MEDICAL GRAND ROUNDS

THE UNIVERSITY OF TEXAS HEALTH SCIENCE CENTER AT DALLAS

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CLINICAL ISSUES IN BREAST CANCER

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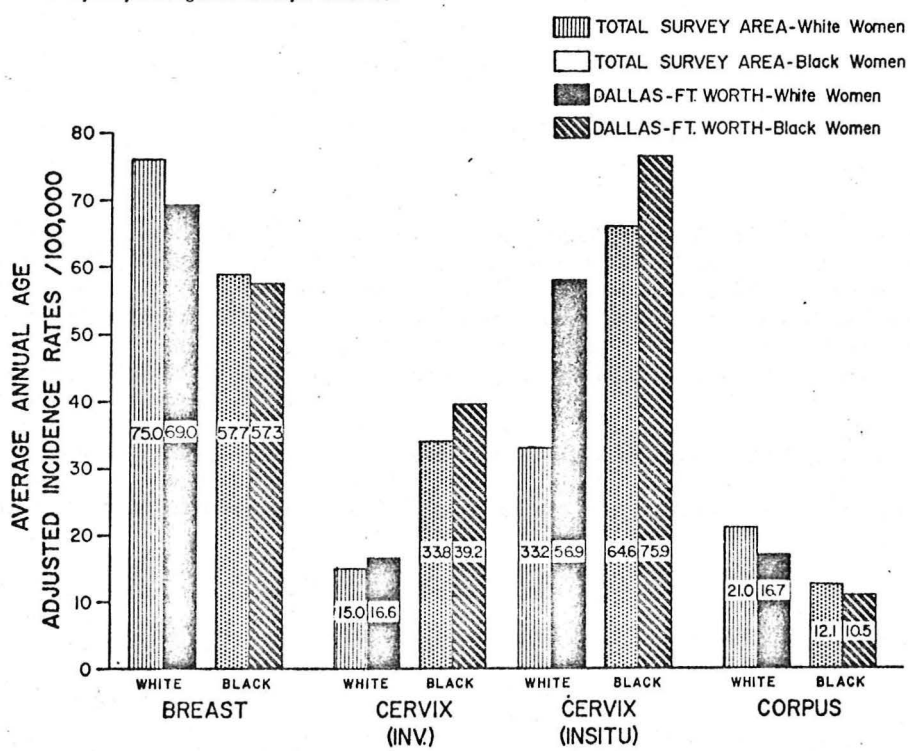
Case #1: A.P.

Thirty-one year old white woman who presented for evaluation of a "lump" in her left breast which she identified while showering. Except for the anxiety generated by the discovery of the mass, she was asymptomatic and had a negative review of systems. The patient had been conscientious about health care and had regularly visited her gynecologist as well as her internist for annual examinations, the most recent visits having been within the previous 3 months. Physical examination revealed a 1 cm mass in the left breast located in the lower outer quadrant approximately 2 cm from the nipple. The remainder of the examination was within normal limits.

I. Magnitude of the Problem:

Accounting for approximately one-fourth of all cancers in women, the current age-corrected incidence rates in the U. S. are approximately 75 per 100,000 white women and 58 per 100,000 for black women, with the rates in the Dallas-Fort Worth area being 69 and 57, respectively (1, 2, 3).

2. Average annual age-adjusted incidence rates per 100,000 population for breast cancer and selected tumors of the female genital tract for white and black women in all areas compared to Dallas-Fort Worth.



(Ref. 3)

Excellent data have been serially compiled by the State of Connecticut over the past 4 decades denoting an increase in incidence in breast cancer which appears to have leveled off during the past decade (4).

Greater significance to the clinical approach for any given woman with carcinoma of the breast focuses upon the survival data accumulated over the past decades. As the most common cause of death in women in the age range 39-54, the death rate has changed little, if at all, in the past two decades (4, 5). This is particularly clear when the data are appropriately expressed in terms of "relative survival rates" adjusting for "normal" mortality (5):

female breast: A

relative survival rates for patients diagnosed 1940-69

	ALL STAGES				LOCALIZED				REGIONAL			
	1940-49	1950-59	1960-64	1965-69	1940-49	1950-59	1960-64	1965-69	1940-49	1950-59	1960-64	1965-69
No. Cases	12184	22105	13828	14911	4652	9342	6338	6956	5228	9144	5780	6160
3-year	63%	71%	73%	72%	86%	89%	91%	91%	56%	65%	67%	68%
5-year	53	60	63		78	83	84		42	51	53	
10-year	40	48			67	73			28	35		
15-year	34	43			59	68			23	29		

Such an expression permits meaningful comparisons of the survival experience of groups of patients that differ with respect to sex, age or calendar period of observation. It is defined as the observed survival rate to the expected rate for a similar group without cancer of the breast (5). This expression permits an evaluation of fate of patients at different ages. The evidence from such data indicates that the mortality risk associated with cancer of the breast is fairly constant with respect to age (5).

In general terms, then, we can estimate approximately 90,000 new cases of cancer of the breast in women this year with 32,500 deaths in the U. S. This translates to approximately 1,000 new cases in the Dallas-Fort Worth area.

II. Projection of Risk Factors:

The high incidence and prevalence of breast cancer in women, the varying incidence in different parts of the world and the obvious hormonal implications have made this lesion a ripe arena for epidemiologic exploration. Such studies are not only relevant to the given patient with a suspected lesion but have been projected as the bases for screening of the asymptomatic woman.

Reasonably relevant variables have been compiled from the data in a variety of studies (6-11):

Table I. Variables Associated with Risk of Female Breast Cancer

Variable	Risk of Breast Cancer	
	Lower	Higher
Age	Young	Old
Race	Oriental	Caucasian
Ethnic group	Gentiles	Jews
Marital status	Married	Single
Number of pregnancies	More	Fewer
Duration of breast feeding	Longer	Shorter
Age at menarche	Later	Earlier
Artificial menopause	Present	Absent
Benign breast disease	Absent	Present
Family history of breast cancer	Absent	Present
Socio-economic status	Lower	Higher

(Ref. 6, 7)

Table II. Characteristics of HIP Study Women and Relative Risks of Breast Cancer

Characteristics	Relative Risk of Breast Cancer
Never married versus married	2.3
1 to 2 pregnancies versus 3 or more	2.0
Age at menarche, under 12 versus 15 or over	1.7
Aggregate years of menstrual activity 30 years or more versus less than 30 years	1.4
Breast conditions, 1 or more versus none	3.1
Sisters - one or more with breast cancer versus none	1.9

(Ref. 8)

A pattern of epidemiologic risk factors has emerged from a variety of family studies (12, 13) and can be broadly generalized (14):

Table III. Who is at Risk of Breast Cancer?

Attribute	RELATIVE RISK: Increased	RELATIVE RISK: Decreased	Commentary
1. Marital status and parity:	Never married		Beyond 40 years of age, mortality 1.4-2.3 times higher in single women.
	Nulliparous		Risk in married nulliparous higher than in married parous.
		Early age at first full term birth	Women first parous before age 18 have one third the risk of those first parous at age 35 or older.
			To be protective, first pregnancy must occur before age 30. Women first pregnant after age 30 appear to be at greater risk than nulliparous women.
2. Menstruation:	Early menarche		Risk in women with menarche before age 16 is almost twice that in women with later menarche.
	Late natural menopause		Women with natural menopause at 55 or older have twice the risk of women with natural menopause before 45.
		Early castration	Castration under age 40 reduces risk by 70-75 per cent. The protective effect is least apparent during the first 10 years after surgical menopause, but is of significance during the remaining decades of life.
3. Family history:	Paternal and/or maternal relatives of women with breast cancer		Mortality in the mothers and sisters of breast cancer patients is increased 2-3 times. First degree relatives of women with bilateral breast cancer have 3 times the risk of relatives of patients with unilateral disease. Familial aggregation of benign breast disease is also demonstrable.
4. Race:	Caucasian	Oriental	Incidence in Japanese women is one fifth that in United States white women.
5. Benign breast disease:	Ductal or lobular hyperplasia, papillomatosis, with cellular atypia		Under the general term "cystic dysplasia," the estimates of increased risk vary between 1.7-4.5. Benign proliferative lesions tend to be multicentric. Although specific dysplastic lesions may be precancerous, the pathogenetic relationship may be an indirect one in that the same causal factors may be stimulating a spectrum of benign and malignant neoplasia.
6. Multiple primary cancers:	Opposite breast Ovary Endometrium Large intestine Major salivary gland		The cumulative risk of a primary cancer in the opposite breast is 4% at 5 years, 6% at 10 years, 9% at 15 years and 13% at 20 years. In women who initially develop breast cancer before 50 years of age, their risk of a second primary breast cancer is more than 8 times the normal risk; the risk is almost 5 times above normal in women who first have a diagnosis of breast cancer at 50 years of age or older. In a patient with primary carcinoma of the ovary, the subsequent risk of breast cancer is increased 3-4 times. In patients with endometrial carcinoma the risk of a subsequent breast carcinoma is increased 1.3-2.0 times. The risk of breast cancer is almost twice that normally expected in women with previous colorectal cancer, and at least two times that normally expected in women with previous carcinoma of a major salivary gland.

(Ref. 14)

Other considered factors:

1. *Hormonal:*

a.) *Prolactin:* Although known to be capable of sustaining mammary carcinoma in animal systems, its role in human disease is uncertain (15, 16). Elevated serum levels have been identified in some high risk groups (16, 17).

b.) *Estriol Hypothesis:* Since the estrogenic derivatives estrone (E1) and estradiol (E2) are capable of supporting experimental mammary neoplasms, the considered thesis relates to reduced excretion of estriol (E3) as being related to increased incidence of breast cancer (17-20).

c.) *Estrogens, "The Pill" and Progesterone:* No supportive evidence in an already voluminous literature (21-26); some "risk" may exist (27).

2. *Drugs:*

As with several other "induction" risks, little definitive evidence. Reserpine, first suggested as a risk agent by the data gathering of the Boston Drug Surveillance Program (28), appears to lack reasonable support (29, 30).

3. *"Chronic Cystic Disease":*

Excellent evidence that young women in this category represent a potential risk category (31).

4. *Radiation Exposure:*

Clearly evident "risk" factor from the Hiroshima-Nagasaki follow-up where 90 rads exposure resulted in a 2- to 4-fold increase in incidence of breast cancer (32).

III. Relevant Aspects of Tumor Cell Kinetics:

In vitro and *in vivo* kinetic measurements reveal great variation in doubling times. Mean values in range of 15 days from *in vitro* studies with 90% cell loss (33) to approximately 3 months seen in the *in vivo* studies (34-36). These kinetic observations have correlated with clinical therapeutic observations (36).

Case #2: R.L.

Fifty-five year old woman visited her family physician and subsequently her family surgeon expressing concern about the possibility of having cancer of the breast. Her anxiety had been generated by the identification of such a lesion in a friend by one of the mass screening programs. Each clinician carefully examined her and found no evident abnormalities.

IV. Diagnostic Aids:

1. *Self Examination of Breast:*

- popular, of value, but with serious underestimated limitations (37).

2. *Clinical Examination:*

- the clinician's role in adequate diagnosis contributes significantly and independent of all of the laboratory "screening" methods; especially in patients under the age of 50 (38).

3. *Related Diagnostic Techniques:*

The efficacy and risk of a variety of screening techniques have generated serious concern regarding the indications and use of these procedures in the asymptomatic patient.

a.) *Thermography:*

- measures infrared radiant energy; no risk of ionizing radiation, inexpensive.

- capable of identifying only 45-70% of cancers; low efficacy in Stage I disease; confusion with non-neoplastic lesions (39).

b.) *Low Dose Film Mammography and Xeromammography:*

- current techniques have reduced the exposure to approximately 1.5 to 2.5 rads per examination (40, 41). False positives (42) occur.

Commonly accepted indications (41):

Primary Examination	Serial Examinations
1. Contemplated breast surgery	1. Post-operative follow-up of opposite breast
2. High risk patients	2. High risk patients
3. Clinically evident mass disease	3. Post mammoplasty
4. Breasts which are difficult to examine	

Clearly these techniques have, independent of other methods, increased the recognition of primary lesions and have helped result in a decrease in case fatality rate (43-46). Controversy has focused on the carcinogenic potential of these studies in patients under the age of 50 (47).

Current NIH guidelines (48):

Asymptomatic women, ages 35-40, to have only a base line study and then repeat no more often than every 3 years.

Patients in high risk category (prior cancer in one breast, family history of disease): frequency at the discretion of the physician.

Asymptomatic women over age 50; studies to be limited to every 2 or 3 years.

c.) *Other Imaging Methods:*

- gallium-67-citrate: of limited value; primarily for detection of metastatic breast carcinoma in the mediastinum (49).

d.) *Ultrasound:*

- promises to have significant value in the serial follow-up of young women with intraductal (pre-malignant) lesions.

V. The Choice of the Initial Therapy:

Since the description of the "standard radical mastectomy" by Halsted (50), the "initial treatment of choice has been this procedure". During the first half of this century "end results" or survival studies showed progressively improved rates encouraging the philosophy of early diagnosis and extensive surgery. For the past two decades, little or no change has been seen in survival rates in a wide variety of studies (51-56). These data can be reasonably encapsulated by the data from the End Results Study of the NIH (5):

RELATIVE SURVIVAL RATES 1955-1964

	Surgery		Surgery + Radiation	
Number of Cases	14,741		5,514	
	5-year	10-year	5-year	10-year
Over-all Survival	75%	62%		
	Localized Disease	Regional Disease	Localized Disease	Regional Disease
% of Cases	62%	34%	24%	69%
% Survival				
5-year	87%	59%	77%	52%
10-year	76%	43%	66%	35%

a.) *Natural History of Untreated Breast Cancer:*

Bloom and co-workers (57) have had the unique opportunity of evaluating data on the natural history of untreated breast cancer in 250 patients seen in the Middlesex Hospital during the years 1805-1933.

Survival data: 3 years: 44%
5 years: 18%
10 years: 4%
15 years: 1%

b.) *Factors Affecting Decision for the Type of Initial Therapy:*

1. Site, size and histology (58, 59)

2. Clinical staging (55, 60)

3. Multicentricity potential (52, 55)

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4. Survival

5. Local recurrence rate

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6. Cosmetic appearance

c.) *The Possible Choices:*

1.) Radical or extended radical mastectomy (50, 52, 54-56, 61)

2.) Modified procedures:

a.) Modified radical (58, 59, 62)

b.) Tylectomy (63-66)

3.) Excision and radiotherapy:

Second only to the churning controversy over the "Crile" approach or tylectomy (67) is the potential role of radiotherapy as a primary and significant therapeutic modality. Long term studies in America (59, 65) and in Europe (68, 69) have served to re-focus upon this approach. An extensive series of 702 patients have been followed over a 25-year period by Mustakallio (70). Finally, Hellman and co-workers at Harvard embarked on a carefully designed study in 1968 to evaluate the results of radiation as the primary therapy program (71, 72).

d.) *The Role of Adjuvant Therapy:*

1. Adjuvant radiotherapy (postoperative radiation): Clearly demonstrated that such therapy fails to provide an advantage, either in terms of disease-free interval or survival (73, 74). In an excellent cooperative study of 1,103 patients in 25 medical centers, for instance, the 5-year disease-free status was 50.6% for those radiated and 50.2% non-irradiated (73). Survival rates were 56% for the radiated group and 62% for the non-radiated group. Admittedly, local recurrences were somewhat lower in the radiated group.

2. Adjuvant castration: Although it may provide a slightly increased disease-free interval, it fails to affect the incidence of metastatic disease or survival (75).

3. Adjuvant chemotherapy: Although chemotherapy as an adjuvant to the primary approach has been investigated for nearly 20 years (76, 77), it is only recently that evidence of efficacy has been documented (78, 79). The rationale for this relative to micrometastases is clear relative to the present status of survival data (80-83).

Two current protocols have documented effectiveness of such adjuvant therapy:

National Surgical Adjuvant Breast Protocol (78)

Alkeran (Melphalan, L-PAM):
0.15 mg/kg/d X 5 days every
6 weeks for 2 years

The effect of such a program on the stem cell reserve is by no means clear (84) and the selection of this agent poses many serious questions.

Milan-Bonadonna Protocol (79)

CMF:

Cytoxan: 100 mg/M^2/d orally days 1-14

Methotrexate: 40 mg/M^2 I.V. days 1 and 8

5-Fluorouracil: 600 mg/M^2 I.V. days 1 and 8

- re-treat every 28 days for 12 cycles

Unresolved is the risk of carcinogenicity (85, 86).

VI. Selected Problems Following Initial Therapy:

1. Pregnancy and lactation (87)
2. The "other" breast (88-91)
3. Prognostic features of recurrence
   a.) Size, histology, status (92-97)
   b.) Character of lymphoid mass (98-101)
   c.) Age (102)
4. Status of metabolic markers of activity
5. Clinical significance of skin recurrences (103)
6. Rehabilitation and contour restoration (104, 105)
7. Spontaneous regression potential (106-107)

Case #3:

A 64-year old female presented with swelling of the left arm of 6 months' duration. At physical examination it was noted that the left breast was scarred and shrunken. In the left axilla there was a mass of hard fixed lymph nodes. Lymph node biopsy revealed an infiltrating carcinoma. The patient stated the deformity of the breast appeared at the time of menopause, 18 years earlier.

VII. The Management of Disseminated Disease:

1. Local therapy
2. Hormonal therapy
3. Chemotherapeutic approaches

Following the demonstration by Cooper (108) of the value of combination therapy in disseminated breast cancer, the evidence for such an approach has been solidly confirmed (111, 112).

A variety of combinations, in sequence and in cycles, have demonstrated improved objective remission rates, disease-free intervals and survival when compared to the earlier single agent therapy programs (111-116). Of these, three therapy programs, employing standard chemotherapeutic agents, have emerged as easily applicable and good (117-119).

a.) Adriamycin-Cytoxan [Salmon *et al.* (117)]

Adriamycin: 40 mg/M^2 - I.V. day 1

Cytoxan: 200 mg/M^2/d - orally days 3-6 (4 days)

- courses are repeated q 21-28 days

b.) "CMF" [Canellos *et al.* (118)]

Cytoxan: 100 mg/M^2 - orally - daily, days 1-14

Methotrexate: 60 mg/M^2 - I.V. - days 1 and 8

5-Fluorouracil: 700 mg/M^2 - I.V. - days 1 and 8

Prednisone: 40 mg/M^2 - orally - daily, days 1-14

- courses are repeated every 28 days

c.) "Cross-Over Sequence" [Bonadonna *et al.* (119)]

Sequence I:

Adriamycin: 75 mg/M^2 I.V. day 1

Vincristine: 1.4 mg/M^2 I.V. days 1 and 8

- no therapy days 9-21 and then repeat the course

Sequence II:

Cytoxan: 100 mg/M^2 - orally - days 1-14

Methotrexate: 40 mg/M^2 - I.V. days 1 and 8

5-Fluorouracil: 600 mg/M^2 - I.V. days 1 and 8

- courses are repeated every 28 days

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