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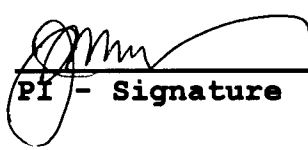
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Introduction

Breast cancer is the most common invasive malignancy affecting American women, accounting for 28% of all tumors diagnosed in this group.¹ It is also a leading cause of cancer related death in the United States. Although the age-adjusted incidence of breast cancer in black women in the U.S. is less than that seen in white women, the mortality rates observed in blacks and whites are virtually identical.² This discrepancy is the result of a significantly lower five year survival rate for black women when compared to white women with breast cancer. The most recent results from the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute have documented an 80% five year relative survival for white women diagnosed with breast cancer between 1983 and 1989; the corresponding rate for black women was only 64%.³ While improvements in the detection and treatment of breast cancer over the last 30 years have led to an improved five year relative survival, there is no evidence that these advances have had an influence on the racial differences in survival.

In order to improve the survival of black women with breast cancer, an understanding of the factors which contribute to their poorer prognosis is necessary. It is known that black women generally have more advanced disease than white women at the time of initial presentation. A tendency toward larger primary tumors as well as a lower incidence of disease confined to the breast and a higher incidence of distant metastases at the time of diagnosis have been documented.³⁻¹³ Environmental, behavioral, and biological factors have also been used to explain the higher incidence of advanced disease in black women with breast cancer. In particular, attention has focused on issues relating to access to medical care and preventive health services. The use of screening mammography has not been shown to be significantly different between healthy black and white women, although the only study of racial differences in breast cancer that has addressed this issue has noted a lower incidence of prior mammography in black women with breast cancer than in their white counterparts.^{12,14} Black women with breast cancer have been found to more often rely on hospital-based or public clinics for their health care, and have been noted by some investigators to have a longer interval between symptom recognition and medical consultation.^{7,15-17} The difference in median time to medical consultation between black and white women has generally been short, however, and has not adequately explained the significant difference in stage of disease at presentation.

There are also several biological differences in breast cancers of black and white women which may contribute to the differences in disease stage and survival seen in these populations. There is an increased incidence of medullary carcinoma among black women, accounting for 6-9% of all breast cancers, compared to white women, where this tumor histology is seen in 2-3% of women.^{2,6,18} Black women have also been noted to have a higher incidence of poorly differentiated tumors of the breast, whether evaluated by architectural grade or nuclear grade, and in one large study higher grade tumors were significantly correlated with disease of more advanced stage.^{5,12,19} A majority of studies which have compared hormone receptor levels in black and white women have documented a lower than expected incidence of estrogen receptor positive tumors in black

women with breast cancer.^{5,6,12,14,19-23} One group of investigators has examined some of the more recently identified markers of breast tumor biology, including DNA ploidy, S-phase fraction, HER-2/*neu* protein levels and p53 protein accumulation. (52) White women had a significantly lower S-phase fraction than either the black or Hispanic populations.²⁴ This finding is not unexpected in light of the higher frequency of poorly differentiated tumors in African American women. The Black/White Cancer Survival Study, the most comprehensive study to date of racial survival differences in breast cancer found that tumor biologic characteristics (tumor grade and hormone receptor status) were second only to tumor stage in contributing to the observed survival difference.²⁵

There are a limited number of studies which have evaluated the treatment of breast cancer in African American women. The Black/White Cancer Survival Study Group has reported that in women of equivalent stage, black women were just as likely to have surgical therapy as part of their primary treatment plan as white women. (73) They did find that black women were less likely to have breast conserving surgery and more likely to have a modified radical mastectomy.²⁶ The use of systemic adjuvant therapy, either chemotherapy or endocrine therapy has generally not been found to vary significantly according to race, although the data in this area is quite limited.^{24,27-9} Even less information is available regarding the efficacy of systemic therapy in preventing relapse or improving survival in African American women with breast cancer. One study, presented only in abstract form, suggested that black women enrolled on Eastern Cooperative Oncology Group chemotherapy studies for breast cancer had a poorer survival than matched controls, although there is not enough information presented to adequately analyze the reported findings.³⁰

Confounding all of this information is the issue of socioeconomic status and its close correlation with race. Observed differences in outcome, particularly if influenced by access to medical care, could certainly be a result of socioeconomic factors and not race. Attempts to control for socioeconomic factors (performed indirectly using census tract data) have not resulted in uniform agreement. Some studies have demonstrated a disappearance of racial differences in survival while others continue to show a significant impact of race upon survival with breast cancer.^{7,11,31-4} Notably, the only prospective study which has collected socioeconomic data from individual patients demonstrated a continued effect of race on stage of disease at presentation.¹² In addition, the noted differences in tumor biology (histology, tumor grade, and hormone receptor status) are less easily explained solely by socioeconomic issues and thus raise the possibility of other factors significantly contributing to the observed survival difference.

We have initiated a prospective study evaluating the clinical, pathologic, and biologic characteristics of newly diagnosed breast cancers in a racially mixed, socioeconomically uniform cohort of patients seen at Truman Medical Center, the public hospital for Kansas City, Missouri. The objectives of the study are: 1) to determine if there are significant differences in breast cancer characteristics at presentation, prognostic factors, or treatment which could explain the survival differences noted between black and white women with the disease and 2) to determine if any documented differences are correlated with the survival of the women in the study.

Methods

Eligibility criteria. The study is being conducted at Truman Medical Center, the public hospital for Kansas City, Missouri. Women who meet the following eligibility requirements are being prospectively enrolled: 1) histologically confirmed invasive adenocarcinoma of the breast, 2) primary surgical therapy for the breast cancer performed at Truman Medical Center, 3) women of African-American or white ethnic background, 4) no prior exposure to radiation therapy or chemotherapy, and 5) written informed consent.

Study enrollment began in November 1991 and continues through the present time.

Demographic data. After study enrollment, demographic information is obtained, including age, race, menstrual history, estrogen exposure, family history of cancer, nutritional measurements, and weekly alcohol consumption.

Tumor analysis. Tumor tissue was obtained from either breast biopsy or mastectomy specimens, after gross examination by a pathologist, and tissue was placed in zinc-buffered formalin for routine histology, frozen for routine quantitative estrogen and progesterone receptor analysis, and sent fresh for drug metabolism parameters. Hematoxylin and eosin stained sections will be examined, and the tumors classified according to the criteria of the World Health Organization. Pathologic stages are defined according to the TNM classification.

DNA ploidy, cell cycle analysis, HER-2/*neu* protein content, p53 protein content, and cathepsin D levels were assessed by immunohistochemical analysis of paraffin embedded tissue. This analysis was performed by an outside reference laboratory with extensive experience in the area of cancer immunohistochemistry (Dianon Laboratories, Stratford, CT) using standard techniques.

Neovascularization in the tumor was evaluated in paraffin-embedded tissue primarily fixed in zinc-buffered formalin. Endothelial cells were stained using antisera against Factor VIII (Dako Polyclonal, Santa Barbara, CA) and the avidin-biotin peroxidase method. Representative areas of the tumor were selected, and microvessel density was assessed using MacMeasure morphometry software (Wayne Rasband, Research Services Branch, NIMH) and a microdigipad (GTCO, Bethesda, MD) with tracings of eighteen x400 photomicrographs of representative areas of each tumor.

Tumor drug metabolism parameters were assessed using fresh tissue. Fresh tumor specimens (at least 500 mg) were minced into small, 2-3 mm pieces and washed twice with cold isotonic saline. Glutathione (GSH) levels were determined in tissue extracts by a specific, and sensitive fluorometric assay using o-phthalaldehyde as the fluorescent agent, as described by Hissin and Hilf.³⁷ GSH concentration will be expressed based on milligram protein and milligram DNA.

Patient follow-up. Breast cancer treatment recommendations and treatment received were recorded for each patient by review of the medical record. Type of surgery was recorded as biopsy, defined as incomplete removal of the tumor for diagnostic purposes only, breast conserving surgery with axillary dissection, simple mastectomy (no

axillary dissection), or modified radical mastectomy. For the purposes of this analysis, women were considered candidates for breast conservation if their primary tumor was $\leq$ 4 cm. in size, not fixed to the chest wall or overlying skin, and there was no evidence of distant metastatic disease.

Adjuvant therapy characteristics, including radiation therapy, chemotherapy, and hormonal therapy were recorded for each patient. Radiation therapy factors considered in this analysis included the site of treatment, the total dose received in relation to the total dose planned, and the timing of the treatment.

Chemotherapy received was classified into two general categories: methotrexate-based (in all instances cyclophosphamide, methotrexate, and 5-fluorouracil--CMF), or doxorubicin-based (cyclophosphamide, doxorubicin, +/- 5 fluorouracil--CAF or AC, and in one instance, doxorubicin alone). A modified approach to calculating chemotherapy drug dose intensity was used as a summary descriptor of dose prescribed and received as well as compliance with therapy and completion of recommended chemotherapy course. To calculate dose intensity as used in this report, the method described by Longo, et al.³⁸ was used with one modification. For subjects who did not complete the prescribed course of therapy, the total time of therapy used in the denominator of the equation was not the actual weeks over which therapy was received, but rather the total number of weeks necessary to complete the entire planned course of chemotherapy. For example, if a subject received only one cycle of a planned six cycles of CMF chemotherapy, the denominator of the dose intensity equation would be 24 weeks, not 4 weeks. If a subject received two cycles of a planned six cycles of chemotherapy, and had a one week treatment delay, the denominator would be 25 weeks, not 9 weeks. This modification was used to allow for the development of a single measure which summarized dose prescribed and received, treatment delays, and compliance with the planned regimen. In all other respects dose intensity was calculated as outlined in the above referenced article.

Because the intent of the analysis was not to compare the different chemotherapy regimens used, but to evaluate the overall quality of the treatment received, the calculated dose intensities were standardized between regimens by dividing the calculated dose intensity by the projected dose intensity,³⁸ yielding a single value for the treatment course, the percent planned dose intensity received by the subject.

Total treatment received for breast cancer was reviewed by one of the investigators, blinded to the race and outcome of the subject, and classified as optimal or suboptimal based upon previously defined criteria. Optimal therapy required the following components: 1) complete surgical resection of the tumor (gross and microscopic) and axillary lymph node dissection was required for all women without distant metastatic disease, 2) radiation therapy was mandatory for all women who underwent breast conserving surgery and for all women with primary tumors larger than 5 cm. in maximal diameter, 3) adjuvant systemic therapy was required as outlined in the reports from the Fourth and Fifth International Conferences on the Adjuvant Therapy of Primary Breast Cancer,^{39,40} except that women with lymph-node negative cancer diagnosed prior to January 1990 were not required to receive adjuvant chemotherapy or hormonal therapy to have their treatment judged as optimal, 4) received chemotherapy dose intensity,

calculated as described above, had to be $\geq 85\%$ of the planned dose intensity, and 5) tamoxifen, if prescribed, had to be continued for at least 5 years. Women not meeting the above five criteria were judged to have received suboptimal therapy.

Patient outcome data including response to therapy, time to relapse, and survival were also obtained by review of the medical record.

Statistical analysis. Differences between blacks and whites in categorical breast cancer biologic characteristics will be analyzed by a chi-square test for independence. Continuous variables will be evaluated by the Student's t test and/or Mann-Whitney U test for ranked data. Relapse-free survival and overall survival will be estimated using the Kaplan-Meier product limit method, with differences in survival between black and white patients assessed by a log rank test.

Results

As of May 1, 1998, 162 women have been enrolled in the study. Clinical information is complete for 154 women, and these women are the subjects of this report. There were 76 black women and 78 white women in the analysis of clinical characteristics at presentation. The demographic characteristics of the total population are described in Table 1. Black women were slightly older, more likely to be covered by Medicare, and less likely to have Medicaid or no health care coverage.

Table 1
Demographic Characteristics

	White (n = 78)	Black (n = 76)	Significance (p value)
Mean age (years)	53.3	56.0	0.20
Post-menopausal (%)	67.9	72.4	0.55
Insurance type (%)			0.03
Medicare	22.5	38.3	
Medicaid	21.2	13.5	
Commercial Insurance	6.6	5.3	
Indigent	49.7	42.9	

Tumor stage at the time of diagnosis was remarkably similar in black and white women. The mean primary tumor size of black women was 3.54 cm. compared with a mean tumor size of 3.49 for white women. The distribution of tumor size by race did not suggest any substantive differences between the two groups, with similar proportions of women presenting with the smallest tumors and similar proportions presenting with very large primary tumors. Likewise, the frequency of cancer spread to the axillary lymph nodes and the number of lymph nodes involved with cancer was very similar between the

two groups. Overall American Joint Committee on Cancer (AJCC) breast cancer stage at diagnosis was not different in the black and white women in this population (Table 2).

Table 2
Tumor Stage at Diagnosis

	White (n = 78)	Black (n = 76)	Significance (p value)
Tumor Stage (%)			0.65
T ₀	0%	1.3%	
T ₁	30.8%	36.8%	
T ₂	44.9%	35.5%	
T ₃	16.7%	17.1%	
T ₄	7.7%	7.9%	
Nodal Stage (%)			0.35
N ₀	43.6%	42.1%	
N ₁	46.2%	40.8%	
N ₂	1.3%	6.6%	
Unknown	9.0%	10.5%	
Metastasis Stage (%)			0.60
M ₀	88.5%	89.5%	
M ₁	11.5%	10.5%	
AJCC Stage (%)			0.96
1	21.8%	27.6%	
2A	29.5%	26.3%	
2B	24.4%	21.1%	
3A	9.0%	10.5%	
3B	3.8%	3.9%	
4	11.5%	10.5%	
Estrogen Receptor (+)	60.9%	50.7%	0.23
Progesterone Receptor (+)	58.0%	47.8%	0.23

Tumor biologic characteristics have been analyzed in the 154 women prospectively enrolled to date. Table 3 below summarizes these results. None of the differences noted between black and white women reach the level of statistical significance ($p = 0.05$) in univariate analysis at this time.

Table 3
Breast Cancer Biologic Characteristics

	White (n = 78)	Black (n = 76)	Significance (p value)
Estrogen receptor positive	60.9%	50.7%	0.23
Progesterone receptor positive	58.0%	47.8%	0.23
DNA Index--Aneuploid	51.5%	41.2%	0.46
S phase fraction high	53.1%	55.3%	0.82
HER-2/ <i>neu</i> expression	32.3%	39.1%	0.43
p53 expression	50.0%	45.3%	0.60
Cathepsin D expression	74.2%	75.0%	0.92
Mean microvessel density	12.4	11.6	0.40

The breast cancer primary treatment characteristics of the 154 studied subjects are outlined in Table 4. Overall, 22.7% of the women had breast conservation surgery, with no differences between black and white women. Of the women with tumor sizes ≤ 4 cm., 30.4% of black women and 26.4% of white women underwent breast conservation surgery. Subject age, race, insurance status, and primary tumor size were examined for their association with use of breast conservation. Women choosing lumpectomy with axillary dissection were younger, had smaller primary tumors, and were more likely to have Medicare insurance. Race had no impact on type of surgery received.

Table 3
Breast Cancer Treatment Characteristics

	White (n = 78)	Black (n = 76)	Significance (p value)
Surgery (%)			0.77
Modified radical mastectomy	73.1%	65.8%	
Breast conservation	20.5%	25.0%	
Simple mastectomy	1.3%	2.6%	
Biopsy only	5.1%	6.6%	
Radiation therapy received (%)	42.3%	38.2%	0.33
Chemotherapy received (%)	55.1%	39.5%	0.10
Chemotherapy type (n = 111)			0.91
CMF	51.1%	46.7%	
Doxorubicin-based	48.9%	53.3%	
Hormonal therapy received (%)	55.1%	59.2%	0.69

Radiation therapy was used in similar proportions of black and white women. Overall, 40.2% of women received radiation to their breast or chest wall in the postoperative period. All women who underwent breast conserving surgery received radiation to their breast.

Chemotherapy (either adjuvant therapy or treatment for distant metastases) was given to 55.1% of white women and 39.5% of black women. Approximately half of the women receiving chemotherapy were treated with CMF and half were treated with doxorubicin containing regimens. There was also no difference between black and white women in the percent of planned chemotherapy dose intensity. Black women received a median of 91% of the planned dose intensity with a range of 11-102%; white women received a median of 87% of the planned dose intensity with a range of 8-116%. Forty percent of women received less than 85% of the planned chemotherapy dose intensity. The cause of the low dose intensity was dose reductions due to toxicity in one third of patients and patient choice to discontinue chemotherapy in two thirds of patients.

Total therapy for primary breast cancer was judged to be optimal in 59.1% of women. Once again, no difference between black and white women was observed. Reasons for suboptimal therapy included therapy-related toxicity (14%), patient choice not to receive recommended therapy (55%), and failure of the physician to recommend the optimal therapy (31%). Subject age, race, insurance type, tumor size, nodal involvement, presence of distant metastasis, and estrogen receptor levels were evaluated as possible factors associated with receipt of suboptimal therapy. Women who received optimal therapy were more likely to have primary tumors smaller than 5.0 cm (odds ratio = 2.7, 95% confidence interval = 1.5 to 4.8) or to have distant metastatic disease (OR = 2.4, 95% CI = 1.0 to 5.6). Age, race, insurance type, nodal status, and estrogen receptor level did not predict likelihood of optimal treatment.

The time to disease progression was very similar between black and white women, as depicted in Figure 1, below. Survival times, in contrast, seem to be different, with white women living longer than black women (Figure 2, log rank $p=0.06$). The reason for the apparent superior survival in white women is not clear. Relapse rates, as outlined in Figure 1 are very similar. In addition, the proportion of women dying from comorbid conditions is very small and not different in black and white women. There is some suggestion that one breast cancer relapses, white women live longer than black women, but we have not had enough events yet to clearly evaluate this issue.

Figure 1
Time to Treatment Failure

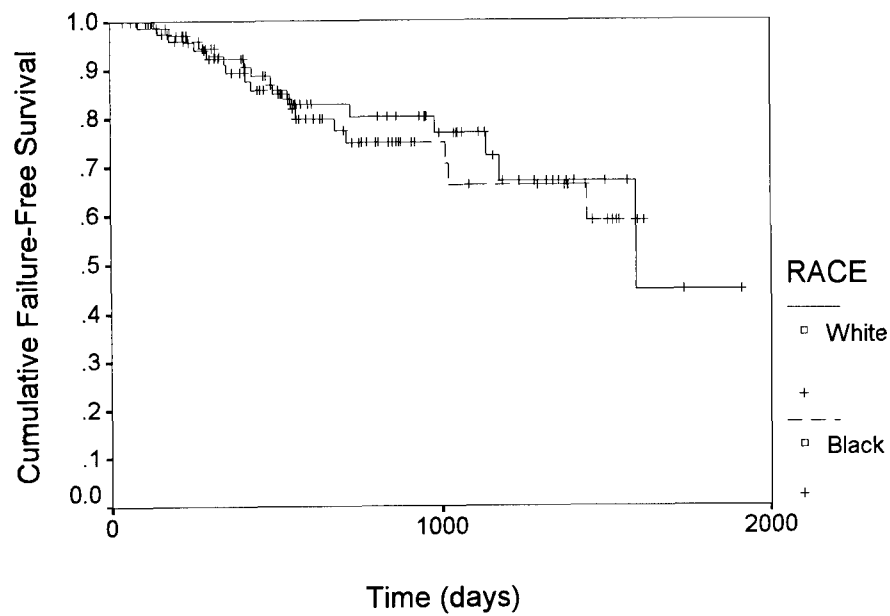
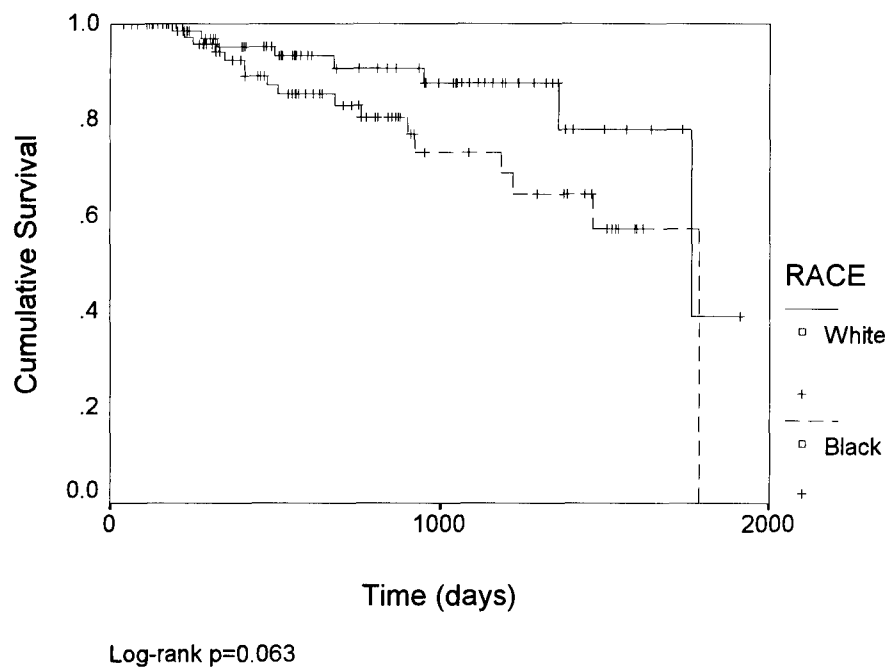


Figure 2
Survival



Conclusions

To date, patient accrual and sample processing has gone very smoothly. The number of women enrolled in the study over the past eighteen months has been slightly less than expected. This is the result of an increasingly common practice at this institution to treat some women with locally advanced breast cancer with neoadjuvant chemotherapy. Most often, the diagnosis of breast cancer in these women has been made by aspiration biopsy or core needle biopsy. The amount of tissue obtained with these techniques is generally insufficient to perform the planned biochemical analyses. While subsequent surgical excision of the tumor often yields residual cancer, we had made the decision when developing this study not to analyze tumor that had been exposed to previous chemotherapy, as the effects of this exposure on the characteristics of the tumor were unknown. It is, therefore, likely, given the present subject accrual rates, that continued patient enrollment will need to extend into the latter half of 1998 to meet the enrollment goal of 200 women.

Our study, focusing only on women of lower socioeconomic status did not reveal any tumor stage differences between black and white women. In addition, the pattern of stage distribution in this racially mixed population did demonstrate a shift towards more advanced disease, very similar to that typically described in black women.^{3,6,17,25} Only 42% of the women in this study were node-negative, compared to the SEER data in which 50% of women were node-negative. Likewise, we observed a higher incidence of distant metastatic disease at the time of diagnosis than is typically recognized (11% in the current study compared to 7% in the SEER data).

To date, we have identified no significant racial differences in the biological characteristics of breast cancer. It is, however, too early to conclude that a difference does not exist. The number of women studied is too small to say confidently that the tumors in black and white women are biologically similar. Firm conclusions in this area will need to await completion of the study.

Consistent with the more recent reports, we found no difference between black and white women in the type of surgery performed for the treatment of the primary breast lesion. Twenty-three percent of all women and 28% of women with tumors ≤ 4 cm. had breast conservation. A relatively high number of women did not have definitive surgical treatment of the breast cancer. Five percent of women had a biopsy only. The large majority of these women had documented distant metastatic disease.

We, likewise, found no substantial racial difference in the frequency with which radiation therapy to the breast or chest wall was employed in the treatment regimen (38% in black women and 42% in white women). Of note, all women in this study who had breast conserving surgery underwent a complete course of post-operative breast irradiation.

We found that white women were slightly more likely to receive chemotherapy than black women, although this difference was not statistically significant. Similar proportions of black and white women received doxorubicin-based chemotherapy. In addition, the proportion of optimal dose intensity received by black and white women

was also very similar (91% of planned dose intensity in black women and 87% of planned dose intensity in white women). Reasons for receiving lower than planned chemotherapy dose intensity were not different in black and white women, with approximately one-third experiencing treatment delays or dose reductions as a result of chemotherapy toxicity, one-third receiving a suboptimal chemotherapy dose for their actual body weight (this was most commonly seen in obese women), and one-third refusing to complete the entire planned course of chemotherapy.

While examining the proportion of women that receive the different treatment modalities provides some insight into possible variations in the care of women with breast cancer, this approach does not directly assess the primary issue of treatment quality. Treatment standards for breast cancer are dependent upon age of the patient, stage of disease, and hormone receptor status. In order to accurately determine if racial differences in breast cancer treatment exist, these factors must be considered. We attempted to incorporate this issue into the current study by calculating the proportion of women that received "optimal" therapy for breast cancer. The recommendations developed by the Fourth and Fifth International Conferences on the Adjuvant Therapy of Breast Cancer^{39,40} were used as a guide for our definition of patient specific "optimal" therapy. In addition to the published suggestions, we included requirements for breast or chest wall irradiation for women with breast conservation surgery or large primary tumors. Minimum acceptable chemotherapy dose intensity guidelines for all women receiving adjuvant chemotherapy were also incorporated into the definition of optimal therapy.^{41,42}

Using these guidelines, we found that 59 women received optimal therapy for their breast cancer. While it is clear that no racial difference in quality of care, as defined by our guidelines, exists, it was disappointing to see that fully one third of women in this cohort received care judged to be suboptimal. Demographic factors did not appear to influence the likelihood of receiving suboptimal therapy.

It is impossible to determine if socioeconomic factors were at all important in determining quality of care. There have been no previously reported rigorous studies of breast cancer treatment quality in an undifferentiated cohort of women more representative of the general population of the United States. A recent study evaluating management of local/regional breast cancer in women insured by Blue Cross/Blue Shield found that only 54% of women under age 51 received adjuvant chemotherapy, suggesting that problems with delivery of optimal therapy exist not only among women served at the public hospitals but also among women with commercial health care insurance.⁴³ Further studies in this area would certainly be helpful in understanding the relationship between socioeconomic status and quality of cancer care.

The only characteristics identified which did change the risk of receiving suboptimal therapy were characteristics related to disease stage. Women with tumors larger than five centimeters were less likely to received optimal therapy, primarily because they were not routinely referred for chest wall irradiation. In a similar manner, women with metastatic disease were more likely to receive optimal therapy, primarily because not all women with local or regional disease were referred to medical oncology for adjuvant systemic therapy. Physician-related issues regarding quality of care only accounted for 31% of the women

who received suboptimal treatment, however. The remaining cases of suboptimal care were a result of patient choice not to receive recommended treatment or treatment toxicity prohibiting optimal therapy delivery.

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21 JUN 2001

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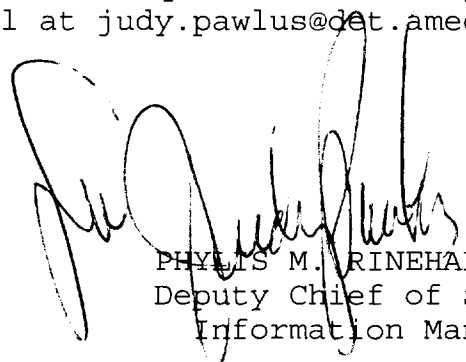
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