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Screening for Breast Cancer

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KEY PRINCIPLES

- Breast cancer is the most common cancer in women and the second most common cause of cancer death in the United States.
 - Mammography, regular breasts exams, and breast self-examination are the key components of early detection and surveillance.
 - Multiple risk factors for the development of breast cancer have been established; these include women: with a personal or family history of breast cancer, age over 60 yr, and atypical proliferative fibrocystic change. However, 45% of women with newly diagnosed breast cancer have no identifiable risk factor.
 - Mammography, although proven to reduce the cancer death in screened women, is not a perfect screening test. It fails to detect 10–20% of cancers.
 - Controversy exists regarding the age to institute mammographic screening, indeterminate findings on the breast biopsy, and genetic testing.
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INTRODUCTION

One hundred eighty thousand (180,000) women were diagnosed with breast cancer in the United States in the year 2000 and about 45,000 women died of this disease (1). The mortality rate and the possibility of breast conservation are linked to the size of the cancer at the time of detection. In general, the smaller the tumor at the time of diagnosis, the

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lower the mortality rate for an individual woman and the more likely breast conservation will be successful (2,3).

These facts support the very important role primary care physicians have in minimizing the mortality and morbidity for their patients with breast cancer. Primary care physicians, by having the most direct contact with their patients, play a key role in early detection. By examining patients annually, ordering baseline and regular mammograms, and educating patients in breast cancer facts and self-examination, primary care physicians can make a major impact on the lives of their patients who may eventually be diagnosed with breast cancer.

EPIDEMIOLOGY

Breast cancer is the most common malignancy in women in the United States (4). It is second only to lung cancer as the most common cause of cancer death (4). The incidence of breast cancer had steadily increased in the United States over the last few decades (5). Since 1997, however, breast cancer mortality has declined each year by 1.8% (6,7).

Internationally, the incidence of breast cancer varies greatly, with the lowest rates in the eastern Asian region (China, Japan, and India) to the highest in Western Europe and the United States, where a fivefold increase is observed (8,9).

Racial variability has been observed within the United States. Whereas breast cancer incidence is higher among premenopausal African-American women, the incidence is lower among postmenopausal African-American women compared to white women of similar age (10).

Multiple risk factors for developing breast cancer have been established (Table 1). Despite this, 45% of women with newly diagnosed breast cancer have no identifiable risk factor (11). Being female is the foremost risk factor. Ninety-nine percent of all breast cancer occurs in women. Male breast cancer accounts for less than 1% of all breast cancers (12). Age is the second most critical factor. The risk of breast cancer increases steadily with age through the childbearing years until the mid-50s, and then abruptly rises into the mid-60s. Thereafter, the incidence continues to rise, but gradually (13). Whereas a physician should have a higher index of suspicion in a woman over 50 with a breast mass, breast cancer has been occasionally, although very rarely, diagnosed in women in their late teens (14).

Family history is important in assessing the risk of developing breast cancer. The risk of breast cancer doubles in patients with a family history of breast cancer in the first-degree relatives (mother, sister, daughter) (15). The risk is more than twofold if more than two first-degree

Table 1
Established Risk Factors for Invasive Breast Carcinoma

High risk (RR>4)
• First-degree relative with history of breast cancer
• Age over 60
• Patient born in North America or northern Europe
• Atypical proliferative fibrocystic change
Moderate risk (RR 2–4)
• Age over 30 at first full-term pregnancy
• Obesity
• History of breast cancer
• Any first-degree relative with history of breast cancer
• Dysplastic mammographic parenchymal pattern
• Chest-wall irradiation
• Proliferative fibrocystic change without atypia
• High socioeconomic status
Low risk (RR 1.1–1.9)
• Nulliparity
• Early menarche
• Late menopause
• Postmenopausal obesity
• History of ovarian or endometrial cancer

relatives have breast cancer and the risk is more than three times if one of those relatives had either premenopausal disease or bilateral breast cancer (16,17).

Certain characteristics of a woman’s reproductive history have also been shown to increase the risk of developing breast cancer. Nulliparous women and women having a first birth after the age of 30 yr have twice the risk of developing breast cancer (18). Absence of breast-feeding also increases the risk (19,20). Early onset of menarche, before the age of 12, and late onset of menopause, after the age of 55, each increases the risk by twofold (21,22).

A diagnosis of atypical hyperplasia on a previous breast biopsy and a 65% or greater area of density on the mammogram poses a four times increased risk of developing breast cancer (23–25). Having cancer in one breast increases the relative risk of developing a second cancer in the contralateral breast by a factor of 2–4. This is most marked if a woman has an associated family history of breast cancer (26).

Other factors associated with increased risk are obesity, as defined by weight >200 lbs., history of endometrial and ovarian carcinoma, and prior radiotherapy to the chest or mediastinum (27).

THE BIOLOGY OF BREAST CANCER

Breast cancer is both a local and a systemic disease. Breast cancer is heterogeneous in its presentation and course. Its propensity for early systemic spread is, more often than not, directly related to an overall cure rate that does not exceed 65% in the United States. Its natural history is protracted over time, making the definition of the “cure” of breast cancer difficult (28,29).

We know that, in general, the smaller the tumor, the less likely there is lymph node involvement, and the better the long-term survival (30–32). Yet, metastases can become apparent as late as 10–20 yr after a disease-free period from initial treatment (33).

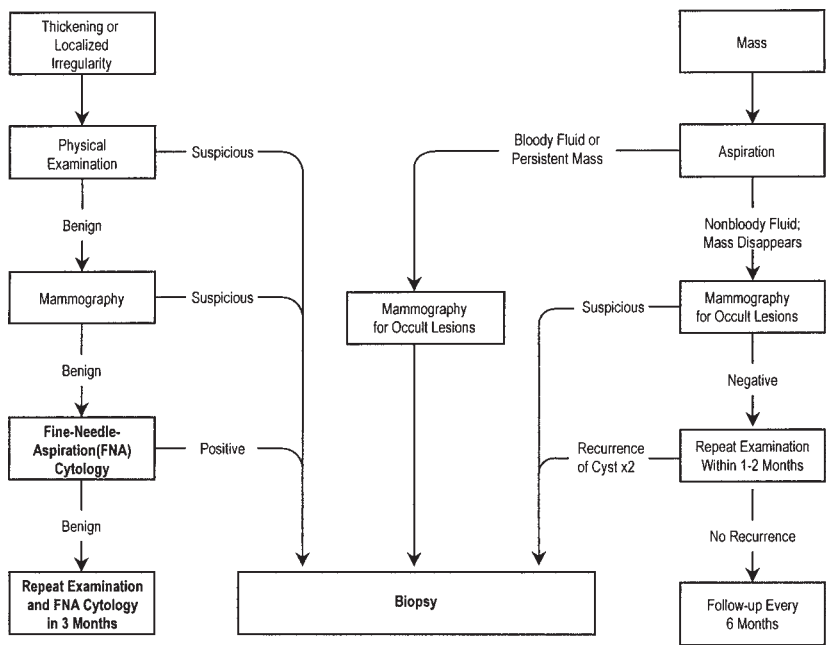
The behavior of the primary tumor within the breast starts as a single malignant cell, which is estimated to take approximately 5–8 yr to reach 1 cm (34). It spreads within the breast by direct infiltration of adjacent tissue, along mammary ducts and through breast lymphatics (35). The systemic problems develop from breast cancer cells metastasizing beyond the breast to regional lymph nodes and distant organs. Axillary lymph nodes are the major regional drainage site for the breast. In half the patients with a clinically palpable breast mass, axillary lymph nodes are involved (32). The internal mammary lymph-node chain and supraclavicular lymph nodes are less frequently involved (36,37).

Metastases to distant organs may be recognized at the time of diagnosis or as late as 10 yr or more after initial treatment (30). In general, the incidence and the time-course to distant metastases correlates with the size of the primary tumor (30). Yet, it is recognized that there are subsets of patients whose tumors do not behave in this predictable manner (28). Distant metastases are most frequently found in the lungs, liver, bone, adrenal glands, pleura, brain, and skin (38–40).

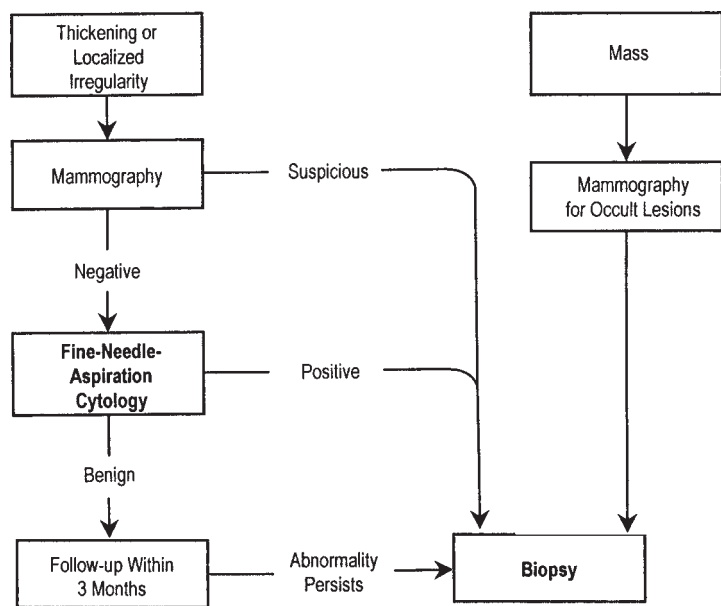
SCREENING FOR BREAST CANCER

The purpose of breast cancer screening is to separate women who are clearly normal from those with abnormalities, with the goal of intervening in the disease process after biologic onset but before symptoms or signs develop (41) (*see* Algorithms 1 and 2). Mammography, regular breast exams, and breast self-examination are the key components of early detection and surveillance (42). Additional radiological modalities will be mentioned as adjuncts, but they are not basic screening tools.

The use of mammography to screen asymptomatic women 40 yr of age and over for early detection of breast cancer has been shown to reduce mortality rates by 20–30% (43–45). A standard screening mammogram includes two views of each breast. Additional views at differ-



Algorithm 1. Evaluation of breast abnormalities in premenopausal women.



Algorithm 2. Evaluation of breast abnormalities in perimenopausal and postmenopausal women.

ent angles or increased compression of the breast tissues may be included for better definition of the character of the breast tissue (46,47).

Although there has been a decade of controversy as to the timing of mammograms, the current consensus, based on recommendations of the American Cancer Society, is as follows:

1. Baseline mammogram at age 40
2. Between ages 40 and 49, a mammogram yearly or every other year
3. At age 50 or older, a mammogram yearly

Mammograms at an earlier age or more frequently are indicated for women with increased risk (42).

Routine, regularly scheduled clinical breast exams by a skilled physician have been shown to play an important role in early detection of breast cancer. When combined with mammography, clinical breast exams decrease mortality from breast cancer (48,49).

At the minimum, breast examination should be performed annually beginning at age 30 and become part of a woman's routine physical examination. However, physicians should practice clinical breast examinations with yearly gynecological or physical exams in younger women as well. Key elements to the success of a clinical breast exam are consistency in the examiner, regular scheduling, and attention to technique.

With a woman disrobed from the waist up, a woman should be examined in both the sitting and supine positions. The breast should be examined for symmetry of the overall appearance, nipple–areolar complexes, and skin texture, with the arms by the sides and also elevated above the head. Note of any retraction or bulging of the breast tissue, skin edema, peau d'orange, or erythema should be made. The nipples should be examined for crusting, bleeding, irregularity, or retraction. Palpation of the breast skin should follow, examining for thickening, nodules, or induration. Again, in both the sitting and supine positions and with the arms beside the torso and raised above the head, the breasts should be firmly but gently palpated in their entirety. Either a concentric circular or radial search pattern is effective, as long as it is complete. Palpation should extend to the clavicle, to the sternum, to the lower rib cage and into the axilla, in which much breast tissue is located, especially in older women. Documentation of any abnormalities should include size, location, mobility, and character.

The final portion of the exam is addressed by examining the node-bearing regions. In the sitting and supine position, the supraclavicular fossae and both axillae should be examined. The axillae are best examined while sitting with the physician supporting the flexed arm with one hand, palpating with the other.

A third and complementary component to breast surveillance is breast self-examination. Although regular breast self-examination alone cannot be linked to a decreased mortality from breast cancer, it does have a measurable impact on earlier detection when carefully practiced (50–52). To be of value, physicians should teach breast self-examination carefully and consistently (53,54). Women should be encouraged to participate in self-examination. Upon finding a mass on self-examination, a woman should be promptly seen and evaluated.

The most important message concerning the roles of mammography, clinical breast examination, and breast self-examination is that they complement, but do not replace, each other (55). It is an important role of the primary care physician to educate his or her patients to the fact that even when a mammogram reveals no lesion in the presence of a palpable mass, a breast cancer may be present and further evaluation should be made. In either the setting of a nonpalpable mammographic lesion or a palpable lesion not seen on a mammogram, surgical consultation is imperative (56).

Other radiological modalities available for breast evaluation include ultrasound and magnetic resonance imaging (MRI). Both of these can add additional information to mammographic and clinical findings, but they are incapable of detecting early-stage cancers with reliability and do not provide a screening tool (47,57). Ultrasound is very useful in distinguishing cysts from solid lesions (58,59).

GENETIC SCREENING

With the discovery of the autosomal dominant genes BRCA 1 and BRCA 2, which transmit a high breast cancer risk, questions arise as to the role of genetic screening. When present, these genes indicate significant susceptibility to developing breast cancer (60,61). The presence of a mutated version of BRCA 1 carries a 90% lifetime risk for developing breast cancer (62).

The current testing, however, is limited in its applicability. Because of technical constraints, its utility is confined to women from a large family in which a relative has been diagnosed with breast cancer and has had a gene alteration identified. Therefore, women to consider for counseling for genetic testing should include the following:

1. Women from large families with relatives with breast and/or ovarian cancer
2. Women from small families with early-onset disease or bilateral cancer, or individual women diagnosed before 40 yr of age
3. Women with male breast cancer relatives (63)

However, genetic testing must be approached cautiously because of the significant long-term implications to a woman. Counseling before testing is imperative and preferably is conducted as part of a research program before proceeding with genetic analysis (64,65). Unexpected adverse reactions of guilt and depression, dilemmas as to treatment options (prophylactic mastectomies, prophylactic tamoxifen), and ethical dilemmas surrounding families who choose not to know their status have been experienced (66). As there is no protection for privacy of genetic information, there are significant implications for discrimination and stigmatization. Insurers can deny coverage for surveillance or prevention if a high-risk gene is identified, or breast cancer care of an affected woman might be denied based on the concept that the condition was pre-existing. Furthermore, documentation of the results in the medical record may result in loss of medical or life insurance coverage and discrimination by an employer (67). Therefore, consideration of genetic testing should be approached cautiously and is best handled with counseling in a research program.

COST-EFFECTIVENESS

The cost-effectiveness of screening for breast cancer in asymptomatic women usually includes the cost of the screening tests, the cost of further workup of abnormal screening tests, cost of false-positive and false-negative screening tests, and the cost of treatment in the unscreened population. The potential possibilities for the latter are multiple and are, therefore, too numerous to discuss in this setting. However, when breast cancer is found at a later stage, more involved surgery, potential radiation to the chest wall, potential reconstruction, chemotherapy and the increased risk of eventual need for metastatic treatment, and numerous resultant periodic tests are the norm. All of these require significant expenditure and increase patient suffering. Most analyses of breast cancer screening have been either mathematical models or related to clinical trials, and virtually all consider it a useful expenditure of resources (68–70).

INDICATIONS FOR REFERRAL TO A SURGEON

After screening results are obtained, the following are guidelines for referral to a general surgeon for further examination.

Mammographic Findings

1. Indeterminate findings or benign findings in a woman at high risk.
2. Suspicious findings or those highly suggestive of cancer.

Physical Findings (Regardless of Mammographic Findings)

1. Palpable mass or irregular thickening in the breast.
2. Bloody nipple discharge.
3. Skin changes of erythema, thickening, or peau d'orange character.
4. Supraclavicular or axillary lymphadenopathy.

CONTROVERSIAL AREAS

Controversy exists regarding the timing of a surgical consultation in a woman with a mammographic abnormality amenable to a core or fine-needle aspiration and/or a palpable mass that is amenable to needle biopsy. Although other physicians are capable of these procedures, because the ultimate responsibility rests in the hands of the surgeon, early surgical consultation before a needle biopsy is preferable. This allows the surgeon to give the patient a full up-front discussion about the possibilities of future treatment should the needle biopsy be positive, allowing the patient a broader sense of the implications of the finding at hand, and the possible course ahead. In palpable lesions, the needle biopsy eliminates the possibility of hematoma formation obscuring physical findings at the time of the surgeon's patient examination and treatment planning.

A higher profile controversy is the age to institute mammographic screening. Multiple studies from around the world have looked at this issue. There is no question that there is a decrease in mortality in women over 50 yr of age receiving screening mammograms. The controversy is in the 40–49-yr-old age group (43,45). Because of the density of breasts in the younger age group, mammograms are not as sensitive in detecting malignancies. After much discussion and review of multiple studies, the American Cancer Society and National Cancer Institute recommend that mammograms be performed in the 40–49-yr-old age group either annually or every other year (42).

The controversy surrounding genetic testing has been described earlier. Presently, each physician needs to weigh the pros and cons of recommending this testing with its inherent limitations. There is no controversy that once genetic testing is discussed with a patient that counseling must be incorporated in the process, and preferably within a research program. As technology advances, legislation catches up with the technology, and future breast cancer chemopreventive agents are discovered, the controversies surrounding breast cancer genetic testing may become more manageable.

One final area of controversy is the use of hormonal replacement therapy (HRT). Although more appropriately discussed in the setting of

treatment rather than screening, the increased risk posed by HRT should be commented upon. Treatment with both estrogen replacement therapy and estrogen–progesterone combination therapy has been shown to increase the risk of developing breast cancer (71,72). This risk increases directly with the duration of treatment. The risk associated with the estrogen–progesterone combination exceeds that of estrogen alone, especially in overweight women (72). Thus, in perimenopausal and postmenopausal women, hormonal replacement therapy should be recognized as an increased risk factor ($RR = 1.4$ at a minimum) for developing breast cancer, with the risk increasing with the duration of treatment.

SUMMARY

Breast cancer is the most common cancer in women. Despite major advances in the diagnosis and treatment of this disease, it carries significant mortality and morbidity. There are about 47 million women above the age of 40 eligible for screening mammography in the United States. Currently about half of the eligible women receive regular screening. One of the most important determinants of a woman's participation in screening is the referral from her primary care physician. Hence, women's access to primary care physicians and their physicians' mammography referral practices are critical steps in the screening and prevention of this disease.

REFERENCE

1. Landis SH, Murray T, Bolden S, et al. (1998) Cancer statistics. *CA Cancer J Clin* 48(1):6–29.
2. Fisher B, Slack NH, Bruss DM, et al. (1969) Cancer of the breast: size of neoplasms and prognosis. *Cancer* 24:1071.
3. Fisher B, Anderson S, Redmond CK, et al. (1995) Reanalysis and results after 12 years of follow-up in a randomized clinical trial comparing total mastectomy and lumpectomy with or without irradiation in the treatment of breast cancer. *N Engl J Med* 333:1456–1461.
4. Boring CC, Squires TS, Tong T, et al. (1994) Cancer statistics. *CA Cancer J Clin* 44:7.
5. Miller BA, Feur EJ, Hankey BF. (1993) Recent incidence trends for breast cancer in women and the relevance of early detection: an update. *CA Cancer J Clin* 43:27.
6. Wingo PA, Ries LAG, Giovino GA, et al. (1999) Annual Report to the nation on the status of cancer, 1973–1996, with a special section on lung cancer and tobacco smoking. *J Natl Cancer Inst* 91:675–690.
7. Wingo PA, Ries LAG, Parker SL, et al. (1998) Long-term cancer patient survival in the United States. *Cancer Epidemiol Biomarkers Prev* 7:271–282.
8. Aoki K, Kurihara M, Hayakawa N, et al. (eds.) (1992) Death Rates for Malignant Neoplasm for Selected Sites by Sex and Five-Year Age Group in 33 Countries, 1953–1957 to 1983–1987. Coop Press, University of Nagoya, Japan.

9. Parkin DM, Muir CS, Whelan SL, et al. (eds.) (1992) Cancer Incidence in Five Continents., IARC Scientific Publication no. 120. Lyon: IARC; vol. 6.
10. Ries LAG, Miller BA, Hankey BF, et al. (eds.) (1994) *Seer Cancer Statistics Review, 1973–1991: Tables and Graphs*. Bethesda, USDHHS National Cancer Institute.
11. Bruzzi P, Green SB, Byar DP, et al. (1985) Estimating the population attributable risk for multiple risk factors using case-control data. *Am J Epidemiol* 122:904.
12. Boreng C, Squires T, Tong T, et al. (1994) Cancer statistics 1994. *CA Cancer J Clin* 44:18.
13. Henderson IC. Breast Cancers. In: Murphy GP, Lawrence Jr WL, Lenhard Jr RE, eds., (1995) American Cancer Society Textbook of Clinical Oncology, 2nd edition, Atlanta, GA: American Cancer Society.
14. Spratt JS, Donegan WL, Greenberg RA. Epidemiology and etiology. In: Donegan WC, Spratt JS, eds., *Cancer of the Breast*. 3rd edition. Saunders, 1988, Philadelphia, PA.
15. Claus EB, Risch NJ, Thompson UD. (1990) Age of onset as an indicator of a familial risk of breast cancer. *Am J Epidemiol* 131:961.
16. Hulka BS, Stark AT. (1995) Breast cancer: cause and prevention. *Lancet* 346:883–887.
17. Kelsey JL. (1993) Breast cancer epidemiology: summary and future directions. *Epidemiol Rev* 15: 256–263.
18. MacMahon B, Cole P, Lin TM, et al. (1970) Age at first birth and breast cancer risk. *Bull WHO* 43:209.
19. Newcomb PA, Storer BE, Longnecker MP, et al. (1994) Lactation and a reduced risk of premenopausal breast cancer. *N Engl J Med* 330:81.
20. Byers T, Graham S, Rzepka T, Marshall J. (1985) Lactation and breast cancer: evidence for a negative association in premenopausal women. *Am J Epidemiol* 121:664.
21. Brinton LA, Schaier CS, Hoover RN, et al. (1988) Menstrual factors and risk of breast cancer. *Cancer Invest* 6:245.
22. Trichopoulos D, MacMahon B, Cole P. (1972) Menopause and breast cancer risk. *J Natl Cancer Inst* 48:605.
23. Dupont WD, Page DL. (1985) Risk factors for breast cancer in women with proliferative breast disease. *N Engl J Med* 312:146.
24. Krieger N, Hiatt RA. (1992) Risk of breast cancer after benign breast diseases: variation by histologic type, degree of atypia, age at biopsy, and length of follow-up. *Am J Epidemiol* 135:619.
25. Saftlas AF, Hoover RN, Brinton LA, et al. (1991) Mammographic densities and risk of breast cancer. *Cancer* 67:2833.
26. Bernstein JL, Thompson WD, Risch N, et al. (1992) The genetic epidemiology of second primary breast cancer. *Am J Epidemiol* 136:937.
27. Brinton LA, Devesa SS. (1996) Etiology and pathogenesis of breast cancer: epidemiologic factors. In: Harris JR, Lippman ME, Morrow M, Hellman S, eds., *Diseases of the Breast*. Philadelphia: Lippincott-Raven, p. 166.
28. Fox M. (1979) On the diagnosis and treatment of breast cancer. *JAMA* 241:489.
29. Hellman S. (1994) The natural history of small breast cancers. David A. Karnofsky Memorial Lecture. *J Clin Oncol* 12:2229.
30. Koscielny S, Tubiana M, Le M, et al. (1984) Breast cancer: relationship between the size of the primary tumor and the probability of metastatic dissemination. *Br J Cancer* 49:709.
31. Koscielny S, Le M, Tubiana M. (1989) The natural history of human breast cancer: the relationship between involvement of auxiliary lymph nodes and the initiation of distant metastases. *Br J Cancer* 59:775.
32. Carter C, Allen C, Henson D. (1989) Relation of tumor size, lymph node status, and survival in 24,740 breast cancer cases. *Cancer* 63:18.

33. Brinkley D, Haybittle J. (1984) Long-term survival of women with breast cancer. *Lancet* 1:1118.
34. Collins V, Loeffler R, Tivey H. (1956) Observations on growth rates of human tumors. *Am J Roentgenol* 76:988.
35. Holland R, Veling S, Mravanac M, et al. (1985) Histologic multi-focality of Tis, T1-2 breast carcinomas. *Cancer* 56:979.
36. Handley R. (1975) Carcinoma of the breast. *Ann R Coll Surg Engl* 57:59.
37. Veronesi U, Cascinelli N, Greco M, et al. (1985) Prognosis of breast cancer patients after mastectomy and dissection of internal mammary nodes. *Ann Surgery* 202:702.
38. Haagensen C. (1986) *Diseases of the Breast*, 3rd edition. Philadelphia: WB Saunders, p. 686.
39. Warren S, Witham E. (1933) Studies on tumor metastases: the distribution of metastases in cancer of the breast. *Surg Gynecol Obstet* 57:81.
40. Saphir O, Parker M. (1941) Metastases of primary carcinoma of the breast with special reference to spleen, adrenal glands and ovaries. *Arch Surg* 42:1003.
41. Rimer BK. (1996) Breast cancer screening. In: Harris JR, Lippman ME, Morrow M, Hellman S, eds., *Diseases of the Breast*. Philadelphia: Lippincott-Raven, p. 307.
42. Leitch AM, Dodd GD, Costanza M, et al. (1997) American Cancer Society guidelines for the early detection of breast cancer: update 1997. *CA Cancer J Clin* 473:150-153.
43. Fletchers S, Black W, Harris R, et al. (1993) Report of the International Workshop on Screening for Breast Cancer. *J Natl Cancer Inst* 85:1644.
44. Baines CJ. (1994) A different view on what is known about breast screening and the Canadian National Breast Screening Study. *Cancer* 74(4):1207-1211.
45. Nystrom L, Rutquist LE, Wall S, et al. (1993) Breast cancer screening with mammography: overview of Swedish randomized trials. *Lancet* 341:973.
46. Sickles EA, Weber WN, Galvin HB, et al. (1986) Mammographic screening: how to operate successfully at low cost. *Radiology* 160:95.
47. Swan CA, Kopans DB, McCarthy KA, et al. (1987) Practical solutions to problems of triangulation and preoperative localization of breast lesions. *Radiology* 163:577.
48. Morrison A, Brisson J, Khalid N. (1988) Breast cancer incidence and mortality in the Breast Cancer Detection Demonstration Project. *J Natl Cancer Inst* 80:1540.
49. Sox Jr HC. (1993) Preventive health services in adults. *N Eng J Med* 330:1589.
50. Foster RS, Costanza MC. (1984) Breast self-examination practices and breast cancer survival. *Cancer* 53:999.
51. Gastrin G, Miller AB, To T, et al. (1994) Incidence and mortality from breast cancer in the MA-MA Program for Breast Screening in Finland, 1973-1986. *Cancer* 73:2168.
52. Grady KE. (1992) The efficacy of breast self-examination. *J Gerontol* 47:69.
53. Champion V. (1992) The role of breast self-examination in breast cancer screening. *Cancer* 69:1985.
54. McKenna Sr RJ, Greene P, Winchester DP, et al. (1992) Breast self-examination and breast physical examination. *Cancer* 69(7):2003.
55. Foster RS, Worden JK, Costanza MC, et al. (1992) Clinical breast examination and breast self-examination. *Cancer* 69:1992.
56. Kopans DB, Meyer JE, Cohen AM, et al. (1981) Palpable breast masses: the importance of preoperative mammography. *JAMA* 246:2819.
57. Heywang-Kobrunner SH. (1994) Contrast-enhanced magnetic resonance imaging of the breast. *Invest Radiol* 29:9.
58. Bassett LW, Kimme-Smith C. (1991) Breast sonography. *Am J Roentgenol* 156:449.
59. Jackson VP. (1990) The role of US in breast imaging radiology. *Radiology* 177(2):305-311.

60. Miki Y, Swensen J, Shattuck-Eidens D, et al. (1994) A strong candidate for the breast and ovarian cancer susceptibility gene BRCA 1. *Science* 266:66.
61. Wooster R, Neuhausen S, Mangion J, et al. (1994) Localization of a breast cancer susceptibility gene, BRCA 2, to chromosome 13q12-13. *Science* 265:2088.
62. Easton D, Bishop D, Ford D, et al. (1993) Genetic linkage analysis in familial breast and ovarian cancer: results from 214 families. *Am J Hum Genet* 52:678.
63. Garber JE, Smith BL. (1996) Management of the high-risk and the concerned patient. In: Harris JR, Lippman ME, Morrow M, Hellman S, eds. *Diseases of the Breast*. Philadelphia: Lippincott-Raven, pp. 327,328.
64. Biesecker B, Boehnke M, Calzone K, et al. (1993) Genetic counseling for families with inherited susceptibility to breast and ovarian cancer. *JAMA* 269:1970.
65. Lynch HT, Watson P, Conway T, et al. (1993) DNA screening for breast/ovarian cancer susceptibility based on linked markers: a family study. *Arch Intern Med* 153:1979.
66. Benjamin CM, Adam S, Wiggins S, et al. (1994) Proceed with care: direct predictive testing for Huntington disease. *Am J Hum Genet* 55:606.
67. Ostrer H, Allen W, Crandall LA, et al. (1993) Insurance and genetic testing: where are we now? *Am J Hum Genet* 55:65.
68. Clark RA. (1992) Economic issues in screening mammography. *Am J Roentgenol* 158(3):527–534.
69. Brown, ML, Fintor L. (1993) Cost effectiveness of breast cancer screening. *Breast Cancer Res Treat* 25(2):113–118.
70. Greenwald P. (1986) Cancer control objectives for the nation. *Natl Cancer Inst Monogr* 2:1.
71. Colditz GA, Hankinson SE, Hunter DJ, et al. (1995) The use of estrogens and progestins and the risk of breast cancer in postmenopausal women. *N Engl J Med* 332:1589–1593.
72. Schairer C, Lubin J, Troisi R, et al. (2000) Menopausal estrogen and estrogen-progestin replacement therapy and breast cancer risk. *JAMA* 283(4):485–491.



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