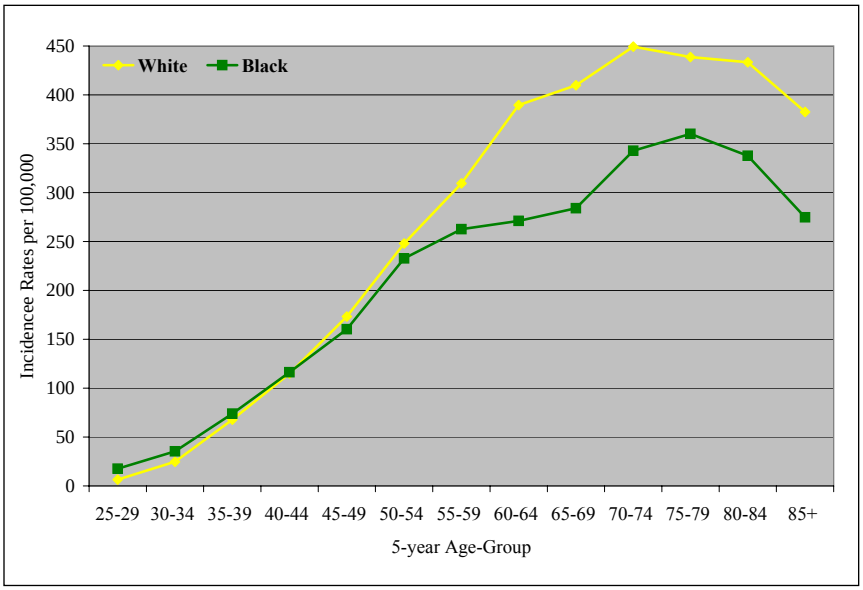

Figure 7. Female Breast Cancer Age-Specific Incidence (1998-2002) Rates per 100,000 in SC by Race and 5-year age-groups

Incidence rates in South Carolina are shown in Figure 1. In 2002, there were 3,350 new cases of breast cancer diagnosed in South Carolina. Of these, 77% occurred in European-American women. Incidence rates from 1996-2001 have remained stable with a somewhat higher age-adjusted incidence among European-American women than among African-American women (129.8/100,000 in European-Americans, and 111.6/100,000 in African-Americans).

There were 566 deaths among women in South Carolina from breast cancer in 2004, underlining that breast cancer is not a very deadly cancer (i.e., mortality is relatively low in comparison to incidence). However, mortality as a function of incidence disfavors African-American women in South Carolina (see Figure 2), whose incidence is lower than that of European-American women but whose mortality rate (33.2 deaths/100,000/year) is 42% higher than European-Americans (23.3 deaths/100,000/year). Nationally this difference is about 32%.[1,4,101] This is due entirely to the difference between African-American rates in SC versus the US rate for African Americans. Rates in South Carolinians of European descent are virtually identical to those seen nationally.[101] Furthermore, for the past several years mortality rates among African-American women have remained relatively constant, while they have been falling among European-American women.[4] Not only does this significant difference suggest interesting and important research possibilities, it causes tremendous hardship in the African-American community.

Early detection through mammograms and clinical breast exams is known to reduce the risk of mortality from breast cancer.[94,102] One potential explanation for the observed racial disparity is that African-American women may be less likely to be screened than European-American women in South Carolina. However, as demonstrated in Figures 3 and 4, the prevalence of mammography and self breast examination is similar among European-American and African-American women, at least among a random sample of women who have a telephone and have participated in the Behavioral Risk Factor Surveillance System (BRFSS) survey.

Both in South Carolina and in the U.S. as a whole, African-American women are more likely to be diagnosed at late stages than European-American women.[77,93,103] As shown in Figures 5 and 6, 27% of European-American women compared to 37% of African-American women are diagnosed with regional stage breast cancers. In addition, only 4% of European-American women present with distant stage disease versus 7% of African American women. Further research has shown that African-American women in South Carolina are more likely to have more aggressive disease within the same age range and tumor size category.[76]

Across racial groups, there is a steady increase in breast cancer incidence which peaks at 65 to 79 years of age and then the rates begin to decline (see Figure 7). Although this pertains to both racial groups, it also is obvious that the relative rate at young ages (when disease tends to be much more aggressive) disfavors African-American women as their rates of disease are slightly higher in the 25 to 39 age groups.

In addition to overall state comparisons between racial groups, it is also useful to examine geographic trends in incidence and mortality by ethnicity within the state. Figures 8 and 9 provide a graphical representation of incidence and mortality in African-Americans compared

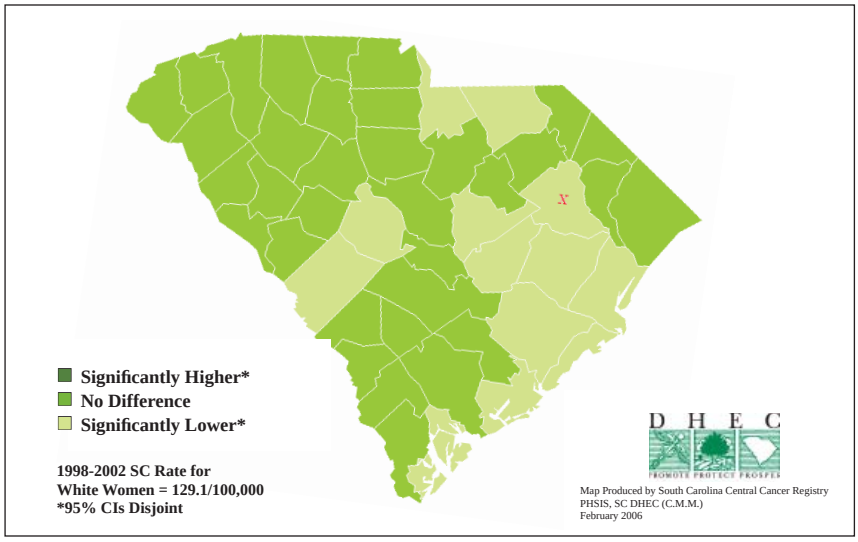

Figure 8. South Carolina Female Breast Cancer: Comparison of the Age-Adjusted, County-Specific Incidence Rate for Black Women vs. the Age-Adjusted, State-Specific Incidence Rate for White Women (1998-2002)

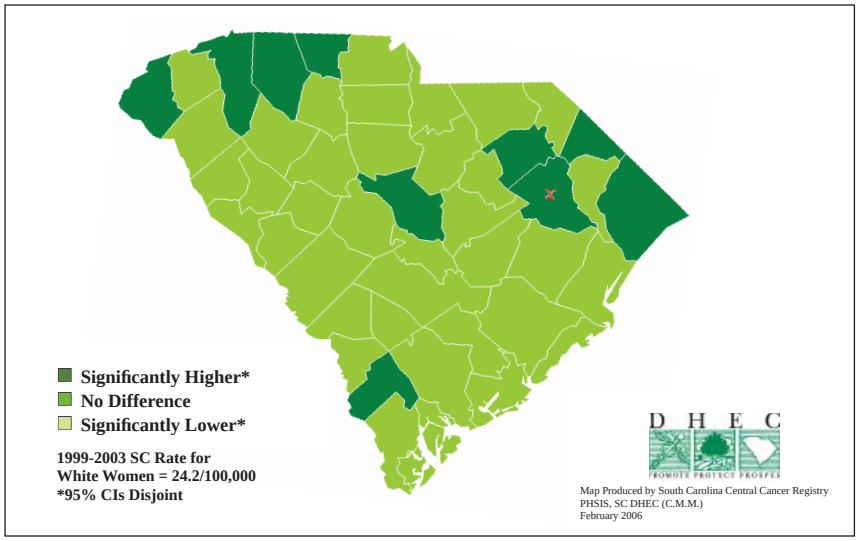

Figure 9. South Carolina Female Breast Cancer: Comparison of the Age-Adjusted, County-Specific Mortality Rate for Black Women vs. the Age-Adjusted, State-Specific Mortality Rate for White Women (1999-2003)

to the state rate for European-Americans. The areas of significantly lower incidence rates among African-American women are found in the coastal and central state regions while areas of significantly higher mortality rates among African-American women are found in the northern regions. It is interesting to note the single county (Florence - indicated by 'X') overlap between the two maps (i.e. counties with significantly lower incidence that also have significantly higher mortality).

Summary

A discrepancy exists between mortality and incidence rates between African-American and European-American women in South Carolina. The relationship between tumor grade and the estrogen/progesterone receptor status is different in African-American and European - American women.[77,79,104] African-American women with breast cancer should be encouraged to participate in clinical trials, with the goal of identifying biological factors that might facilitate the detection of tumors at an earlier stage and the development of more effective therapies. The most important of our goals is to design studies to reduce the incidence of the disease and interventions to improve survival and quality of life. The importance of participation in research cannot be overstated.

Reproductive factors such as early pregnancy and multiple pregnancies are strongly related to breast cancer risk, however, promotion of these factors as a "prevention strategy," clearly does not lead to cogent, comprehensive public health messages. Data from ecological and migrant studies point clearly to other factors that may be important such as diet. Additional research around primary prevention strategies is needed. In addition, yearly mammograms (secondary prevention) are recommended for women over 50 years old or those with relatives who have developed breast cancer.[94] The Best Chance Network, as a provider of screenings to low-income, uninsured women, has helped to narrow the racial gap in screening that otherwise might exist (see Figures 3 and 4) to a large extent.

The determination for timing of surgery after diagnosis needs additional consideration. For example, factors such as effective screening in younger women, timing of screening and surgery in relationship to the ovulatory cycle, and season of screening and surgery may have a great impact on outcomes and may offer some insight[105-107] into the process of carcinogenesis and therapeutic efficacy. Research into this area is so novel that the impact on possible ethnic disparities is completely unknown.

The South Carolina Cancer Disparities Community Network (SCCDCN) has identified the following areas as potential research foci:

- Identification of small media interventions as an effective strategy to motivate targeted populations, especially those least likely to seek screening for

breast cancer and those least likely to participate in research programs (African-Americans).

- Utilization of breast cancer survivors, self-identified as community natural helpers can share their experiences with their church congregation. A replication of such a program in South Carolina has great potential because of the strong presence of the church, especially in rural parts of the state. Programs that closely integrate religion with screening women for breast cancer are promising in this state.

- Development of a mammography registry whereby information on all mammography procedures would be collected within a single database system (much like a central cancer registry). This would aid in identifying population groups that could be targeted for special programs and in the examination and exploration of the most appropriate modalities of detection. Such a resource could also be a useful tool to encourage screening. Thus, this focus area has the potential to benefit epidemiologic and health promotion research on many different levels.

Additional breast cancer screening methods should not be overlooked as a potential research focus. Mammography is not the only valid screening method for breast cancer. Magnetic resonance imaging has shown some promise for screening among women with a genetic predisposition for cancer.[108] Another promising avenue is thermography. Because detection rates may depend on age, ethnicity, and breast mammographic characteristics, women for whom regular screening methods do not detect their cancers (e.g. older age, African-American ethnicity, dense breasts) must be identified and other screening methods promoted within these populations. The above-mentioned mammography registry would support this type of research.

Acknowledgement

We would like to acknowledge the South Carolina Central Cancer Registry (SCCCR) for the state cancer incidence and mortality data provided. The SCCCR is funded by the CDC National Program of Cancer Registries, cooperative agreement number U55CCU421931, and SCDHEC. We would also like to acknowledge funding of the South Carolina Cancer Disparities Community Network (SCCDCN) through grant number 1 U01 CA114601-01 from the National Cancer Institute (Community Networks Program).

The authors wish to thank Dr. Leslie Bernstein of the University of Southern California for her insightful review of this manuscript.

References

1. US Cancer Statistics Working Group. United States Cancer Statistics: 2001 Incidence. 2004. Atlanta (GA), DHHS/CDC/NIH-NCI.
2. American Cancer Society. Cancer Facts and Figures 2005. 2005. Atlanta, GA, ACS.
3. South Carolina Central Cancer Registry. South Carolina Central Cancer Registry Incidence (finalmast2005-stat) and Mortality (cancermortality9403-stat) files. 2006. Office of Public Health Statistics and Information Services, Department of Health and Environmental Control.
4. Ries LAG, Eisner MP, Kosary CL, Hankey BF, Miller BA, Clegg L, Edwards BK. Cancer Statistics Review 1975-2002. 2005. Bethesda, MD, National Cancer Institute.
5. Prentice R, Pepe M, Self S. Dietary fat and breast cancer: A quantitative assessment of the epidemiological literature and a discussion of methodologic issues. Cancer Res 1989; 49:3147-3156.
6. Thomas D, Karagas M. Cancer in first and second generation Americans. Cancer Res 1987; 47:5771-5776.
7. Armstrong B, Doll R. Environmental factors and cancer incidence and mortality in different countries with special references to dietary practices. Int J Cancer 1975; 15:617-631.
8. Hebert JR, Rosen A. Nutritional, socioeconomic, and reproductive factors in relation to female breast cancer mortality: findings from a cross-national study. CCnacer Detect Prev 1996; 20:234-244.
9. LeMarchand L, Kolonel LN, Nomura A. Breast cancer survival among Hawaii-Japanese and Caucasian women. Am J Epidemiol 1985; 122:571-578.
10. Buell P. Changing incidence of breast cancer in Japanese American women. J Natl Cancer Inst 1973; 51:1479-1483.
11. Gray GE, Pike MC, Henderson BE. Breast cancer incidence and mortality rates in different countries in relation to known risk factors and dietary practices. Br J Cancer 1979; 39:1-7.
12. Hirohata T, Shigematsu T, Nomura AM, Nomura Y, Horie A, Hirohata I. Occurrence of breast cancer in relation to diet and reproductive history: a case-control study in Fukuoka, Japan. NCI Monogr 1985; 69:187-190.
13. Hebert J.R., Miller D.R., Toporoff E., Teas, Barone. Black-white differences in U.S. cancer rates: a discussion of possible dietary factors to explain large and growing divergencies. Cancer Prev 1991; 1:141-156.
14. Madigan MP, Ziegler RG, Benichou J, Byrne C, Hoover RN. Proportion of breast cancer cases in the United States explained by well-established risk factors. J Nat Cancer Inst 1995; 87:1681-1685.
15. Weight control and physical activity Lyon: IARC Press, 2002.
16. Ballard-Barbash R. Anthropometry and breast cancer. Body size--a moving target. Cancer 1994; 74:1090-1100.
17. Colditz G. Hormone replacement therapy increases the risk of breast cancer. Ann N Y Acad Sci 1997; 833:129-133.
18. Hebert JR, Wynder EL. Dietary fat and the risk of breast cancer. N Engl J Med 1987; 317:165-166.
19. Kushi LH, Sellers TA, Potter JD, Nelson CL, Munger RG, Kaye SA, Folsom AR. Dietary fat and postmenopausal breast cancer. J Natl Cancer Inst 1992; 84:1092-1099.
20. Willett WC, Stampfer MJ, Colditz GA, Rosner BA, Hennekiens CH, Spiezer FE. Dietary fat and the risk of breast cancer. N Engl J Med 1987; 316:22-28.
21. Howe GR, Hirohata T, Hislop TG, Iscovich JM, Yuan JM, Katsouyanni K, Lubin F, Marubini E, Modan B, Rohan T, et a. Dietary factors and risk of breast cancer: combined analysis of 12 case-control studies. J Natl Cancer Inst. 1990; 82:561-569.
22. Lund E. The search tide ebbs for the dietary fat hypothesis in breast cancer. Epidemiol 1995; 5:387-388.
23. Prentice RL. Measurement error and results from analytic epidemiology: Dietary fat and breast cancer. J Natl Cancer Inst 1996; 88:1738-1747.
24. Adlercreutz H, Mousavi Y, Hackerstedt K. Diet and breast cancer. Acta Oncol 1992; 31:175-81.
25. Wynder EL, Taioli E, Rose DP. Breast cancer--the optimal diet. Adv Exp Med Biol 1992; 322:143-153.
26. Schatzkin A, Greenwald P, Byar DP, Clifford CK. The dietary fat -- breast cancer hypothesis is alive. JAMA 1989; 261:3284-3287.
27. Rose DP. Dietary Fat and Breast Cancer: Controversy and Biological Plausibility.In: Diet and Breast Cancer ed Weisburger EK, New York: Plenum Press, 1994: 1-10.
28. Wynder EL, Cohen LA, Muscat JE, Winters B, Dwyer JT, Blackburn G. Breast cancer: weighing the evidence for a promoting role of dietary fat. J Natl Cancer Inst 1997; 89:766-775.
29. Prentice RL, Caan B, Chlebowski RT, Patterson R, Kuller LH, Ockene JK, Margolis KL, Limacher MC, Manson JE, Parker LM,

Paskett E, Phillips L et al. Low-fat dietary pattern and risk of invasive breast cancer: the Women's Health Initiative Randomized Controlled Dietary Modification Trial. JAMA 1908; 295:629-642.
30. Prentice RL, Caan B, Chlebowski RT, Patterson R, Kuller LH, Ockene JK, Margolis KL, Limacher MC, Manson JE, Parker LM, Paskett E, Phillips L et al. Low-fat dietary pattern and risk of invasive breast cancer: the Women's Health Initiative Randomized Controlled Dietary Modification Trial. JAMA 2006; 295:629-642.
31. Henderson B, Pike M, Bernstein L, Ross R. Breast cancer.In: Cancer Epidemiology and Prevention eds Schottenfield D, Fraumeni J, New York, NY: Oxford University Press, 1996.
32. Davis D, Axelrod D, Osborne M, Telang N, Bradlow H, Sittner E. Avodiable causes of breast cancer: the known, unknown, and the suspected. Ann N Y Acad Sci 1997; 833:112-128.
33. Key TJ, Verkasalo PK, Banks E. Epidemiology of breast cancer. Lancet Oncol 2001; 2:133-140.
34. McPerson K, Steel C M and Dixon J M. Breast Cancer: Epidemiology, Risks Factors and Genetics (ABC of Breast diseases). Br Med J 2000; 321:624.
35. Kelsey JL, Horn-Ross P. Breast cancer: magnitude of the problem and descriptive epidemiology. Epidemiol Rev 1993; 15:7-16.
36. Kabuto M, Akiba S, Stevens RG, Neriishi K, Land CE. A prospective study of estradiol and breast cancer in Japanese women. Cancer Epidemiol Biomarkers Prev 2000; 9:575-579.
37. Toniolo PG. Endogenous estrogens and breast cancer risk: the case for prospective cohort studies. Environ Health Perspect 1997; 105 Suppl 3:587-592.
38. Key TJ, Wang DY, Brown JB, Hermon C, Allen DS, Moore JW, Bulbrook RD, Fentiman IS, Pike MC. A prospective study of urinary oestrogen excretion and breast cancer risk. Br J Cancer 1996; 73:1615-1619.
39. Helzlsouer KJ, Alberg AJ, Bush TL, Longcope C, Gordon GB, Comstock GW. A prospective study of endogenous hormones and breast cancer. Cancer Detect Prev 1994; 18:79-85.
40. Rosenberg CR, Pasternack BS, Shore RE, Koenig KL, Toniolo PG. Premenopausal estradiol levels and the risk of breast cancer: a new method of controlling for day of the menstrual cycle. Am J Epidemiol 1994; 140:518-525.
41. Kato I, Beinart C, Bleich A, Su S, Kim M, Toniolo PG. A nested case-control study of mammographic patterns, breast volume, and breast cancer (New York City, NY, United States). Cancer Causes Control 1995; 6:431-438.
42. Boyd NF, Byng JW, Jong RA, Fishell EK, Little LE, Miller AB, Lockwood GA, Tritchler DL, Yaffe MJ. Quantitative classification of mammographic densities and breast cancer risk: results from the Canadian National Breast Screening Study. J Natl Cancer Inst. 1995; 87:670-675.
43. Byrne C, Schairer C, Wolfe J, Parekh N, Salane M, Brinton LA, Hoover R, Haile R. Mammographic features and breast cancer risk: effects with time, age, and menopause status. J Natl Cancer Inst 1995; 87:1622-1629.
44. Hankinson SE, Willett WC, Manson JE, Hunter DJ, Colditz GA, Stampfer, Longcope C, Speizer FE. Alcohol, height, and adiposity in relation to estrogen and prolactin levels in postmenopausal women. J Natl Cancer Inst 1995; 87:1297-1302.
45. LaVecchia C, Negri E, Franceschi S, Ralamini R, Bruzzi P, Palli D, Decarli A. Body mass index and postmenopausal breast cancer: an age-specific analysis. Br J Cancer 1997; 75:441-444.
46. Pujol P, Galtier-Dereure F, Bringer J. Obesity and breast cancer risk. Hum Repro 1997; 12:116-125.
47. Ziegler R, Hoover R, Nomura A, West D, Wu A, Pike M, Lake A, Horn-Ross P, Kolonel L, Siiteri P, Fraumeni J, Jr. Relative weight, weight change, height, and breast cancer risk in Asian American women. J Natl Cancer Inst 1996; 88:650-660.
48. Huang Z, Hankinson SE, Colditz GA, Stampfer MJ, Hunter DJ, Manson JE, Hennekens CH, Rosner B, Speizer FE, Willett WC. Dual effects of weight and weight gain on breast cancer risk. JAMA 1997; 278:1407-1411.
49. Bruning PF, Bronfrer JMG, Ansink A, Russell NS, Jong-Bakker M. Why is breast cancer so frequent in the Netherlands? Eur J Surg Oncol 1988; 14:115-122.
50. DeWaard F. Breast cancer incidence and nutritional status with particular reference to body weight and height. Cancer Res 1975; 35:3351-3356.
51. DeWaard F, Poortman J, DePedro-Alvarez FM, Baanders-vanHalewijn EA. Weight reduction and estrogen excretion in obese post-menopausal women. Maturitas 1982; 4:155-162.
52. Siiteri PK. Adipose tissue as a source of hormones. Am J Clin Nutr 1987; 45:277-282.
53. Swain W. Human health consequences of consumption of fish contaminated with organochlorine compounds. Aquatic Toxicol 1988; 11:357-377.
54. Matthews CE, Hebert JR, Ockene IS, Saperia G, Merriam PA. The relationship between leisure-time physical activity and selected dietary variables in the Worcester Area Trial for Counseling in Hyperlipidemia. Med Sci Sports Exerc 1997; 29:1199-1207.
55. Thune I, Brenn T, Lund E, Gaard M. Physical activity and the risk of breast cancer. N Engl J Med 1997; 336:1269-1275.
56. Bernstein L, Henderson BE, Hanisch R, Sullivan-Halley J, Ross RK. Physical exercise and reduced risk of breast cancer in young women. J Natl Cancer Inst 1994; 86:1403-1408.
57. Friedenreich CM, Thune I, Brinton LA, Albanes D. Epidemiologic issues related to the association between physical activity and breast cancer. Cancer 1998; 83:600-10.
58. Baranowski T. Validity and reliability of self report measures of physical activity: an information-processing perspective. Res Q Exerc Sport 1988; 59:314-327.
59. Durante R, Ainsworth B. The recall of physical activity: using a cognitive model of the question-answering process. Med.Sci.Sports Exerc 1996; 28:1281-1291.
60. Adams SA, Matthews CE, Ebbeling CB, Moore CG, Cunningham JE, Fulton J, Hebert JR. The effect of social desirability and social approval on self-reports of physical activity. Am J Epidemiol 2005; 161:389-398.
61. Friedenreich C. Physical Activity and Cancer Prevention: From Observational to Intervention Research. Cancer Epidemiol Biomarkers Prev 2001; 10:287-301.
62. Friedenreich CM, Orenstein MR. Physical activity and cancer prevention: etiologic evidence and biological mechanisms. J Nutr 2002; 132:3456S-3464S.
63. Shephard RJ, Shek PN. Associations between physical activity and susceptibility to cancer: possible mechanisms. Sports Med 1998; 26:293-315.
64. McTiernan A, Ulrich C, Slate S, Potter J. Physical activity and cancer etiology: associations and mechanisms. Cancer Epidemiol Biomarkers Prev 1998; 9:487-509.
65. Schoenborn CA, Benson V. Relationships between smoking and other unhealthy habits: United States, 1985. NCHS Advancedata 1988; 154:1-8.
66. Romieu I, Willett WC, Stampfer MJ, Colditz GA, Sampson L, Rosner B, Hennekens CH, Speizer FE. Energy intake and other determinants of relative weight. Am J Clin Nutr 1988; 47:406-412.
67. Flatt JP. Dietary fat, carbohydrate balance, and weight maintenance: effects of exercise. Am J Clin Nutr 1987; 45:296-306.
68. Matsuya T. Alcohol intake and smoking habits of Japanese telephone employees and their effects on dietary patterns. J Formosan Med Assoc 1982; 81:857-867.
69. Hebert JR, Kabat GC. Differences in dietary intake associated with smoking status. Eur J Clin Nutr 1990; 44:185-193.
70. Morabia A, Bernstein M, Heritier S, Khatchatrian N. Relation of breast cancer with passive and active exposure to tobacco smoke. Am J Epidemiol 1996; 143:918-928.
71. Gail MH. Estimating individualized absolute risks of breast cancer from large cohorts with embedded case-control studies. MDACC. 1992. 4-29-0092.
72. Costantino JP, Gail MH, Pee D, Anderson S, Redmond CK, Benichou J, Wieand HS. Validation studies for models projecting the risk of invasive and total breast cancer incidence. J Natl Cancer Inst 1999; 91:1541-1548.
73. U.S. P. Chemoprevention of breast cancer: recommendations and rationale. Ann "Intern Med 2002; 137:56-58.
74. Tice JA, Cummings SR, Ziv E, Kerlikowske K. Mammographic breast density and the gail model for breast cancer risk prediction in a screening population. Breast Cancer Res Treat 2005; 94:115-122.
75. Rockhill B, Spiegelman D, Byrne C, Hunter DJ, Colditz GA. Validation of the Gail et al. model of breast cancer risk prediction and implications for chemoprevention. J Natl Cancer Inst. 2007; 93:358-366.

76. Cunningham JE, Butler W.M. Racial Disparities in Female Breast Cancer in South Carolina: Clinical Evidence for a Biological Basis. Breast Cancer Res Treat 2004; 88:161-176.
77. Butler WM, Cunningham J. Ethnic Differences in Breast Cancer Characteristics. (Volume 4). 2001. Breast Cancer Online.
78. Campbell JB. Breast cancer-race, ethnicity, and survival: a literature . Breast Cancer Res Treat 2002; 74:187-192.
79. Li CI, Malone KE, Daling JR. Differences in breast cancer hormone receptor status and histology by race and ethnicity among women 50 years of age and older. Cancer Epidemiol Biomarkers Prev 2002; 11:601-607.
80. Chen V, Correa P, Kurman R, Wu X, Eley J, Austin D, Muss H, Hunter C, Redmond C, Sobhan M. Histological characteristics of breast carcinoma in blacks and whites. Cancer Epidemiol Biomarkers Prev 1994; 3:127-135.
81. Edwards M, Gamel J, Vaughan W, Wrightson W. Infiltrating Ductal Carcinoma of the Breast: The Survival Impact of Race. J Clin Oncol 1998; 16:2693-2699.
82. Chang S, Alderfur J, Asmar L, Buzdar A. Inflammatory Breast Cancer: The Influence of Race, Menopausal Status and Body Size on Survival. Proc Annu Meet Am Assoc Cancer Res 1999; 18.
83. Lannin D, Mathews H, Mitchell J, Swanson M, Swanson F, Edwards M. Influence of Socioeconomic and Cultural Factors on Racial Differences in Late-Stage Presentation of Breast Cancer. JAMA 1998; 279:1801-1807.
84. El-Tamer M B, Homel P, Wait R. Is race a poor prognostic factor in breast cancer? J Am Coll Surg 1999; 189:41-45.
85. Connor C, Touijer A, Krishnan L, Mayo M. Local recurrence following breast conservation therapy in African American women with invasive breast cancer. Am J Surg 2000; 179:22-26.
86. Freeman HP. The meaning of Race in Cancer of the Breast. Cancer J Sci Am 1997; 3:76-77.
87. Heimann R, Ferguson D, Powers C, Suri D, Weichselbaum R, Hellman S. Race and Clinical Outcome in Breast Cancer in a Series With Long-Term Follow-Up Evaluation. J Clin Oncol 1997; 15:2329-2337.
88. Yood M, Johnson C, Blount A, Abrams J, Wolman E, McCarthy B, Raju U, Nathanson D, Worsham M, Wolman S. Race and Differences in Breast Cancer Survival in a Managed Care Population. J Natl Cancer Inst. 1999; 91:1487-1491.
89. Moorman PG, Jones BA, Millikan RC, Hall IJ, Newman B. Race, anthropometric factors, and stage at diagnosis of breast cancer. Am J Epidemiol 2001; 153:284-291.
90. Krieger N, Quesenberry C, Jr., Peng T, Horn-Ross P, Stewart S, Brown S, Swallen K, Guillermo T, Suh D, Alvarez-Martinez L, Ward F. Social class, race/ethnicity, and incidence of breast, cervix, colon, lung, and prostate cancer among Asian, Black, Hispanic, and White residents of the San Francisco Bay Area, 1988-92 (United States). Cancer Causes Control 1999; 10:525-537.
91. Liu L, Deapen D, Bernstein L. Socioeconomic status and cancers of the female breast and reproductive organs: a comparison across racial/ethnic populations in Los Angeles County, California (United States). Cancer Causes Control 1998; 9:369-380.
92. Chlebowski RT, Chen Z, Anderson GL, Rohan T, Aragaki A, Lane D, Dolan NC, Paskett ED, McTiernan A, Hubbell FA, Adams-Campbell LL, Prentice R. Ethnicity and breast cancer: factors influencing differences in incidence and outcome. J Natl Cancer Inst 2005; 97:439-448.
93. Jacobellis J, Cutter G. Mammography screening and differences in stage of disease by race/ethnicity. Am J Public Health 2002; 92:1144-1150.
94. Smith RA, Cokkinides V, Eyre HJ. American Cancer Society guidelines for the early detection of cancer, 2003. CCa Cancer J Clin 2003; 53:27-43.
95. Moller B, Weedon-Fekjaer H, Hakulinen T, Tryggvadottir L, Storm HH, Talback M, Haldorsen T. The influence of mammographic screening on national trends in breast cancer incidence. Eur J Cancer Prev 2005; 14:117-128.
96. Tornberg S, Codd M, Rodrigues V, Segnan N, Ponti A. Ascertainment and evaluation of interval cancers in population-based mammography screening programmes: a collaborative study in four European centres. J Med Screen 2005; 12:43-49.
97. Ringash J, Canadian T. Preventive health care, 2001 update: screening mammography among women aged 40-49 years at average risk of breast cancer. CMAJ 2001; 164:469-476.
98. de K. Mammographic screening: evidence from randomised controlled trials. Ann Oncol 2003; 14:1185-1189.
99. Miller AB. Is mammography screening for breast cancer really not justifiable?. Recent Results Cancer Res 2003; 163:115-128.
100. US Department of Commerce. Personal Income By State. Washington, DC: Bureau of Economic Analysis, 2003.
101. Sanders L, Hardy W, Ashford-Carroll T, Bolick-Aldrich S. South Carolina Cancer Facts and Figures: 2001-2002. 2001. South Carolina Central Cancer Registry,Office of Public Health Statistics and Information Services,South Carolina Department of Health and Environmental Control; American Cancer Society,Southeast Division.
102. Srivastava S, Rossi SC. Early detection research program at the NCI. Int J Cancer 1996; 69:35-37.
103. Harris DM, Miller JE, Davis DM. Racial differences in breast cancer screening, knowledge and compliance. J National Med Assoc 2003; 95:693-701.
104. Gordon NH. Socioeconomic factors and breast cancer in black and white Americans. Cancer Metastasis Rev 2003; 22:55-65.
105. Hrushesky WJ, Bjarnason GA. Circadian cancer therapy. J Clin Oncol 1993; 11:1403-1417.
106. Hrushesky W, Lester B, Lannin D. Circadian coordination of cancer growth and spread. Int J Cancer 1999; 83:365-373.
107. Retsky M, Demicheli R. Wounding from biopsy and breast-cancer progression. The Lancet North Am Ed 2001; 357:1048.
108. Warner E, Plewes DB, Hill KA, Causer PA, Zubovits JT, Jong RA, Cutrara MR, DeBoer G, Yaffe MJ, Messner SJ, Meschino WS, Piron CA et al. Surveillance of BRCA1 and BRCA2 mutation carriers with magnetic resonance imaging, ultrasound, mammography, and clinical breast examination. JAMA 2004; 292:1317-1325. ■

Author Affiliations

1. Department of Epidemiology and Biostatistics, Arnold School of Public Health, University of South Carolina, Columbia, SC
2. South Carolina Cancer Center, Columbia, SC
3. Cancer Prevention and Control Program, University of South Carolina, Columbia, SC
4. Statewide Cancer Prevention & Control Program, Hollings Cancer Center, Medical University of South Carolina, Charleston, SC
5. South Carolina Central Cancer Registry, South Carolina Department of Health and Environmental Control, Columbia, SC
6. South Carolina Cancer Alliance, Columbia, SC
7. SC Department of Health and Environmental Control, Bureau of Community Health and Chronic Disease. Prevention, Columbia, SC
8. Department of Basic Pharmaceutical Sciences, College of Pharmacy, University of South Carolina
9. Department of Health Promotion, Education, and Behavior, Arnold School of Public Health, University of South Carolina, Columbia, SC
10. Department of Surgery, Medical University of South Carolina, Charleston, SC
11. Department of Obstetrics and Gynecology, School of Medicine, University of South Carolina, Columbia, SC
12. South Carolina Oncology Associates, Columbia, SC
13. Division of Cancer Control and Population Sciences, National Cancer Institute, Bethesda, MD. *Work carried out while at the South Carolina Cancer Center, Columbia, SC