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This is a follow-up study of a cohort of African-American and Caucasian women who were diagnosed with breast cancer in the late 1980's. Its purpose is to examine race differences (black/white) in breast cancer survival. In addition to measuring survival and examining racial differences in survival, this study also seeks to identify prognostic factors related to survival for the study population and to determine if the prognostic indicators are the same for women of both races.

At the end of year one of this four-year project, our preliminary results indicate a survival disadvantage for black women compared with white women with breast cancer, before and after adjustment for stage at diagnosis. Early findings suggest that the survival differential is not explained by race differences in socioeconomic status as measured with years of education. Over the course of the study, these findings will be expanded using more complete data on vital status, cause of death, and time to recurrence. Additionally, we will evaluate the prognostic significance of a wide range of factors including medical care and psychosocial variables, other tumor characteristics, and molecular alterations, thus permitting a multidisciplinary approach to understanding the black/white survival difference in breast cancer.
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Beth A. Oehr 7/21/97
PI - Signature Date
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INTRODUCTION

This is a follow-up study of a cohort of African-American and Caucasian women who were diagnosed with breast cancer in the late 1980’s. Its purpose is to examine race differences (black / white) in breast cancer survival. In addition to measuring survival and examining racial differences in survival, this study also seeks to identify prognostic factors related to survival for the study population and to determine if the prognostic indicators are the same for women of both races.

PROGRESS WITH REGARD TO STATEMENT OF WORK

Data on Survival / Vital Status

In January 1997, vital status data were obtained from the Connecticut Tumor Registry (CTR). These data included information on vital status (alive or deceased), date of death and underlying cause of death if applicable, date last seen at a follow-up visit if alive, and some information on treatment received.

The follow-up data from the CTR were merged into the study database and also added to existing SAS data sets. The acquisition of the vital status information enabled us to conduct preliminary analyses to determine the magnitude of race differences in overall survival within this cohort of women. These analyses were included in an extended abstract submitted to the U.S. Army Medical Research and Materiel Command Breast Cancer Research Program for the fall, 1997 Era of Hope conference. This abstract is included in Appendix I.

Data on Tumor Prognostic Factors via Archived Tissue Specimens

A second arm of this follow-up study involves the retrieval and testing of archived breast cancer tumor tissue specimens at the Yale University Critical Technologies laboratories.

The first step in the archived tissue retrieval process involved submitting the protocol to the Institutional Review Boards (IRBs) of the twenty-two hospitals which participated in the original study. The protocol was submitted to all hospitals in the fall of 1996, and approvals have been received by twenty-one hospitals to date, with one pending. The second step in tissue retrieval involved re-examining the original medical chart abstracts of the participants to prepare comprehensive lists of the pathology report numbers, dates, and specimen types held at each hospital. The complexity of this task was heightened by the presence of multiple specimens per individual, and the fact that many patients had specimens housed at more than one hospital in the state. This task was completed in the fall of 1996, and reports listing the relevant information for each hospital were generated to facilitate collection of the relevant slides and paraffin blocks once the approval process has been completed. As hospitals and pathology departments have different policies regarding the release of slides and blocks, four alternative plans for accessing the materials were developed and pathology departments will be asked to endorse the plan that best accommodates their policies on release of materials (see Appendix III).
In the months to come, as slides and blocks are brought to the study office from the hospitals around the state, the selection and testing process will commence. First, the study pathologist, Dr. Mary Lachman, will select the most appropriate paraffin block for further testing. This will involve a review of tumor slides and possibly some preliminary staining or preparation of new slides. Following the identification of the most appropriate block for analysis of the tumor, Dr. Christine Howe of the Critical Technologies laboratory at Yale will perform the following laboratory tests: histopathologic grade, tumor grade, estrogen receptors, progesterone receptors, DNA ploidy, S-Phase fraction, presence and type of p53 mutations, and overexpression of erbB-2.

Data on Treatment For Breast Cancer

While treatment data are important in a study of breast cancer survival and related prognostic indicators, this information is not easily obtained.

Our first step in determining treatment received (using broad categories of surgery, chemotherapy, radiation, endocrine therapy) involved a re-examination of the original interview instruments for information on treatment modalities. The original study questionnaire included one structured question and several open-ended questions about treatments received for breast cancer. As most of the interviews were conducted during the three to twelve month period following diagnosis, courses of treatment were frequently underway or completed at the time of the in-person interview. The 322 completed interview instruments were re-abstracted for treatment indications during the first three months of 1997, and this information has been incorporated into the study database.

A second step in the determination of treatment received involves examination of the variables provided by the CTR. These data have also been entered into the database and will augment the interview data.

A third step in the determination of treatment involves contacting the patient’s physician(s) to access more detailed information on treatment administered. A brief two-page questionnaire has been developed that requests that physicians provide information on treatment administered, course of disease, date of first remission if applicable, vital status, and date last seen (Appendix IV). This information will supplement that received from both the CTR and the abstraction of medical documentation and interview data.

During the past year, several tasks have been completed that are integral to the process of contacting and surveying the physicians that treated this cohort of breast cancer patients. First, a brief instrument was designed, as mentioned above, to access the relevant information. Second, the 322 original interviews were reviewed and abstracted for the names and unique identifiers of the physicians (most frequently primary care physician, surgeon, oncologist, and radiation therapist) involved in the care of each study subject. This information (patient’s study identification followed by the unique identifier of each physician seen) was incorporated into the database. Third, a physician name and address database was developed to enable a merge
mailing based on unique identifiers. This physician database is underway and presently has over 325 names and addresses.

Ideally, contact with physicians will also enable determinations of disease course and dates of remission, if applicable. This information will be used to construct another outcome variable, disease-free survival (operationalized as date of diagnosis to date of first recurrence). As data concerning the date of first recurrence are not available via the CTR, contact with physicians represents the best avenue for accessing this information.

GOALS FOR THE UPCOMING YEAR

The tasks of the past year have laid the foundation for substantive gains during the year ahead. During the next few months, collection of slides and blocks will commence, which will enable the pathologist to choose the most appropriate tissue blocks and will allow the Critical Technologies laboratory to begin performing the aforementioned tests on the archived tissue specimens. The extensive abstracting for physicians' names and input of names, unique codes and addresses into the study database will allow the execution of the physician mailing later this year. This will supplement the information already accessed from the CTR on treatment, vital status and disease course. Toward the end of the upcoming year, information from the CTR will be downloaded, again, into our files, to provide an update concerning additional deaths and second primary tumors that might have occurred during the past year. Data management utilizing Microsoft Access, and preliminary analyses via SAS software will continue and intensify as data becomes available.

PRELIMINARY RESULTS

Preliminary results indicate that as of January, 1997, 113 of the 322 women with breast cancer (35.1%) had died, with an average time to death of 4.2 years. Eighty-two (72%) of the deaths were confirmed breast cancer deaths. Among survivors, women were followed for a maximum of 9.6 years, with an average follow-up of 7.2 years. Black women were significantly more likely to die than were white women during the follow-up period (age-adjusted Risk Ratio [RR] = 1.70, Confidence Interval [CI] 1.16 - 2.50). After adjustment for stage at diagnosis (in situ/local vs. regional/remote), black women were still significantly more likely to die from their disease than were their white counterparts (RR = 1.52, CI 1.03 - 2.24). Further adjustment of the model for a measure of socioeconomic status (years of education) did not alter these results.

Several tumor characteristics were also found to differ by race group, with black women more likely to be in the higher risk category. Using data abstracted from the medical chart, and adjusting for age, black women were more likely to have high grade tumors (Odds Ratio [OR] = 2.53, CI 1.08-5.91), lymphatic invasion (OR = 1.91, CI 0.99-3.69), necrosis (OR = 1.48, CI 0.87-2.53), skin involvement (OR = 1.88, CI 0.66-5.36), nipple involvement (OR = 1.95, CI 0.77-4.99), estrogen receptor (ER) negative tumors (OR = 1.29, CI 0.70-2.39), and progesterone receptor (PR) negative tumors (OR = 1.50, CI 0.81-2.78). While several of these factors do not
differ significantly between race groups, they suggest a trend toward more aggressive tumors in black women. The extended abstract appears in its entirety in Appendix I.

In addition, we have included (in Appendix II) a manuscript that will appear in the American Journal of Epidemiology (September, 1997). These findings suggest that obesity may play an important prognostic role in survival from breast cancer. This work will be incorporated into the appropriate analyses of this study.

PERSONNEL AND OTHER SUPPORT RECEIVED

Personnel

As was discussed with project staff last year, Dr. Robert Dubrow resigned from his faculty position at Yale shortly after the funding for this project began. In consultation with the DOD, we arranged to hire him as a consultant. As it happened, we did not require his services during the past year; that is, most of our efforts have been spent on securing IRB approvals and performing data collection, tasks that did not involve Dr. Dubrow. Furthermore, Dr. Dubrow has recently decided that he would prefer not to serve as a consultant on this study. However, as we move into our second year and begin interfacing with the Critical Technologies laboratory and our pathologist, we will now need the assistance of a person who has a basic science background to perform the role originally described for Dr. Dubrow.

We are proposing that Susan Taylor Mayne, Ph.D. replace Dr. Dubrow on this project. Dr. Mayne is an Associate Professor in the Department of Epidemiology and Public Health. She is also Associate Director of the Yale Cancer Center, and is responsible for the Cancer Prevention and Control Research Program and has oversight responsibility for the Cancer Genetics Program at Yale. She has an established working relationship with the Critical Technologies laboratory at Yale in her own research. In the immediate future, she will perform the role of liaison with the laboratory arm of this project. Dr. Mayne is trained in chemistry and biochemistry and maintains her own laboratory at Yale. As we continue with statistical analysis, and incorporate the results of genetic and other laboratory testing into our database, Dr. Mayne’s expertise and background will be an invaluable asset to this project. Her biographical sketch is included in Appendix V.

Other Support

During the past year, there have been no changes in other support received by the Principal Investigator. Dr. Kasl’s and Dr. Mayne’s Other Support are included as Appendix VI.
CONCLUSION

At the end of year one of this four-year project, our preliminary results indicate a survival disadvantage for black women compared with white women with breast cancer, before and after adjustment for stage at diagnosis. Early findings suggest that the survival differential is not explained by race differences in socioeconomic status as measured with years of education. Over the course of the study, these findings will be expanded using more complete data on vital status, cause of death, and time to recurrence. Additionally, we will evaluate the prognostic significance of a wide range of factors including medical care and psychosocial variables, other tumor characteristics, and molecular alterations, thus permitting a multidisciplinary approach to understanding the black/white survival difference in breast cancer.
REFERENCES


APPENDIX I: EXTENDED ABSTRACT

RACE DIFFERENCES (BLACK/WHITE) IN BREAST CANCER SURVIVAL. EARLY FINDINGS.

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Despite a somewhat lower incidence of breast cancer in African American women relative to white women, there is a substantial black/white difference in survival from breast cancer. Data from the Surveillance, Epidemiology, and End Results (SEER) program for the years 1986-1992 indicate a five-year survival rate of 85% for white women compared with 70% for black women. While the survival rates for women of both races have improved significantly since the mid 1970s, the survival rates reported for black women in this latest time period are comparable to the survival rates achieved for white women nearly twenty years ago. The purpose of the current investigation is to evaluate the survival in a cohort of black and white women who were diagnosed with breast cancer in Connecticut between 1987 and 1989, and to identify important prognostic factors, with special emphasis on explaining the black/white survival differential.

This follow-up study builds on the results of a completed, population-based investigation aimed at understanding social, psychological, and medical care factors that might explain the observed black/white difference in stage at diagnosis of breast cancer. Previously collected data (from the time of diagnosis) will be combined with newly collected data on molecular alterations (p53 and erbB-2) and tumor characteristics (e.g., DNA ploidy, estrogen receptor status) derived from laboratory testing of archived tissue blocks, as well as vital status information retrieved from the Connecticut Tumor Registry (CTR) to determine the following: 1) predictors of survival from breast cancer for all study subjects; 2) race-specific predictors of survival; and 3) the explanatory potential of prognostic variables in the black/white survival differential.

Keywords: Race, Survival, Blacks, Prognostic Factors, Breast Cancer

This work was supported by the U.S. Army Medical Research and Materiel Command under DAMD-17-96-1-6101
This is a population based study of 145 black women and 177 white women who were diagnosed with breast cancer in Connecticut between January, 1987 and May, 1989. Women were identified through active surveillance of 22 Connecticut hospitals. Extensive baseline information was collected from in-person interview and medical chart abstraction. In this first year of the follow-up study, information on vital status and cause of death has been obtained from the CTR. Preliminary data analysis includes bivariate analyses of race and potential prognostic factors using chi-square tests; predictors of survival have been evaluated with Kaplan-Meier product limit estimates and Cox proportional hazards models. In these preliminary analyses, all cause mortality is the outcome variable.

As of January, 1997, 113 women of the 322 breast cancer cases (35.1%) had died, with an average time to death of 4.2 years. Eighty-two (72%) of the deaths were confirmed breast cancer deaths. Among survivors, women were followed for a maximum of 9.6 years with an average follow-up of 7.2 years. Black women were significantly more likely to die than were white women during the follow-up period (age-adjusted Risk Ratio [RR] = 1.70, Confidence Interval [CI], 1.16-2.50). Although adjustment for stage at diagnosis (in situ/ local vs. regional/remote) reduced the predictive value of race, black women were still significantly more likely to die from their disease than were their white counterparts (RR = 1.52, CI 1.03-2.24). Further adjustment of this model for one measure of socioeconomic status (years of education) did not alter these results.

Several tumor characteristics differed by race group, with black women more likely to be in the higher risk category. Using data abstracted from the medical chart, and adjusting for age, black women were more likely to have high grade tumors (Odds Ratio [OR] = 2.53, CI 1.08-5.91), lymphatic invasion (OR = 1.91, CI 0.99-3.69), necrosis (OR=1.48, CI 0.87-2.53), skin involvement 1.88 (0.66-5.36), nipple involvement (OR = 1.95, CI 0.77-4.99), estrogen receptor (ER) negative tumors (OR = 1.29, CI 0.70-2.39), and progesterone receptor (PR) negative tumors (OR= 1.50, CI 0.81-2.78). While several of these factors do not differ significantly between race groups, they suggest a tendency toward more aggressive tumors in black women. The lack of statistical significance may be a function of missing data as not all laboratory tests were performed on all tumors. Of the tumor characteristics listed above, only skin involvement remained a significant predictor of mortality after adjustment for age, race, and stage at diagnosis.

These preliminary results demonstrate a survival disadvantage for black women compared with white women with breast cancer, before and after adjustment for stage at diagnosis. Early findings suggest that the survival differential is not explained by race differences in socioeconomic status as measured with years of education. Over the course of the study, these findings will be expanded using more complete data on vital status, cause of death, and time to recurrence. Additionally, we will evaluate the prognostic significance of a wide range of factors including medical care and psychosocial variables, other tumor characteristics, and molecular alterations, thus permitting a multidisciplinary approach to understanding the black/white survival difference in breast cancer.
Severe Obesity as an Explanatory Factor for the Black/White Difference in Stage at Diagnosis of Breast Cancer

Beth A. Jone,1 Stanislav V. Kasi,1 Mary G. McCrea Cuman,1 Patricia H. Owens,1 and Robert Dubrow2

Black women with breast cancer are less likely than white women to be diagnosed while their disease is still at a localized stage. Racial differences in the prevalence of obesity in the United States have also been documented. This study was undertaken to determine the extent to which the observed racial difference in stage at diagnosis of breast cancer could be explained by racial differences in obesity, specifically severe obesity. This was a population-based, retrospective study of 148 black women and 177 white women in Connecticut who were diagnosed with breast cancer between January 1987 and March 1989. Severe obesity was associated with both race and stage at diagnosis: Black women were significantly more likely than white women to be severely obese (28% vs. 7%, respectively), and severe obesity was significantly associated with diagnosis at TNM stage II or greater (multivariate-adjusted odds ratio = 3.10; 95% confidence interval (CI) 1.28-7.52). Adjustment for severe obesity in a logistic regression model reduced the risk of later stage at diagnosis in blacks relative to whites by 33%, from an odds ratio of 1.83 (95% CI 1.22-2.61) to one of 1.66 (95% CI 1.02-2.73). The higher prevalence of severe obesity among black women may play an important role in explaining their relative disadvantage in stage at diagnosis of breast cancer. Am J Epidemiol 1997;146: 594-404.

It is well established that African-American women are more likely than white women to be diagnosed with breast cancer that has progressed beyond a localized stage (1-11). Black/white differences in body mass index and the prevalence of obesity in the United States have also been documented. Age-adjusted data from the first phase of the Third National Health and Nutrition Examination Survey (1988-1991) indicate that 48.5 percent of non-Hispanic black women aged 20 years or older are overweight (≥120 percent of desirable weight), as compared with 32.1 percent of non-Hispanic white women (12). The tendency for black women to be heavier than white women has also been reported in studies of breast cancer cases (13-17). The reported associations of race with both obesity and breast cancer stage at diagnosis raise the question of whether these associations are more than independent. As part of a larger investigation of racial differences in stage at diagnosis of breast cancer, we

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Abbreviations: CI, confidence interval; OR, odds ratio; BMI, body mass index; TNM, tumor-node-metastasis.
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cases in white women had been diagnosed in the participating hospitals. The study population was composed of 145 (45 percent) black women and 177 (55 percent) white women who had been diagnosed with a first primary breast cancer in Connecticut between January 1987 and March 1989. All eligible black breast cancer patients whose cases were diagnosed in these hospitals were selected for possible interview. A white breast cancer patient was randomly selected, using a computerized random digit generator, from all eligible breast cancer cases diagnosed in white women in the same hospital and within the same 1- to 3-week period as the eligible black patient. The slight departure from a 1:1 black:white ratio occurred in the earliest phase of the study, before all hospitals were enrolled in the surveillance network (for administrative reasons, more whites than blacks were recruited).

Eligibility criteria included previous malignancy (at either the same site or a different site), race other than black or white, unknown race, or age greater than 79 years. Race was verified by the respondent at the time of the interview. Participants were interviewed in their homes using a standardized instrument administered by trained interviewers. The instrument was a modified version of the questionnaire used in the National Cancer Institute’s Black/White Cancer Survival Study (18), and it covered a wide range of sociodemographic, health history, medical care, and psychosocial factors. Among all eligible subjects selected for enrollment, the participation rate was 76 percent. Non-participants included individuals who refused (including physician referrals to allow contact), were lost to follow-up, moved, died, or were too ill to be interviewed. Participation did not vary by race.

We abstracted hospital medical records for each case in order to obtain complete information on stage at diagnosis and medical history. Photocopies of pathology reports, operative reports, admission notes, discharge summaries, referral correspondence, and staging reports were obtained. Further information was obtained, when necessary, from physicians’ office records.

Measures

TNM (tumor—node—metastasis) stage, as established by the American Joint Committee on Cancer (19), was the outcome of primary interest. Stage was assigned to each case by study physicians and was confirmed with a computerized check using an algorithm which incorporated the individual TNM components. The TNM staging system consists of three components: 1) T—tumor size; 2) N—absence or presence and extent of regional lymph node metastasis; and 3) M—absence or presence of distant metastasis. Eleven cases could not be assigned a stage at diagnosis because of missing data on lymph node status; the majority of these patients were white women. These cases were excluded from all but the descriptive analyses.

A dichotomous division of TNM stage groups was used as the outcome variable: carcinoma in situ or stage I (≤2 cm and node-negative) versus stage II or higher (>2 cm and/or positive lymph nodes or distant metastasis). Because our task was to explain the black/white difference in stage at diagnosis, rather than simply document its existence, we chose a stage dichotomy which highlighted the racial difference in the distribution of TNM stages in the study population. In some analyses, the dependent variables were two of the individual components of the TNM system, tumor size and nodal status.

Height and weight were taken from the medical record and used to compute body mass index (weight (kg)/height (m)²). For individuals for whom either item was not recorded in the medical record (n = 17), these measures were taken in-person interview (usual adult height and weight before the onset of symptoms or diagnosis). For two individuals, no measure of body mass was available from either source; these subjects were excluded from all but descriptive analyses. Exclusion of the 17 cases who were missing medical record data on either height or weight did not change the reported results.

One concern was that measurements taken at the time of diagnosis might reflect possible weight loss after the onset of illness. However, in comparison with self-reported usual adult weight, as given in the interview (mean = 67.6 kg), the actual weights obtained from the hospital records at the time of diagnosis were somewhat greater (mean = 72.5 kg). In addition, the mean value of the difference between self-reported usual adult weight and self-reported current weight at the time of interview was in a direction opposite to that which would be consistent with weight loss resulting from illness. Another consideration was that illness-associated weight loss would presumably only occur in the most advanced cases. In this study, very few women (n = 9) were diagnosed with distant metastasis.

Obesity was defined as a body mass index greater than or equal to 27.30, and severe obesity was defined as a body mass index greater than or equal to 32.3. Those values correspond to the 85th and 95th percentiles, respectively, of the body mass distribution of women aged 20-29 years, and are used by the National Center for Health Statistics to classify “overweight” and “severely overweight” adult females (20). The severe obesity classification used in this study represents approximately 140 percent of desirable
weight (defined as the midpoint of the range of weights for women with a medium frame derived from 1983 Metropolitan height and weight tables (21)).

Among the interview variables included in descriptive and multivariate analyses were the following: age (continuous variable); marital status (married vs. not married); two lifestyle factors, history of occasional alcohol consumption (yes vs. no) and history of cigarette smoking (ever vs. never smoking cigarettes regularly for more than 6 months); socioeconomic status, defined in terms of education (<12 vs. ≥12 years), family income (<$25,000 vs. ≥$25,000 per year), and occupational ranking (an adaptation of the Duncan Socioeconomic Index (22, 23), using a combined spouse-pair score, dichotomized at the median); reproductive factors, including menopausal status (postmenopausal vs. pre- or perimenopausal) and parity (0 vs. ≥1); and breast cancer screening history: zero vs. ≥1 mammogram in the 3 years before symptoms appeared (or before diagnosis of breast cancer in the case of women who were asymptomatic), clinical breast examination (0 vs. ≥1) in the 2 years prior to diagnosis or onset of symptoms, and breast self-examination in the year prior to diagnosis or onset of symptoms—an index (dichotomized at the median value) that measured both frequency and familiarity with recommended practice.

Analytic methods

The relation of obesity to race and stage at diagnosis was evaluated with logistic regression using unconditional maximum likelihood. Odds ratios and 95 percent confidence intervals are reported here. The extent to which obesity explained the excess number of late-stage breast cancers diagnosed in blacks relative to whites was determined by change-in-estimate. We observed the change in the odds ratio for the relation of race to stage at diagnosis after adding the severe obesity variable to a logistic regression model (24).

RESULTS

General characteristics

Descriptive data on the study subjects are shown in table 1. Consistent with other reports (1, 10, 25, 26), black women with newly diagnosed first primary breast cancer were significantly younger than white women (46 percent of blacks vs. 31 percent of whites were younger than age 50 years). For all study subjects, the age range was 25–79 years. Black women were disadvantaged relative to white women on all three measures of socioeconomic status: education, family income, and occupational ranking. Black women were less likely to report a history of alcohol use (statistically significant) and less likely to report ever having smoked cigarettes on a regular basis (not significant). With age adjustment, African-American breast cancer patients were more likely than white breast cancer patients to be postmenopausal (not statistically significant).

Stage at diagnosis

As we have reported previously (11), black women had more advanced breast cancer than white women, as measured by TNM stage at diagnosis. A black woman’s risk of a diagnosis of TNM stage II or greater was twice that of her white counterpart (age-adjusted odds ratio (OR) = 2.01, 95 percent confidence interval (CI) 1.24–3.24) (table 2). Examination of individual components of TNM stage revealed that black women were both more likely than white women to be diagnosed with larger tumors (age-adjusted OR = 1.83, 95 percent CI 1.17–2.93) and more likely to have cancerous lymph nodes (age-adjusted OR = 1.72, 95 percent CI 1.07–2.75). The proportion of cases diagnosed with distant metastasis was small for both races and did not differ significantly between black and white women.

Obesity

As expected, there were significant racial differences in body weight and body mass in these data. Black women were considerably heavier than white women (age-adjusted mean weight = 78.2 kg in blacks vs. 68.0 kg in whites; p < 0.001), despite similar heights (164 cm vs. 163 cm). The age-adjusted mean body mass index was 29.1 in blacks and 25.5 in whites (p < 0.001). Table 1 shows that black women were twice as likely to be moderately obese and were more than six times as likely to have a body mass index greater than or equal to 32.30, the cutoff point for severe obesity. Because the largest racial difference occurred for the severe obesity cutoff point rather than the obesity cutoff (figure 1), the focus of this analysis is on severe obesity.

Table 3 shows that 26 percent of black women compared with 7 percent of white women were severely obese (OR = 4.81 (95 percent CI 1.87–12.35), adjusted for age, marital status, socioeconomic status, breast cancer screening history, and selected reproductive and lifestyle factors). This table also shows that women who were severely obese were more than three times as likely as women who were not severely obese to be diagnosed with cancer at TNM stage II or higher (multivariate-adjusted OR = 3.10, 95 percent CI 1.26–7.52). In other multivariate analyses, severe obesity was also associated with two components of TNM stage at diagnosis: tumor size >2 cm (OR = 2.30, 95

<table>
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<th>White (n = 177)*</th>
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<td>50</td>
<td>113</td>
<td>35.4</td>
<td>31.1</td>
</tr>
<tr>
<td>Occupation rank</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low score</td>
<td>101</td>
<td>66</td>
<td>72.1</td>
<td>39.3</td>
</tr>
<tr>
<td>High score</td>
<td>56</td>
<td>110</td>
<td>27.9</td>
<td>60.7</td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever</td>
<td>80</td>
<td>148</td>
<td>58.3</td>
<td>82.9</td>
</tr>
<tr>
<td>Never</td>
<td>62</td>
<td>22</td>
<td>41.7</td>
<td>17.1</td>
</tr>
<tr>
<td>Regular smoker</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever</td>
<td>73</td>
<td>108</td>
<td>50.7</td>
<td>61.4</td>
</tr>
<tr>
<td>Never</td>
<td>70</td>
<td>92</td>
<td>49.3</td>
<td>38.6</td>
</tr>
<tr>
<td>Menopausal status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>89</td>
<td>127</td>
<td>63.1</td>
<td>71.8</td>
</tr>
<tr>
<td>Pre/postmenopausal</td>
<td>92</td>
<td>50</td>
<td>36.9</td>
<td>28.2</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20</td>
<td>37</td>
<td>12</td>
<td>39.7</td>
<td>6.9</td>
</tr>
<tr>
<td>20–29</td>
<td>43</td>
<td>19</td>
<td>29.9</td>
<td>46.8</td>
</tr>
<tr>
<td>≥30</td>
<td>84</td>
<td>119</td>
<td>44.4</td>
<td>67.4</td>
</tr>
</tbody>
</table>

* Numbers for each characteristic may not sum to total because of missing data.
† Adjusted for age (continuous variable) and menopausal status (married vs. never).
‡ Danish Socioeconomic Index (28, 29), adapted for spouse pairs (median vs. median).
§ Adjusted for age.
¶ Weight (kg)/height (m²).

percent CI 1.06–4.89) and positive axillary nodes (OR = 3.65, 95 percent CI 1.71–7.80). Race-specific findings were similar to findings in the total sample. In blacks, severe obesity was significantly associated with cancer of T2 or higher (age-adjusted OR = 2.89, 95 percent CI 1.98–7.70); in whites, the small number of severely obese women produced a wide confidence interval that included 1.00 (age-adjusted OR = 1.06, 95 percent CI 0.90–2.07).

To assess the potential for severe obesity to explain the race-stage association, we first compared a model that included age and race with a model that included age, race, and severe obesity (yes/no). Introduction of the severe obesity variable into a multivariate model that included age and race reduced the odds ratio for the race-stage association from 1.98 (95 percent CI 1.23–3.19) to 1.68 (95 percent CI 1.01–2.73) (table 2). This represents a relatively large change in estimates, a reduction of 32.7 percent. In analyses in which T3M components were substituted for the outcome variable (data not shown), inclusion of severe obesity reduced the race-tumor size association by 32.9 percent and the race-lymph node stage association by 46.4 percent. The explanatory effect of severe obesity remained at 29 percent, even when it was included in a model with all other potentially explanatory variables. That is, its explanatory effect was independent of the explanatory effects of socioeconomic status, history of breast cancer screening, and selected lifestyle and reproductive factors. However, this fully adjusted model was less stable than the simpler model because of the reduced sample size (n = 279) resulting from missing data on selected variables (e.g., family income) (table 4).

The endocrinologic effects of increased body weight and adiposity are well documented. Among other hormonal effects, excess body weight has been associated with increases in bioavailable estrogen. It is this aspect of obesity that is believed to increase the risk of breast cancer in postmenopausal women (27–29). We therefore hypothesized that the effects of obesity on T3M stage at diagnosis would be stronger in postmenopausal women, and in

women with estrogen receptor-positive tumors compared with women with estrogen receptor-negative tumors. Table 5 shows that, when data were stratified according to menopausal status, the association between stage at diagnosis and severe obesity appeared to point in a direction opposite of that hypothesized. However, the estimate for premenopausal women was very unstable, because only one severely obese premenopausal woman was diagnosed at a less advanced stage. The term for statistical interaction was not significant ($p = 0.13$), indicating that the effect of severe obesity on stage at diagnosis was not modified by menopausal status. Table 5 also shows that the association between stage at diagnosis and severe obesity was observed in estrogen receptor-positive women (OR = 7.02, 95 percent CI 1.91–25.84) but not in estrogen receptor-negative women (OR = 0.83, 95 percent CI 0.14–4.75). Although these results are consistent with our hypothesis, the statistical interaction between estrogen receptor status and severe obesity did not reach statistical significance ($p = 0.11$). When tumor size and nodal status were substituted as

\[ \text{FIGURE 1. Racial differences in obesity among female breast cancer cases diagnosed in Connecticut, January 1987-May 1989.} \]  

\[ \text{Am J Epidemiol Vol. 146, No. 5, 1997} \]
TABLE 5. Relation of severe obesity to race and tumor characteristics among female breast cancer patients, Connecticut, 1987-1989

Race, Obesity, and Breast Cancer Stage 399

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Various</th>
<th>NOS</th>
<th>OR</th>
<th>95% CI</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>87 (26.7)</td>
<td>107</td>
<td>74.3</td>
<td>6.02$</td>
<td>2.46–10.27</td>
<td>4.81</td>
</tr>
<tr>
<td>White</td>
<td>12 (8.0)</td>
<td>154</td>
<td>93.2</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>TNM stage</td>
<td>50 (30.7)</td>
<td>148</td>
<td>79.3</td>
<td>3.10$</td>
<td>1.37–7.04</td>
<td>3.10*</td>
</tr>
<tr>
<td>Stage I</td>
<td>8 (8.0)</td>
<td>113</td>
<td>96.4</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Tumor size</td>
<td>54 (22.5)</td>
<td>119</td>
<td>77.8</td>
<td>2.00*</td>
<td>1.28–3.41</td>
<td>2.00*</td>
</tr>
<tr>
<td>≥5 cm</td>
<td>16 (8.0)</td>
<td>152</td>
<td>81.0</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Lymph node status</td>
<td>91 (24.8)</td>
<td>96</td>
<td>76.4</td>
<td>3.18*</td>
<td>1.87–5.39</td>
<td>3.18*</td>
</tr>
<tr>
<td>Positive</td>
<td>16 (8.0)</td>
<td>100</td>
<td>91.4</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>6 (8.0)</td>
<td>18</td>
<td>94.4</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
</tr>
</tbody>
</table>

* Numbers for each characteristic may not sum to total because of missing data.
† OR, odds ratio; CI, confidence interval; TNM, tumor-node-metastasis.
$ Odds ratios shown in this column are based on similar numbers than those listed in the table because of missing data on some variables.
© Adjusted for age (continuous variable).
§ Adjusted for age (continuous variable), marital status (not married vs. married), lifestyle variables: history of occasional alcohol consumption (<1 drink per week vs. >1 drink per week), ever smoking cigarettes (ever vs. never), and history of eczema or eczema-like conditions (ever vs. never), socioeconomic status: education (<12 years vs. ≥12 years), family income (<$25,000 vs. ≥$25,000), and occupation (professional vs. nonprofessional) (62% vs. 38%).
©©© Adjusted for age, race and marital status.

Outcome variables, the results were very similar to those reported for TNM stage at diagnosis.

Despite the limitations of using these observational data to determine a causal pathway, we further hypothesized that in severely obese women, the ability to detect breast tumors at an early stage with screening is compromised. If this were so, the increased risk of late-stage disease associated with severe obesity should be stronger in those women who had a positive history of screening mammography compared with those who had a negative history. Table 5 presents the results of multivariate analyses of the association between severe obesity and stage at diagnosis, stratifying the data according to history of screening mammographic examinations. The risk of late-stage at diagnosis in severely obese women compared with women who were not severely obese was only slightly greater in women with a history of screening mammography than in women without such a history, and the mammography-severe obesity interaction term was clearly nonsignificant (p = 0.51). In analyses not presented here, it was clear that stratification according to other breast cancer screening modalities (clinical breast examination and breast self-examination) also did not support this hypothesis.

DISCUSSION

To our knowledge, this is the first report to identify obesity as a major explanatory factor in the excess risk of late-stage breast cancer in black women relative to white women. Adjustment for the greater prevalence of severe obesity in black women decreased the racial difference in disease stage at diagnosis by almost one-third. Severely obese women were significantly more likely than other women to be diagnosed with breast cancer of a more advanced TNM stage. Furthermore, severe obesity was significantly associated with both larger tumor size and positive lymph node status. The severe obesity-stage association did not differ significantly by race. While it is well documented in national survey data (12, 20) that black women are more obese than white women, we demonstrated that the significant racial difference in obesity persisted after adjustment for a number of potentially confounding variables.


T
Table 6. Change in estimate for the association between race and TNM stage among female breast cancer cases after adjustment for severe obesity and other covariates, Connecticut, 1987-1989

<table>
<thead>
<tr>
<th>Model and Independent variables modeled</th>
<th>No.</th>
<th>OR (95% CI)</th>
<th>% change (model 1 vs. model 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1</td>
<td>200</td>
<td>1.99 (1.22-3.21)</td>
<td>-61.7</td>
</tr>
<tr>
<td>Age</td>
<td>200</td>
<td>1.99 (1.22-3.21)</td>
<td>-61.7</td>
</tr>
<tr>
<td>Race</td>
<td>200</td>
<td>1.99 (1.22-3.21)</td>
<td>-61.7</td>
</tr>
<tr>
<td>Model 2</td>
<td>279</td>
<td>1.99 (1.22-3.21)</td>
<td>-61.7</td>
</tr>
<tr>
<td>Age</td>
<td>279</td>
<td>1.99 (1.22-3.21)</td>
<td>-61.7</td>
</tr>
<tr>
<td>Race</td>
<td>279</td>
<td>1.99 (1.22-3.21)</td>
<td>-61.7</td>
</tr>
</tbody>
</table>

† TNM, Tumor-Node-Metastasis
‡ Independent variable: TNM stage all versus carcinoma in situ and TNM stage 1 (logistic regression analysis).
§ Independent variables: age (continuous variable); race (African-American vs. white); severe obesity (body mass index ≥35.0 kg/m²); marital status (married vs. nonmarried); educational status (less than high school graduate vs. high school graduate); history of smoking (ever vs. never); history of drinking (ever vs. never); history of breast cancer screening (yes vs. no); family history of breast cancer in first-degree relatives (yes vs. no); household income (less than $10,000 vs. more than $10,000); and occupation (professional vs. nonprofessional).

Although obesity is a known risk factor for breast cancer, the effect being limited to postmenopausal women (27, 30-32), the relation of obesity to stage at diagnosis and breast cancer survival is less clear. Many authors have demonstrated decreased stage-adjusted survival with increasing weight or body mass (14, 15, 33-38), but reports on the relation between body weight and stage at diagnosis, or its individual components, show some inconsistencies. Associations between obesity and/or increased body mass and stage at diagnosis (35, 39, 40) and both larger tumors and lymph node involvement have been reported (41, 42). However, other researchers have reported only that there is a positive relation between obesity and tumor size (14, 38). An absence of an association between obesity and TNM tumor stage, tumor size, or axillary node involvement has also been reported (43).

Studies in which African-American women are adequately represented are relatively uncommon; thus, it is difficult to determine whether these associations between obesity and stage at diagnosis or stage-adjusted survival hold for women of both races. Although we are not the first investigators to postulate that the greater body mass indices seen in black women may partly explain the observed survival dif

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T
TABLE 5. Odds of later stage at diagnosis (THM* stage 21 vs. earlier stages in all/THM stage 1) in relation to severe obesity (MEN index >26,9 vs. <23,9) among female breast cancer cases, by menopausal status, estrogen receptor status, and history of screening mammography, Connecticut, 1987–1989

<table>
<thead>
<tr>
<th>Determinant variable</th>
<th>Severe obesity</th>
<th>Odds ratio</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Menopausal status</td>
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<td></td>
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<tr>
<td>Premenopausal</td>
<td>Yes</td>
<td>10.42</td>
<td>1.26–88.22</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>Yes</td>
<td>2.36</td>
<td>0.93–6.00</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Estrogen receptor status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>Yes</td>
<td>0.88</td>
<td>0.14–4.78</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>Yes</td>
<td>7.02</td>
<td>1.91–26.84</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>History of screening mammography</td>
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<td></td>
<td></td>
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<tr>
<td>Negative</td>
<td>Yes</td>
<td>2.84</td>
<td>1.05–8.26</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>Yes</td>
<td>3.88</td>
<td>0.90–14.22</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>1.00</td>
<td></td>
</tr>
</tbody>
</table>

* THM, tumor-node-metastasis.
† Number fluctuations because of missing data for some variables.
‡ Adjusted for race (black vs. white) and age (continuous variable).
§ Number of screening mammograms (0 vs. 2) in 2 years before diagnosis of symptoms or diagnosis of breast cancer (in the case of asymptomatic women).

In contrast to blacks and whites (15, 44), a recent report from the National Cancer Institute’s Black/White Cancer Survival Study does not support this hypothesis. In that study’s data, adjustment for body mass index and other comorbid conditions reduced the black/white difference in survival relatively little, once stage at diagnosis was included in a proportional hazards survival model (44). In a separate report from this National Cancer Institute study, Hunter et al. (16) reported that body mass index was associated with stage at diagnosis in black women but not in white women.

The inconsistent findings reported in the literature may reflect the inconsistencies in the measures of obesity that have been used in breast cancer research. In the data reported here, a relation between obesity and stage at diagnosis was observed only when the severe obesity cutoff was used, and the relation was not significant when the more moderate cutoff for obesity was used, which suggests a possible threshold effect.

The mechanism of the effect of obesity on breast cancer risk or progression is not clear, although most investigators lean toward an endocrinologic explanation (27–29, 31, 45). Among the proposed mechanisms is an increase in bioavailable estrogen, as has been demonstrated in obese women (46–49). Additionally, body weight has been negatively associated with sex hormone-binding globulin (SHBG) in breast cancer patients (45, 50). Because the estrogen which is not taken up by SHBG remains available, the level of SHBG can influence the amount of estrogen that is available to interact with breast tissue (51). Our results are consistent with this hypothesis in that the effect of severe obesity on stage at diagnosis was limited to women whose tumors were estrogen receptor-positive.

If the mechanism of the effect of obesity on stage at diagnosis is similar to that believed to confer a risk of breast cancer, one might expect the relation between severe obesity and stage at diagnosis to be stronger in postmenopausal women than in premenopausal women. Although this was not the case in the data reported here, our results are not inconsistent with those from studies which have shown that the adverse effect of obesity on survival is not modified by menopausal status (14, 36, 32). Furthermore, the findings cited above by Schapiro et al. (30) indicated decreased levels of SHBG in premenopausal breast cancer patients rather than in postmenopausal patients.

Recent reports of significant roles for body fat distribution (53–56), weight gain (54, 57, 58), and possibly skinfold thickness (59) in breast cancer risk suggest that these measures may also be more informative in our understanding of the role of obesity in

stage at diagnosis than the relatively crude measure of body mass index. Although measures of body fat distribution were not available in this investigation, it is likely that severely obese women have upper body fat, the fat distribution pattern most often associated with altered hormonal metabolism (45, 53–55). This may further explain why we observed an explanatory role for severe obesity rather than for the moderate obesity cutoff.

The interpretation of studies on the prognostic role of obesity is further complicated by the likelihood that obese individuals, relative to the nonobese, consume more dietary fat (29). Although most of the reports on the role of obesity in breast cancer etiology or prognosis do not include dietary information, there is some evidence that dietary fat may be associated with recurrence of breast cancer (60) and increased risk of death from breast cancer after adjustment for stage at diagnosis and obesity (61). More recent findings point to endocrinologic mechanisms, in that relatively low fat/high fiber diets have resulted in lower concentrations of serum estrogen (62, 63), and in at least one other study (64), dietary fat intake was weakly associated with increased risk of tumors that were both estrogen receptor- and progesterone receptor-positive.

We cannot rule out the possibility that the observed effects of obesity on stage at diagnosis were confounded or mediated by dietary fat, which was not measured in this investigation.

Although mammograms of fatty breasts are easier to read than those of dense breasts (65), we further hypothesized that severely obese women, who are more likely to have large breasts (66, 67), might have been more likely to receive substandard mammography in that special procedures generally used for large-breasted women may not have been routine in the late 1980s—e.g., multiple views for visualization of the entire breast or use of large film cassettes and grids. However, these data do not show the association between obesity and stage at diagnosis to be stronger in women with a history of recent screening compared with women without such a history.

While the proposed mechanisms (changes in the hormonal milieu and interference with screening tests) are not mutually exclusive, these data suggest that the negative impact of severe obesity on stage at diagnosis is more likely to be mediated by endocrinologic processes than by screening processes. To further our understanding of the mechanisms by which obesity influences stage at diagnosis, this issue should be examined in a larger biracial population that would include a greater number of severely obese women.

The significance of our finding that the increased prevalence of severe obesity among African-American women can explain almost one third of their excess risk for later stage at diagnosis must be considered in the context of other possibilities. Historically, hypothesized causes for the later stage at diagnosis in blacks relative to whites have included racial differences in socioeconomic status, differences in access to health care, and the related issue of screening behavior (18). In our own data, one measure of socioeconomic status (occupational ranking) also played an explanatory role in the race-stage association, yet controlling for this variable did not diminish the role of severe obesity. Additionally, as we reported previously (11), we have shown that adjustment for racial differences in history of breast cancer screening accounts for less than 10 percent of the observed racial difference in stage at diagnosis. Given what is certainly a multifactorial phenomenon, a one-third reduction in the race-stage association is a relatively impressive explanatory effect. It is encouraging to note that this physical characteristic is potentially more amenable to intervention than some of the more intractable social/cultural influences to which the racial difference in stage at diagnosis has traditionally been attributed.

ACKNOWLEDGMENTS

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REFERENCES


Race, Obesity, and Breast Cancer Stage: A Cochrane Systematic Review


47. Ingwen DM, Notte JM, Wilcocks DI, et al. Overweight blind...
APPENDIX III: SLIDE AND BLOCK RETRIEVAL PROTOCOL

ALTERNATIVE BLOCK AND SLIDE RETRIEVAL PROTOCOLS
RACE DIFFERENCES IN BREAST CANCER SURVIVAL

INTRODUCTION

Race Differences in Breast Cancer Survival is a follow-up study of a cohort of female African-American and Caucasian residents of Connecticut diagnosed with breast cancer in 22 Connecticut hospitals during the years 1987-1989. As a part of this follow-up study, information on the vital status and current disease status of these subjects will be collected, as will information on tumor characteristics. With respect to this latter arm of the study, tumor specimens for the 322 cases are being requested from the appropriate hospital pathology departments.

The tests to be conducted on the tumor specimens include: histopathologic grade, tumor grade, estrogen receptors, progesterone receptors, DNA ploidy, S phase fraction, presence and type of p53 mutations, and overexpression of erbB-2. These tests will be conducted by Christine Howe, Ph.D., of the Yale Program for Critical Technologies. In order to perform the requisite tests, a minimum of 15 thin sections (four microns each) and 6 to 10 thick sections (50 microns each) of a block with tumor present are needed.

As the policies regarding the release of slides and blocks differ considerably across pathology departments, we have identified four alternative plans for accessing the necessary sections of tissue. We ask that you select the plan that is best suited to your department’s guidelines and procedures. The study is funded to reimburse your department for costs incurred on behalf of the research.

OVERVIEW OF THE FOUR PLANS

A. PATHOLOGY DEPARTMENT RELEASES ALL SLIDES AND BLOCKS

As the requested specimens are eight to ten years old and, in most cases, have limited clinical relevance, many hospital pathology departments have indicated that they would be amenable to releasing all slides and blocks, which would then be returned at a later date. A numerically-sorted list of pathology specimens for each hospital has been prepared. As for the actual retrieval of materials, you may prefer that your staff pull the slides and blocks, or you may prefer that the material be pulled by a member of the Rapid Case Ascertainment (RCA) field staff who regularly visits your department.

In either case, RCA staff will hand-carry the material from your department to Yale. Dr. Mary Lachman, a pathologist, would then review the slides to determine the appropriate paraffin block(s) for testing (one that has a sufficient quantity of tumor tissue). Dr. Howe would then cut the required number of sections from the identified block to perform the aforementioned tests. Upon completion of the testing, the slides and blocks would then be hand-carried back to your
department by RCA. This plan is preferred by the study investigators as it assures standardization of the technical procedures, thereby enhancing the scientific reliability of the study.

B. DEPARTMENT REVIEWS SLIDES AND SENDS BLOCKS WITH TUMOR

If your department is reluctant to release slides, you may be comfortable with the following option. Your pathologist would review the existing slides for each specimen on the list provided, identify at least two blocks that have tumor present (in accordance with study criteria), and those selected blocks would be hand-carried by RCA to Yale for testing and returned at the completion of the protocol.

This option involves no release of slides, and a limited release of blocks (2-3), but does involve some time expenditure by your pathologist in choosing the appropriate blocks.

C. DEPARTMENT RELEASES ALL BLOCKS AND NO SLIDES

For departments that are reluctant to release slides, but will release blocks, this option may be most preferable as it involves minimal time expenditure on the part of your pathologist. Under this plan, your department staff or a member of the RCA field staff would retrieve the blocks for each specimen (from the numerical list provided) and RCA would hand-carry them to Yale. At Yale, Dr. Howe would prepare slides for H & E staining. The newly created slides would be reviewed in order to select the most appropriate block for further testing. At the conclusion of testing, all blocks would be returned to the hospital. The slides prepared by Dr. Howe would be retained by the study.

D. DEPARTMENT EVALUATES SLIDES, Chooses BLOCK, AND CUTS FRESH SECTIONS FOR ANALYSIS: NO RELEASE OF SLIDES OR BLOCKS

This plan is designed for those departments that prefer not to release their archived material. Under this plan, your pathologist would review the slides for each specimen, determine the appropriate blocks for testing (in accordance with study criteria) and would cut the required sections from the block. Dr. Howe would provide the coated slides for thin sections and cassettes for thick sections.

This plan involves greater time expenditure on the part of your department, and also requires greater communication and coordination with RCA, as the newly cut sections must be stained as soon as possible after cutting.
SELECTION OF PLAN AND INITIATION OF PROCESS

Once you have had a chance to review the four plans, please select the one that best fits the policies of your department, and check the appropriate box on the Tissue Retrieval Preference Form. In addition, please provide the name of a pathologist in your department who can be contacted about this project. Plans B and D necessitate a greater role for your department, and therefore an increased need for communication. We have also left space for comments and questions. If some modifications to a plan are necessary, please indicate them here, or if there are any other constraints on the process that apply, please indicate these on the form.

Please feel free to contact a member of the study team if you have any additional questions or concerns. For general questions, you may want to contact Meredith Glazer, Project Coordinator. For questions related to the RCA or the pulling or retrieval of specimens, you may wish to contact Judie Fine, the Director of the RCA Shared Resource of the Yale Cancer Center. If you have questions related to the selection of blocks or testing of tissue, Dr. Christine Howe is the Director of the Yale Program for Critical Technologies. The phone numbers for these individuals and the other members of the study team are provided below.

Thank you for your consideration of this request, your return of the Retrieval Form, and your overall contribution to this project. We appreciate your time, effort and commitment.

STUDY PERSONNEL PHONE NUMBERS

Beth A. Jones, Ph.D., M.P.H., Principal Investigator 203-785-2890
Meredith Glazer, Ph.D., Project Coordinator 203-764-9966
Judie Fine, Director, RCA Shared Resource 203-764-9087
Christine L. Howe, Ph.D., Director, Critical Technologies 203-737-4198
Mary Lachman, M.D., Pathologist 203-380-4593
TISSUE RETRIEVAL PREFERENCE FORM

RACE DIFFERENCES IN BREAST CANCER SURVIVAL

Please complete the following and mail or fax to:

Ms. Judie Fine, Director
RCA Shared Resource
200 College Street
New Haven, CT 06510

Fax Number: (203) 764-9072
Phone Number: (203) 764-9087

******************************************************************************

Plan Selection

☐ A
☐ B
☐ C
☐ D

Hospital Name:

Contact Pathologist’s Name

& Phone Number: ( ) -

& Fax Number if available: ( ) -

Is there a specific staff person that RCA should contact? Please provide name and phone number:

_________________________________________________________ ( ) -

Comments, Amendments or Questions:

Thank you for your participation in and contribution to this study.
PATIENT NAME:
Patient Date of Birth:
Yale Study ID Number:
Physician Name:
Date of Diagnosis with Breast Cancer:

I. Vital Status and Disease Status
Please provide the following information to the best of your knowledge and with as much detail as you are able. If precise dates are unknown, please provide month and year or closest approximation.

1. Do you know the vital status of this patient?
   a. Alive, with no clinical evidence of breast cancer
   b. Alive, with clinical evidence of breast cancer
      ■ Localized disease
      ■ Regional disease
      ■ Distant metastases
   c. Deceased
      Date of Death ___ / ___ / _______
      Cause of Death
      ■ Breast Cancer Related
      ■ Unrelated to Breast Cancer
      ■ Do not have any information on cause of death
   d. Do not know

2. In order to compute the length of disease-free survival (time of diagnosis to first recurrence), it is necessary to know the date of first recurrence. When, if at all, did this patient experience a first recurrence of breast cancer?
   a. First recurrence diagnosed ___ / ___ / _______
   b. The patient did not have a first or any recurrence of breast cancer and has remained in remission up until the present or until death from causes unrelated to breast cancer.
   c. The patient never achieved a remission of the cancer after diagnosis, and thus did not have a recurrence per se nor any disease-free period after diagnosis.
   d. Other, please explain:

3. To your knowledge, was the patient diagnosed with any other primary cancers after the specified diagnosis with breast cancer?
   a. Yes, the patient had a second primary cancer
      Site: ___________ Date of Diagnosis: ___ / ___ / _______
   b. No, the patient was not diagnosed with any other cancers
   c. Do not know

4. When did you last see this patient? ___ / ___ / _______

5. What was the health status of this patient at that time?
   a. Patient was without clinical evidence of disease (breast cancer).
   b. Patient had clinical evidence of disease (breast cancer)
      ■ Localized Disease
      ■ Regional Disease
      ■ Distant Metastatic Disease
II. Treatments Received for Breast Cancer

Please provide any information that you have available on the treatment protocol for breast cancer that was administered to this patient. For example, if you know that the patient received chemotherapy, but you were not the provider and/or you do not know the particular regimen or dates, please include the information that you do have.

**Surgeries**  (e.g. lumpectomy, mastectomy, axillary node excision)

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<tr>
<th>Surgical Procedure Name</th>
<th>Date</th>
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**Chemotherapy**

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<tr>
<th>Drugs Administered</th>
<th>Number of Tx’s</th>
<th>Start Date</th>
<th>End Date</th>
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**Radiation**

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<tr>
<th>Dosage</th>
<th>Number of Tx’s</th>
<th>Area Covered</th>
<th>Start Date</th>
<th>End Date</th>
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**Hormone Therapy (e.g. Tamoxifen)**

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<th>Drugs Used</th>
<th>Dosage</th>
<th>Start Date</th>
<th>End Date/or Ongoing</th>
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**Other Treatment Modalities Administered** (e.g. bone marrow transplant, other drugs)

Please provide Name of Treatment, Dates and Duration Administered, Relevant Information
BIOPGRAPHICAL SKETCH

Give the following information for the key personnel and consultants and collaborators. Begin with the principal investigator/program director. Photocopy this page for each person.

NAME
Susan Taylor Mayne, Ph.D., F.A.C.E.

POSITION TITLE
Associate Professor

EDUCATION (Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)

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<thead>
<tr>
<th>INSTITUTION AND LOCATION</th>
<th>DEGREE</th>
<th>YEAR CONFERRED</th>
<th>FIELD OF STUDY</th>
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<tr>
<td>Yale University, New Haven, CT</td>
<td>Post-Doc</td>
<td>1988</td>
<td>Epidemiology</td>
</tr>
</tbody>
</table>

RESEARCH AND/OR PROFESSIONAL EXPERIENCE: Concluding with present position, list in chronological order previous employment, experience, and honors. Key personnel include the principal investigator and any other individuals who participate in the scientific development or execution of the project. Key personnel typically will include all individuals with doctoral or other professional degrees, but in some projects will include individuals at the masters or baccalaureate level provided they contribute in a substantive way to the scientific development or execution of the project. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. DO NOT EXCEED TWO PAGES.

Professional Experience:
1982-1987 Graduate Research Assistant, Division of Nutritional Sciences, Cornell University.
1987-1988 Post-Doctoral Fellow, Department of Epidemiology and Public Health, Yale University School of Medicine.
1988-1989 Research Faculty, Department of Epidemiology and Public Health, Yale University School of Medicine; and Cancer Prevention Research Unit for Connecticut at Yale.
1989-1990 Research Faculty and Lecturer, Department of Epidemiology and Public Health, Yale University School of Medicine; and Cancer Prevention Research Unit for Connecticut at Yale.
1990-1995 Assistant Professor, Department of Epidemiology and Public Health, Yale University School of Medicine.
1993- Program Director, Cancer Prevention and Control Research Program, Yale Cancer Center.
1995- Associate Director for Cancer Prevention and Control, Yale Cancer Center.
1995- Associate Professor, Department of Epidemiology and Public Health, Yale University School of Medicine.

Selected National/International Professional Activities:
- Reviewer, National Cancer Institute and National Institutes of Health (7 review groups since 1991).
- Reviewer, Department of Defense.
- Associate editor, Pharmacology and Therapeutics.
- Steering Committee, Carotenoid Research Interaction Group (CARIG), 1993-present.

Honors and Awards:
- Merck Award in Chemistry, University of Colorado, 1981.
- Phi Beta Kappa, 1981.
- Andrew D. White Fellowship, Cornell University, 1982-84.
- National Research Service Award, Cornell University, 1984-87.
- National Research Service Award, Yale University, 1987-88.
- Graduate Women in Science Award for Excellence, Cornell, 1986.
- Shannon Award, National Institutes of Health, 1992.
- Fellow, American College of Epidemiology, 1996.

Bibliography: (Selected publications since 1991)


OTHER SUPPORT

Kasl, S.V.
Active
T-32 AG 00153 (Kasl) 7/1/93-6/30/98 10%
NIA $212,517
Research Training in the Epidemiology of Aging

The major goals of this project are to train pre-doctoral and post-doctoral fellows in the methods and content of the epidemiology of aging.

T-32 MH 14235 (Kasl) 7/1/95-6/30/00 10%
NIMH $220,802
Research Training in Mental Health Epidemiology

The major goals of this project are to train pre-doctoral and post-doctoral fellows in the methods and content of psychiatric and psychosocial epidemiology.

R01 CA 70731 (Jones) 9/26/95-6/30/99 15%
NCI $185,956
Race Differences in the Screening Mammography Process

The major goals of this project are to examine racial differences in mammography screening in order to understand impact on race differences in stage at diagnosis.

1P60 AG10469 (Kasl) 8/1/97-7/31/02 15%
NIA $165,819
Claude Pepper Center - Older American Independence Center, Research Development Core

The major goals of this project are to facilitate the development and testing of cost-effective interventions that maintain or increase functional ability among elderly persons.

1P60 AG10469 (Marottoli) 8/1/97-7/31/02 10%
NIA $168,876
Driver-related Rehabilitative Intervention for the Elderly

The major goals of this project are to design an intervention to improve driving skills among frail elderly.
Kasl, S.V. (Continued)
Page 2

DAMD17-96-1-6101 (Jones)  7/1/96-6/30/00  10%
U.S. Army  $197,568
Race Differences in Breast Cancer Survival

The major goals of this project are to examine biological, clinical and psychosocial variables as they influence race differences in stage-adjusted survival.

1DMR 81 DF96-163 (Baker)  1/1/97-12/31/97  5%
Donaghue Medical Research Foundation  $60,000
Depression in Elderly Meals-on-Wheels Recipients

The major goals of this project are to establish prevalence of depression in frail, home-bound, poor elderly.

Pending
T32-AG00153 (Kasl)  5/1/98-4/30/03  10%
NIA  $267,746
Research Training in the Epidemiology of Aging
MAYNE, SUSAN T. (Ph.D.)

ACTIVE

RO1 CA/ES62986-04 (Zhang)  9/30/93 - 9/29/97  5%
NIH/NCI
$370,962

Organochlorine Compounds and Risk of Female Breast Cancer

The major goal of this project is to examine organochlorine compounds as risk factors for female breast cancer by measuring organochlorine compound levels in breast adipose tissue from breast cancer cases and benign breast disease controls.

5P30 CA 16359-22 (DeVita)  7/01/94 - 6/30/98  10%
NIH/NCI
$1,210,390

Comprehensive Cancer Center Core Support Grant

The major goal of this project is to provide administrative support and developmental funds for new faculty and support for Cancer Center core facilities.

RO1 CA64567-03 (Mayne)  9/09/94 - 6/30/98  40%
NIH/NCI
$392,123

Beta-Carotene Chemoprevention of Head and Neck Cancer

The major goal of this project is to determine whether supplemental Beta-Carotene reduces the incidence of second malignancies in patients curatively treated for early stage cancer of the oral cavity, pharynx or larynx.

1 RO1 CA74567-01 (Cartmel)  4/01/97 - 11/30/00  10%
NIH/NCI
$162,251

Increasing Fruit & Vegetable Intake in Head and Neck Cancer Patients

The aim of this project is to determine if the use of a tailored intervention based on the stage of change model will increase intake of fruit and vegetables in head and neck cancer patients and thereby increase plasma carotenoid levels by 30%. The intervention will be designed to be translatable to the normal medical care of these patients.

PENDING

NONE

OVERLAP

NONE