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SCHOOL OF PUBLIC HEALTH

Dissertation

BREAST CANCER ETIOLOGY, THERAPY, AND SIDE-EFFECTS OF THERAPY

by

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Breast Cancer Etiology, Therapy, and Side-effects of Therapy

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ABSTRACT

Breast cancer is an important cause of morbidity and mortality among women. The American Cancer Society estimated that 178,700 women were diagnosed with breast cancer in 1998 and that 43,500 women died from the disease. Those women who survive the disease face short- and long-term consequences of their therapy that affect their quality of life. The studies described herein address three important aspects of public health efforts to reduce the impact of breast cancer.

The first study measured the effect of exposure to active and passive cigarette smoke on breast cancer occurrence using a case-control design. Ever-active smokers had an odds ratio of 2.0 (95 percent confidence interval 1.1–3.6) and passive-only smokers had an odds ratio of 2.0 (95 percent confidence interval 1.1–3.7) compared with never-active, never-passive smokers. The pattern of associations between

exposure to cigarette smoke and breast cancer occurrence corresponded with a model of breast carcinogenesis.

The second study assessed the effect of patient characteristics and therapy on self-reported upper-body function and discomfort immediately after and approximately two years after primary breast cancer therapy. Women with a cardiopulmonary comorbidity score of four or more had an odds ratio for any early upper-body function decline of 3.6 (95 percent confidence interval 1.6–7.8) relative to women with a score of zero. The odds of any early upper-body function decline among women who underwent axillary dissection, relative to women who did not, was 3.7 (95 percent confidence interval 1.2–11). Women who had axillary dissection were also more likely to report numbness or pain in the armpit (OR = 13; 95 percent confidence interval 1.5–117) and swelling or other arm problems (OR = 4.3; 95 percent confidence interval 0.5–37) than women who did not have axillary dissection.

The third study measured the effect of less than definitive care for early stage breast cancer on recurrence and survival. Patients were diagnosed between 1984 and 1986 and were treated at one of eight Rhode Island hospitals. Three hundred and ninety women ages 45 to 90 with local or regional disease were followed through 31 December 1996. Patients who received less than definitive prognostic evaluation and less

than definitive treatment had an adjusted relative hazard of breast cancer recurrence of 2.3 (95 percent confidence interval 1.3–4.0) and an adjusted relative hazard of breast cancer-specific mortality of 3.0 (95 percent confidence interval 1.6–5.4) compared with patients who received definitive care.

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1. INTRODUCTION

Breast cancer is an important cause of morbidity and mortality among women. The American Cancer Society estimated that 178,700 women were diagnosed with breast cancer in 1998 and that 43,500 women died from the disease (1). Those women who survive the disease face short- and long-term consequences of their therapy that affect their quality of life. The studies described herein address three important aspects of public health efforts to reduce the impact of breast cancer.

The first study investigated the effect of modifiable behaviors on the risk of developing breast cancer using a case-control design. The behaviors studied were active and passive exposure to tobacco smoke, ingestion of alcohol, and the use of estrogen replacement therapy.

The second study measured the effect of different types of breast cancer therapy and patient characteristics on persistent upper body limitations. Women who have been treated for breast cancer often experience upper body dysfunction for three to twelve months following treatment. Upper body limitation adversely affects quality of life and is an important predictor of independent living in older women. The study provided information on whether the different types of therapy are associated with different risk of upper-body limitations and characterized

the type of patients most likely to have some decline in upper-body function.

The third study measured the effect of age-dependent variations in breast cancer therapy on breast cancer recurrence, breast cancer-specific mortality, and overall survival. Numerous studies have documented an inverse relation between a woman's age and the likelihood that she will receive definitive treatment for early stage breast cancer. One cohort in which these treatment variations were observed provided an opportunity to measure the effect of age-dependent variations in treatment on outcomes. Four hundred and ninety-four women with local or regional breast cancer were identified at eight Rhode Island hospitals from 1984 to 1986. Researchers recorded each patient's demographic characteristics, breast cancer treatment, and comorbid disease status. In this study we followed these patients' history of breast cancer recurrence, breast-cancer specific mortality, and overall survival through 31 December 1996 and measured the association between these outcomes and receipt of less than definitive care.

1.1. LITERATURE CITED

1. *Breast Cancer Facts & Figures – 1998.* Atlanta: American Cancer Society, 1998.

2. A Case-Control Study of the Effect of Modifiable Behaviors on Breast Cancer Occurrence

2.1. Introduction

The well-established risk factors for breast cancer offer few opportunities for intervention and account for less than half of breast cancer cases (1). Most of these factors involve aspects of a woman's reproductive course that are intimately related to her lifestyle and culture — so are difficult to predict and therefore to change — or are currently immutable (*e.g.*, genotype). While pharmaceutical intervention with tamoxifen has recently demonstrated a prophylactic benefit in high-risk women (2), recommendations for lifestyle changes to reduce the risk of breast cancer in low risk women remain elusive. The present study measured the effects on breast cancer occurrence of three risk factors that do offer opportunities for intervention. These three risk factors are tobacco smoke, alcohol ingestion, and estrogen replacement therapy.

Moolgavkar *et al* (3) proposed a model for breast carcinogenesis that requires two heritable and irreversible events in a progenitor cell. Each heritable change arises from a mutation and becomes irreversible following cell division. Few breast cell mutagens have been identified, but estrogen-induced mitogenesis has been well characterized (4).

To induce cancer, mutagenesis must act while breast tissue is vulnerable and prior to mitogenesis. As depicted in Figure 1, breast tissue development and differentiation determines its susceptibility to mutagenesis (5). Prior to puberty, breast tissue contains mostly undifferentiated structures called lobules 1. During sexual maturity, these lobules 1 differentiate to lobules 2. Pregnancy causes further differentiation to lobules 3 and lactation causes differentiation to lobules 4. Breast cells derived from lobules 1 are susceptible to chemical mutagens, but breast cells derived from lobules 3 are immune to the mutagens that have been tested (5).

The model of carcinogenesis proposed by Moolgavkar (3), in combination with the effect of breast tissue development on its susceptibility to mutagenesis (5), suggests that the time of exposure to breast carcinogens ought to affect susceptibility to carcinogenesis. Breast tissue exposed to mutagenic events while the proportion of lobules 1 is high should have increased susceptibility. Promotion of the exposed and susceptible tissue by mitogenic estrogen compounds ought to further increase the risk of tumor development (6), whereas inhibition of mitogenesis ought to reduce the risk (4).

The definition of index (exposed) and reference (unexposed) conditions in epidemiologic studies of the etiology of breast cancer

should reflect this model of breast carcinogenesis. Before conducting the present analyses, we hypothesized index conditions for active and passive exposure to cigarette smoke that would cause breast cancer while breast tissue contains primarily lobules 1 and 2, or that would prevent breast cancer through anti-estrogenic mechanisms in later stages of breast tissue development. These careful definitions of exposure to tobacco smoke revealed substantial estimated effects on the risk of breast cancer, which would have been obscured by simpler definitions.

2.2. METHODS

We identified 334 incident cases of breast cancer from 1983 to 1986 arising among female permanent residents of five Massachusetts towns and reported to the state cancer registry. We used three methods to select a single set of female control subjects from the base population of permanent residents of the towns during 1983 to 1986. We selected an age-stratified random sample of living subjects <65 years old who resided in the towns during the case ascertainment period *via* random-digit dialing. We selected an age-stratified random sample of living subjects ≥65 years who resided in the towns from lists provided by the Health Care Financing Administration (HCFA). Third, we selected an age-stratified random sample of deceased subjects from a list furnished

by the Massachusetts Department of Vital Statistics and Research of all resident deaths in the towns from 1983 through 1989. Age strata for all three methods corresponded to decades of birth. We selected deceased controls to approximately balance the proportion of proxy interviews completed by next-of-kin respondents in the case and control groups. Approximately three controls were selected for every case to improve the precision of the estimates of effect.

Trained interviewers conducted structured interviews to obtain information on demographic characteristics, smoking, alcohol consumption, medical conditions, and reproductive events. Interviews were conducted between 10 April 1989 and 8 January 1990.

Of the 334 breast cancer cases, 33 were never found, 6 were ineligible because they were not actually residents of one of the five towns, and physicians refused to allow contact with 30. We interviewed 265 cases (88 [33%] by proxy) and 763 controls (346 [45%] by proxy). The proportion of proxy respondents was higher among controls than among cases because of the original study design. The original study investigated several types of cancer, most of which have worse survival rates than breast cancer. Only one set of controls was selected for all cancers, frequency matched to cases on vital status. Because breast cancer survival rates are higher than for the other cancers, the

proportion of living case respondents was higher than the proportion of living control respondents. Proxy respondents were the next of kin listed in the Massachusetts Department of Vital Statistics records.

We interviewed 75 percent of eligible random-digit dialing controls, 76 percent of eligible HCFA controls, and 79 percent of eligible next of kin controls. We conducted 86 percent of all interviews by telephone and the remainder in-person. We set each case's index year equal to the year of breast cancer diagnosis. We randomly assigned index year to all controls combined so that the distribution of index year in controls matched the distribution in cases.

We categorized cases and controls into three groups of cigarette exposure: any history of active cigarette smoking (ever-active smokers); any history of passive exposure to cigarette smoke in the residence, but no history of active cigarette smoking (passive-only smokers); and no history of active cigarette smoking or passive exposure to cigarette smoke in the residence (nonsmokers, the reference condition throughout). We did not measure exposure to passive cigarette smoke outside of the residence.

To measure the effect of first exposure to active cigarette smoking on the occurrence of breast cancer, we divided ever-active smokers into categories demarcated by their age at first exposure or bounded by their

first term pregnancy (all before first term pregnancy, all after first term pregnancy, or both before and after first term pregnancy). We also categorized ever-active smokers by the intensity of their smoking habit measured as cigarettes per day. To measure the effect of smoking cessation, we categorized ever-active smokers by the number of years that passed between cessation and the index year (year of breast cancer diagnosis or control selection).

To measure the effect of first exposure to passive smoke, we divided passive-only smokers into categories demarcated by their age at first exposure or bounded by their first term pregnancy (all before first term pregnancy, all after first term pregnancy, or both before and after first term pregnancy). We created categories of age at first exposure to correspond to milestones of breast tissue development. The first category included women whose first exposure occurred before age 12, which is the approximate age of onset of puberty. In the present study, 90 percent of the 446 control women with known age of menarche had age at menarche at twelve years or older. The second category included women whose first exposure occurred between the ages of 12 and 20, which is the period of breast tissue development. The third category included women whose first exposure occurred at age 21 or older, after breast tissue development but not necessarily before first pregnancy. In the present study, 81 percent of the 551 control women with at least one

term pregnancy had their first term pregnancy at age 21 years or older. We also categorized passive-only smokers by the total duration of their passive smoking history.

Finally, to measure the effect of passive smoking among ever-active smokers, we divided ever-active smokers into the categories of age at first exposure described above for passive-only smokers.

We categorized cases and controls into two groups of alcohol exposure: any history of drinking alcohol (ever-drinkers) or no history of drinking alcohol (never-drinkers — the reference condition throughout). We further categorized ever-drinkers by their usual number of drinks per day during the time that they drank. We also categorized ever-drinkers by the duration of time between quitting drinking and their index year.

Only women who reported that they were perimenopausal or postmenopausal were asked whether they used estrogen replacement therapy. Estrogen replacement therapy was defined as any "female hormone medication such as Premarin or other estrogens for hot flashes or other menopausal symptoms." We categorized the postmenopausal women into two groups of estrogen replacement users: any history of estrogen replacement therapy (ever ERT) or no history of estrogen replacement therapy (never ERT — the reference condition throughout). We further categorized the ever-ERT group by the duration of time

between quitting estrogen replacement therapy and their index year and by the duration of estrogen replacement therapy. We also estimated the effect of ever-ERT versus never-ERT within strata of ever-drinkers and never-drinkers.

Unless otherwise specified in the tables, we adjusted estimates of effect for confounding by age (categories of <50, 50-<60, 60-<70, 70-<80, and ≥80 years at index year), parity (categories of 0, 1, 2, or >2 term pregnancies), family history of breast cancer (categories of sister or mother with breast cancer or not), body mass index (categories of <19, 19-25, or >25 kg/m^2 based on usual adult body weight), history of benign breast disease, history of breast cancer other than the index diagnosis, and history of medical radiation therapy. Control for these confounders influenced the estimate of effect by 10 percent or more in at least one analysis. We considered, but did not control for, age at first birth and menopausal status at index year because control for these potential confounders did not influence the estimates of effect by 10 percent or more after control for the confounders listed above.

We estimated the crude relative risks (RR) using logistic regression to adjust for age, which is the frequency matched variable. The crude relative risk in a matched case-control study must be adjusted for the matched factors to account for the selection bias introduced by the

matching. We estimated the adjusted relative risks and their corresponding 95 percent confidence intervals (CI) using multivariable logistic regression. To test the homogeneity of relative risks within subgroups, we calculated the log-likelihood under the model with variables indicating the subgroup variables and under the model with a single variable representing exposure. The p-value for the test of homogeneity is obtained from the chi-square distribution with two times the difference in log-likelihood as the test-statistic and degrees of freedom equal to the number of subgroups minus one.

When appropriate, we estimated the relative excess risk due to interaction and its 95 percent confidence interval by the methods of Hosmer and Lemeshow (7).

2.3. Results

Table 1 shows the distribution of selected demographic characteristics and confounding variables among the cases and controls. Approximately 90 percent of cases and controls were postmenopausal, so the following results may not apply to premenopausal women.

2.3.1. Active cigarette smoking

Ever-active smokers had an age-only adjusted relative risk of 1.3 (95 percent confidence interval 0.9–2.0) and a fully adjusted relative risk of 2.0 (95 percent confidence interval 1.1–3.7) compared with

nonsmokers (never-active, never-passive smokers). Breast cancer risk factors accounted for about half of the confounding (relative risk due to confounding equaled 0.81) and drinks per day of ethanol accounted for the remainder (relative risk due to confounding equaled 0.80). Table 2 shows the relative risks in ever-active smokers. The relative risk of breast cancer declined with increasing intensity and duration of ever-active smoking in a manner consistent with an antiestrogenic mechanism, although the overall trend was weak.

The estimated effect of smoking on risk of breast cancer did depend on whether women smoked before or after their first pregnancy (p-value for test of homogeneity of relative risks within subgroups bounded by first pregnancy versus ever-active smoking equals 0.006). Women who smoked only before their first pregnancy had a relative risk of 5.6 (95 percent confidence interval 1.5–21). Women who smoked only after their first pregnancy had relative risk of 2.1 (95 percent confidence interval 1.1–4.0). Women who began to smoke before their first pregnancy, and who continued to smoke after their first pregnancy, did not share the elevated relative risk (RR of 1.1; 95 percent confidence interval 0.6–2.0). The estimated effect of smoking did not depend on age at initiation of active-smoking (p-value for test of homogeneity equals 0.98), so this variable could not be considered a surrogate measure for initiation and termination of smoking prior to first pregnancy.

Women who quit smoking less than five years before their index year, or who were smoking at the time of their index year, had a relative risk of 2.3 (95 percent confidence interval 0.8–6.8). Women who quit smoking five to fifteen years before their index year, the period during which estrogen promotion of smoking-initiated breast cancer may be most potent, had a relative risk of 3.9 (95 percent confidence interval 1.4–10). Women who quit smoking more than fifteen years before their index year had a relative risk of 2.2 (95 percent confidence interval 1.0–4.9).

2.3.2.Passive-only cigarette smoking

Passive-only smokers had an age-only relative risk of 1.0 (95 percent confidence interval 0.7–1.6) and a fully adjusted relative risk of 2.0 (95 percent confidence interval 1.1–3.7) (see Table 3 for relative risks in passive-only smokers). Breast cancer risk factors accounted for somewhat more than half of the confounding (relative risk due to confounding equaled 0.67) and drinks per day of ethanol accounted for the remainder (relative risk due to confounding equaled 0.75). The relative risk of passive-only smokers approximately equals the risk of ever-active smokers, which emphasizes the importance of using never-active, never-passive smokers as the reference population. Had the never-active, never-passive smokers been combined with passive-only smokers to form the reference group, the odds ratio associated with ever-

active smoking would have equaled 1.2 (95 percent confidence interval 0.8–1.7).

The risk of breast cancer varied inversely with the duration of exposure to passive smoke (p-value for test of homogeneity equals 0.19). Passive smokers with 20 or fewer years of residence with an active smoker had an adjusted relative risk of 3.2 (95 percent confidence interval 1.5–7.1). Passive smokers with more than 20 years of residence with an active smoker had an adjusted relative risk of 2.1 (95 percent confidence interval 1.0–4.1).

Passive-only smokers' relative risk did not depend on whether their exposure preceded or followed their first pregnancy (p-value for test of homogeneity equals 0.91), as it did for ever-active smokers. The age of first exposure to passive smoke, however, did confer an elevated relative risk of breast cancer (p-value for test of homogeneity equals 0.36). Women first exposed to passive smoke prior to age twelve had a relative risk of 4.5 (95 percent confidence interval 1.2–16), women first exposed between ages 12 and 20 had a relative risk of 3.8 (95 percent confidence interval 1.1–13), and women first exposed at age 21 or older had an adjusted relative risk of 2.4 (95 percent confidence interval 0.9–6.1). We measured the same relationship among women who were ever-active smokers and who lived with another active smoker (p-value for test of

homogeneity equals 0.44). In this group, women first exposed to passive smoke prior to age twelve had a relative risk of 7.5 (95 percent confidence interval 1.6–36), women first exposed to passive smoke between ages 12 and 20 had an adjusted relative risk of 3.9 (95 percent confidence interval 0.8–20), and women first exposed to passive smoke at age 21 or older had an adjusted relative risk of 4.7 (95 percent confidence interval 1.6–14).

Overall, then, passive exposure to cigarette smoke appears to affect the first stage of breast carcinogenesis. First exposure at an age prior to breast tissue development confers the highest risk. First exposure during adolescence or as a young adult confers an intermediate risk and first exposure as an adult confers the lowest risk. Active cigarette smoking, which does not usually begin prior to breast tissue development, does not show the same dependence on age of initial exposure.

Women whose entire exposure to active cigarette smoking preceded their first pregnancy were at high risk, although the same dependence was not observed for exposure to passive smoke. Finally, women who quit smoking during a plausible induction period when estrogen might play an important role in breast cancer promotion also had a high risk.

2.3.3.Alcohol

Women with any history of alcohol ingestion had a 1.2-fold risk of breast cancer relative to non-drinkers (95 percent confidence interval 0.7–1.9) (see Table 4 for relative risks of drinking alcohol). The risk of breast cancer did not increase with the number of usual drinks per day or depend on years since cessation of alcohol drinking.

2.3.4.Estrogen Replacement Therapy

In the subgroup of perimenopausal and postmenopausal women, those who had ever used estrogen replacement therapy had a relative risk of 2.0 (95 percent confidence interval 1.2–3.3) compared with women who had never used estrogen replacement therapy (see Table 5 for relative risks of estrogen replacement therapy). The relative risk did not depend on the number of years between cessation of estrogen replacement therapy and index year. The relative risk associated with estrogen replacement therapy for 1 to 5 years (RR = 2.8; 95 percent confidence interval 1.6–4.9) exceeded the relative risk associated with estrogen replacement therapy for more than five years (RR = 0.9; 95 percent confidence interval 0.4–2.3).

The risk of estrogen replacement therapy also depended on whether women had ever consumed alcohol. Compared with women who never consumed alcohol and never used estrogen replacement therapy,

women who ever used estrogen replacement therapy and never consumed alcohol had a relative risk of 6.8 (95 percent confidence interval 1.8–26); women who never used estrogen replacement therapy and ever consumed alcohol had a relative risk of 1.6 (95 percent confidence interval 0.8–3.1); and women who ever used estrogen replacement therapy and ever consumed alcohol had a relative risk of 2.6 (95 percent confidence interval 1.2–5.7). The risk of estrogen replacement therapy appears greatest in postmenopausal women who never consumed alcohol and the risk of alcohol ingestion appears only in postmenopausal women who ever used estrogen replacement therapy. The relative excess risk due to interaction among women who ever used estrogen replacement therapy and ever consumed alcohol was –4.8 (95 percent confidence interval –14, 4.1).

2.4. Discussion

2.4.1. Tobacco Smoke

Until recently exposure to tobacco smoke has been thought not to cause breast cancer (8). Most studies of the effect on breast cancer indicate either a weakly positive or a null effect (8–13). Two studies measured a protective effect (14,15). Variability in the distribution of N-Acetyltransferase 2 and other polymorphisms within populations may account for the inconsistent pattern of effects observed across studies (16,17). A direct association between passive tobacco smoking and the

occurrence of breast cancer has been more consistently observed (18–20).

Unique perspectives on measuring the effect of tobacco smoke on the occurrence of breast cancer (18) and studies of genetically susceptible populations exposed to tobacco smoke (16,21) argue for further investigation. Tobacco smoke may have no effect on the occurrence of breast cancer. It may be, though, that the exposure metrics used to measure the association between tobacco smoking and other cancers are not adequate to measure the association with breast cancer. The timing of exposure to tobacco smoke relative to milestones of breast tissue development may be important in defining exposure. Early exposure, especially before a woman's first term pregnancy, may cause breast cancer through genotoxic mechanisms (20), whereas later exposure may prevent breast cancer through the anti-estrogenic effects of tobacco smoke (22,23). On balance, lifelong exposure may yield a null effect. In addition, the definition of index and reference conditions should take account of exposure to both active and passive smoking (18).

The only previous study (20) that separated the effects of active and passive smoking and accounted for breast tissue susceptibility measured an excess risk of breast cancer among both ever-active smokers and passive-only smokers. The definitions of index conditions

employed in the earlier study preclude a direct comparison with the results described in the present study.

The measurements in the present study of risk associated with active smoking and passive exposure to cigarette smoke comport with the expectations derived from the biologic model for breast carcinogenesis and the carcinogenic and anti-estrogenic effects of cigarette smoke. Passive exposure to cigarette smoke appears to affect the first stage of breast carcinogenesis. First exposure at an age prior to breast tissue development confers the highest risk. First exposure during adolescence or as a young adult confers an intermediate risk and first exposure as an adult confers the lowest risk. This pattern of declining risk with age of first exposure to passive smoke likely reflects the declining susceptibility of breast tissue to chemical mutagens, as depicted in Figure 1. Age of first exposure to active cigarette smoke does not reflect the same pattern, possibly because few women were active smokers at ages when breast tissue is most susceptible.

These risks then decline with the duration of exposure to passive cigarette smoke and with the intensity and duration of exposure to active cigarette smoking. The inverse dose-response relation between the relative risk of breast cancer and duration of exposure to passive or active cigarette smoke or intensity of exposure to active cigarette smoke

may reflect the antiestrogenic potency of cigarette smoke. Women whose entire exposure to active cigarette smoking preceded their first pregnancy were also at high risk. The breast tissue of these women would still be susceptible and would not sustain the anti-estrogenic effect of later exposure to cigarette smoke. Women who quit smoking during a plausible induction period — when estrogen might play an important role in breast cancer promotion — also had a higher risk.

2.4.2.Alcohol ingestion

Numerous studies have measured a direct effect of alcohol ingestion on the occurrence of breast cancer (24), and a positive dose-response has been observed between the rate of alcohol ingestion — usually measured in g/day — and the incidence of breast cancer in both case-control and follow-up studies (25, 26, 27). Some studies have found a stronger association between alcohol ingestion and the occurrence of breast cancer when drinking habits before age 30 were used to define exposure (28, 29), when only breast cancer arising at an early age or pre-menopausally were considered (30, 31), or when only women simultaneously taking non-contraceptive estrogen were considered (32, 33). For each of these findings, other studies reported an inconsistent result (24). Swanson *et al.* (34) for example, measured an effect that depended only on recent alcohol ingestion and that demonstrated a threshold in the dose-response relationship. Body

weight has been suggested as a modifier of the relation — with leaner women at higher risk for alcohol-associated breast cancer than obese women (35, 36) — although the modification of alcohol risk by weight has not been a consistent finding (37).

Several mechanisms by which ingestion of alcohol might cause breast cancer have been postulated (24,37). Perhaps the most plausible of these is that alcohol ingestion modifies the metabolism and clearance of estrogen compounds, thereby increasing the exposure of breast tissue to this hormonal promoter of breast tissue growth. After controlling for age, height, smoking status, and body mass index, alcohol consumption was positively and statistically significantly associated with estrone sulfate concentrations in post menopausal women (38). Post-menopausal women who consumed 30 or more grams of alcohol per day (approximately two or more drinks) had a 33 percent higher estrone sulfate level compared with women who did not drink or consumed less than one drink per month. The effect of alcohol consumption on estrone sulfate concentration is important because intracellular formation of estradiol from estrone sulfate may play an important role in the estrogenic milieu in subjects with low peripheral concentrations of estradiol, such as post-menopausal women (39). Estrone sulfate itself has no estrogenic effect (40). The effect of alcohol on estrogen sulfate may be important in premenopausal women as well, since estrone sulfate

is the major plasma estrogen compartment in equilibrium with plasma estrone and estradiol (41). Indeed, alcohol ingestion affects estrogen concentrations in premenopausal women. When administered with a controlled diet, 30 grams per day of alcohol for three of six menstrual cycles increased the total estrogen levels and amount of bioavailable estrogen (42). These effects may have been mediated by the effect on estrone sulfate.

The only effect of alcohol ingestion that we observed occurred in perimenopausal and postmenopausal women who had ever-used estrogen replacement therapy. Other investigations have also suggested that the effect of alcohol is limited to women who have had estrogen replacement therapy (32,33). The estrogen replacement therapy results must be considered carefully, however, because the effect estimated for ever-use of estrogen replacement therapy (RR = 2.0; 95 percent confidence interval 1.2–3.3) exceeds the estimates from most other studies (43). The retrospective study design and reliance on self-reported ERT status are susceptible to disease dependent recall, which might account for at least part of the apparent effect.

In the total study population, the relative risk of breast cancer did not depend on the amount of alcohol consumption or on the latency between alcohol ingestion and index year.

2.4.3.General

We considered whether the effects might be attributable to alternative explanations. We ascertained exposure by retrospective survey, so the study design is susceptible to recall bias. The substantial estimates of effect were within strata defined by time periods that we calculated from a series of responses. For example, we did not ask women whether their entire history of cigarette smoking preceded, followed, or overlapped their first pregnancy. Rather, we calculated from responses the date of first term pregnancy, the date of smoking initiation, and the date of smoking termination. We do not expect these derived exposures to be susceptible to recall bias. Furthermore, neither active nor passive exposure to cigarette smoke has been closely related to risk of breast cancer, so recall of smoking exposure should not depend on disease status. The widely held perception that smoking causes cancer may, however, contribute some disease-dependent recall of exposure to tobacco smoke.

We considered whether misclassification, in several forms, might account for the observed measurements. We did not ascertain whether respondents were exposed to passive smoke in their workplaces. The reference population of never-active, never-passive smokers may include respondents with substantial exposure to passive smoke in the workplace, primarily as adults. Workplace exposure to passive smoke in

the reference group could be anti-estrogenic, reducing their risk of breast cancer and biasing the estimates of effect away from the null. To reach this conclusion, one would have to assume that residential exposure to passive smoke is inversely related to the frequency of workplace exposure to passive smoke and is antiestrogenic. If workplace exposure to passive smoke is similarly distributed among those with history of passive smoking and those without, then no differential bias would exist.

A second form of misclassification might arise from the ever-active smokers' exposure to their own passive smoke. Should we attribute the excess risk among ever-active smokers to their exposure to self-generated passive smoke? Wells (19) argued that exposure to cigarette tar in vapor phase may be the primary constituent that affects breast cancer risk. Cigarette tar in passive smoke is primarily in vapor phase, whereas tar in actively inhaled cigarette smoke primarily adheres to particulate matter (44). If vapor phase tar is the primary breast cancer hazard from cigarette smoke, then the effect on active cigarette smokers may derive mostly from exposure to their own passive smoke. Our measurements provide some evidence that the effects of active and passive smoking are distinct, in that active smoking only before first pregnancy conferred a markedly increased risk compared with active smoking only after first pregnancy. We did not observe the same difference in relative risk for pregnancy-demarcated passive smoking.

Model misspecification provides a third opportunity for misclassification. In many analyses, we included a term for duration of passive smoking, duration of active smoking, and/or intensity of active smoking. These terms all indicated a downward trend in relative risk with increasing exposure. We interpret this downward trend as a measure of the anti-estrogenic effect of cigarette smoke. Under these models, women with a smoking duration of zero years and an intensity of zero cigarettes per day would have the highest risk. Logically, that cannot be true. Rather, some minimum exposure must be necessary to confer the initial risk, which is then mitigated by the anti-estrogenic effects. These data are not sufficient to measure the necessary minimum exposure. The effects of age at first exposure to passive smoke persisted, though they were reduced, in models with no measure of duration or intensity of exposure.

Further model misspecification may arise from including a continuous measure of duration and/or intensity in the logistic model. The continuous terms force exponential dose-response relations (45), which may not be appropriate. The relative risks estimated from the coefficients were very near the null, however, so the deviation from a linear dose-response would not be substantial.

Many respondents, and particularly subjects with proxy respondents, could not be characterized with respect to some covariates. For example, we did not know age at menarche for 407 of 1028 women and age at menopause for 254 of 770 post-menopausal women. Age at menopause depends on smoking status (23), so we would not have included that variable in any event. Adjusting for pre- or post-menopausal status at index year had no effect on the relative risk measures. We adjusted for age at menarche in the subset of 621 subjects for whom this information was reported. The estimates of effect migrated away from the null. However, the estimates of effect increased in the subset of subjects relative to the estimates measured in the complete data set whether or not the measure of age at menarche was included, which suggests that the changes in estimated effects are more properly attributed to selection of the subset of subjects than to control of confounding by age at menarche.

One might suggest that the effects measured in this study are anomalous. Consider, though, that the effects measured for alcohol ingestion were essentially null and that alcohol ingestion correlates with exposure to cigarette smoke in this population (data not shown). Were the effects of smoking anomalous, one would expect to observe anomalous measures of the effect of alcohol ingestion as well.

The precision of some of the measures of effect is low. The widest 95 percent confidence interval that does not include the null ranges from 1.6 to 36. It surrounds the estimate of a relative risk of 7.5 among ever-active smokers first exposed to passive smoke before age 12. Were the estimate of effect null, the interval would range from 0.2 to 4.8, still certainly a wide interval. The imprecision, in combination with a coherent picture of effects based on underlying biology, the known carcinogenic effect of cigarette smoking, and its known anti-estrogenic potency, emphasizes the importance of examining these exposures in larger studies.

Should the measurements described herein prove to be valid and accurate, then certain implications would merit consideration. Tarone *et al.* measured a downward trend in U.S. mortality rates for all birth cohorts beginning in about 1940 (46). They explained that the downward trend reveals a change in the prevalence of a causal or protective risk factor other than those currently identified. Our data suggest one possible explanation. The unidentified factor may be the anti-estrogenic potency of tobacco smoke acting in women with lifelong history of active smoking or with lifelong history of exposure to passive smoke. However, as ex-smokers become more prevalent and active smokers less prevalent (47), women will have exposure to only the initiating stages of active and passive cigarette smoke, and the birth cohort trend may reverse

direction. This concern becomes all the more urgent given the recent increase in the prevalence of smoking among female teenagers (48).

Studies of the effect of weight gain on the risk of postmenopausal breast cancer have usually measured a relative risk of about 1.5 associated with gaining 15 kilograms or more as an adult (49–64). The association has seldom been observed for diagnosis of premenopausal breast cancer (54–64). Smoking cessation is strongly associated with adult weight gain (65–66), including weight gain during menopause (67). Nonetheless, few studies controlled for potential confounding by smoking cessation of the association between adult weight gain and risk of breast cancer. One review explicitly excluded smoking from the list of etiologic factors with particular relevance to elucidating observed associations between body size and breast cancer (68). We crudely estimated change in body weight as the difference between usual adult body weight and body weight at interview for living respondents. As expected (66), among controls the recent quitters and current smokers had the highest average weight gain (see Table 6). Women who quit five or more years before their index year had a lower average weight gain, and nonsmokers had a small average weight loss. Table 6 shows that our measures of the effect of cessation before the index year persisted after adjustment for the crude measure of change in body weight. It would be illuminating to

know whether the effects of weight gain measured by others persist after controlling for smoking cessation and its induction period.

The measurements of relative risk in this study, while imprecise, comport with an underlying biologic model of breast carcinogenesis. Cigarette smoking causes cancer in organs that are not in direct contact with smoke (69), but it is also anti-estrogenic (22,23). Taken together, these observations suggest the need for further examination of the relation between exposure to cigarette smoke and the occurrence of breast cancer. Future studies might focus on the segregation of the effects of passive smoking and active smoking, the minimum duration and intensity of active and passive smoking necessary to initiate breast carcinogenesis, the interaction between time of exposure and milestones of breast tissue development, or the precise interval of susceptibility to smoking cessation.

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Table 1: Characteristics of Cases and Controls

	Cases N (%)	Controls n (%)
Age (years)		
<50	31 (12%)	53 (7%)
50-59	38 (14%)	82 (11%)
60-69	82 (31%)	252 (33%)
70-79	71 (27%)	213 (28%)
≥80	43 (16%)	163 (21%)
Proxy or Self Interview		
Self (living subjects)	177 (67%)	417 (55%)
Proxy (dead subjects)	88 (33%)	346 (45%)
Age at Menarche (years)		
≤12	66 (25%)	133 (17%)
13 or 14	76 (29%)	213 (28%)
≥15	33 (12%)	100 (13%)
missing	90 (34%)	317 (42%)
Menopausal Status		
premenopausal	31 (12%)	63 (8%)
postmenopausal	234 (88%)	700 (92%)

Table 1: Characteristics of Cases and Controls

	Cases N (%)	Controls n (%)
Body Mass Index (kg/m2)		
≤19	18 (7%)	49 (6%)
19-25	185 (70%)	492 (64%)
≥25	52 (20%)	187 (25%)
missing	10 (3%)	35 (5%)
Parity (term pregnancies)		
0	76 (29%)	175 (23%)
1	31 (12%)	106 (14%)
2	57 (21%)	165 (22%)
≥3	95 (36%)	305 (40%)
missing	6 (2%)	12 (1%)
Age at first birth		
no birth	76 (29%)	175 (23%)
<30 years	139 (52%)	452 (59%)
≥30 years	34 (13%)	99 (13%)
missing	16 (6%)	37 (5%)

Table 1: Characteristics of Cases and Controls

	Cases N (%)	Controls n (%)
History of Benign Breast Disease		
Yes	26 (10%)	107 (14%)
No	213 (80%)	594 (78%)
missing	26 (10%)	62 (8%)
Mother or Sister with Breast Cancer		
Yes	46 (18%)	60 (8%)
No	197 (74%)	619 (81%)
missing	22 (8%)	84 (11%)

Table 2: Measured relative risks of breast cancer associated with exposures to active cigarette smoking

Exposure Condition	Case/Control Ratio	RR[c]	95% CI	RR*	95% CI
Never-active, Never Passive	40/139	1.		1.	
Ever-active†	137/338	1.3	0.9–2.0	2.0	1.1–3.7
Cigarettes per day‡ (p-value for test of homogeneity = 0.38)					
≤ 20 cigarettes per day	84/160	1.6	1.0–2.4	2.1	1.0–4.6
> 20 cigarettes per day	16/42	0.8	0.5–1.5	1.6	0.6–4.3
Duration of smoking§ (p-value for test of homogeneity = 0.14)					
0–19 years	34/54	2.0	1.1–3.6	2.6	1.2–5.5
20–39 years	46/117	1.2	0.7–2.0	1.5	0.7–3.2
40 or more years	54/147	1.4	0.8–2.3	2.4	1.1–5.5

Table 2: Measured relative risks of breast cancer associated with exposures to active cigarette smoking

Exposure Condition	Case/Control Ratio	RR[c]	95% CI	RR*	95% CI
Term pregnancy demarcated smoking (p-value for test of homogeneity = 0.006)					
only before first pregnancy	7/6	3.9	1.2–13	5.6	1.5–21
only after first pregnancy	63/110	2.0	1.2–3.2	2.1	1.1–4.0
both before and after first pregnancy	57/175	1.0	0.6–1.6	1.1	0.6–2.0
Cessation before index year‡§ (p-value for test of homogeneity = 0.21)					
< 5 years or current	22/75	1.3	0.8–2.1	2.3	0.8–6.8
5–15 years	33/54	2.2	1.2–3.8	3.9	1.4–10
> 15 years	82/209	0.9	0.5–1.7	2.2	1.0–4.9

Table 2: Measured relative risks of breast cancer associated with exposures to active cigarette smoking

Exposure Condition	Case/Control Ratio	RR[c]	95% CI	RR*	95% CI
Age started smoking‡§ (p-value for test of homogeneity = 0.98)					
< 17 years	28/75	1.2	0.7–2.1	2.4	0.8–7.2
17–20 years	60/138	1.5	0.9–2.4	2.3	1.0–5.5
21 years or older	47/106	1.6	0.9–2.6	2.4	1.0–5.7

[c] Adjusted only for age, the frequency matched variable.

* Adjusted for age, history of medical radiation therapy, body mass index, history of mother or sister with breast cancer, history of breast cancer, parity, and history of benign breast disease.

† Also adjusted for usual number of alcoholic drinks per day.

‡ Also adjusted for duration of active smoking (RR of 10 additional years of active smoking = 0.93; 95 percent confidence interval 0.76–1.14).

§ Also adjusted for number of cigarettes per day (RR of 10 additional cigarettes per day = 0.85; 95 percent confidence interval 0.66–1.09).

Table 3: Measured relative risks of breast cancer associated with exposures to passive cigarette smoke in the residence

Exposure Condition	Case/Control Ratio	RR[c]	95% CI	RR*	95% CI
Never-active, Never Passive	40/139	1.		1.	
Passive-only	80/267	1.0	0.7–1.6	2.0	1.1–3.7
Duration of passive smoking (p-value for test of homogeneity = 0.19)					
≤ 20 years	28/56	1.9	1.0–3.4	3.2	1.5–7.1
> 20 years	43/148	1.2	0.7–2.0	2.1	1.0–4.1

Table 3: Measured relative risks of breast cancer associated with exposures to passive cigarette smoke in the residence

Exposure Condition	Case/Control Ratio	RR[c]	95% CI	RR*	95% CI
Term pregnancy demarcated passive smoking (p-value for test of homogeneity = 0.91)					
all before first pregnancy	6/15	1.5	0.5–4.2	2.8	0.8–9.9
all after first pregnancy	35/102	1.4	0.8–2.4	2.4	1.2–5.1
both before and after first pregnancy	21/63	1.4	0.8–2.4	2.2	1.1–4.7
Age of first exposure, passive-only smokers† (p-value for test of homogeneity = 0.36)					
< 12 years	14/25	2.0	1.0–4.4	4.5	1.2–16
12–20 years	11/30	1.3	0.6–3.0	3.8	1.1–13
≥ 21 years	34/118	1.2	0.7–2.0	2.4	0.9–6.1

Table 3: Measured relative risks of breast cancer associated with exposures to passive cigarette smoke in the residence

Exposure Condition	Case/Control Ratio	RR[c]	95% CI	RR*	95% CI
Age of first exposure to passive smoke, ever-active smokers†‡					
(p-value for test of homogeneity = 0.44)					
< 12 years	26/33	3.1	1.6–6.1	7.5	1.6–36
12–20 years	10/31	1.3	0.6–2.9	3.9	0.8–20
≥ 21 years	46/105	1.8	1.0–3.0	4.7	1.6–14

[c] Adjusted only for age, the frequency matched variable.

* All measures of effect were adjusted for age, history of medical radiation therapy, body mass index, history of mother or sister with breast cancer, history of breast cancer, parity, and history of benign breast disease.

† Also adjusted for duration of passive smoking (RR of 10 additional years of passive smoking = 0.96; 95 percent confidence interval 0.76–1.22).

‡ Also adjusted for duration of active smoking (RR of 10 additional years of active smoking = 0.93; 95 percent confidence interval 0.76–1.14) and number of cigarettes per day (RR of 10 additional cigarettes per day = 0.85; 95 percent confidence interval 0.66–1.09).

Table 4: Measured relative risks of breast cancer associated with drinking alcohol

Exposure Condition	Case/Control Ratio	RR[c]	95% CI	RR*	95% CI
Never drank alcohol	41/153	1.		1.	
Ever drank alcohol	222/605	1.3	0.9–1.9	1.2	0.7–1.8
Usual drinks per day (p-value for test of homogeneity = 0.58)					
0 to < 1	128/375	1.2	0.8–1.7	1.1	0.7–1.8
1 to < 2	45/98	1.6	1.0–2.6	1.3	0.7–2.5
2 to < 3	12/31	1.3	0.6–2.8	1.0	0.4–2.5
3 or more	9/30	1.0	0.4–2.3	0.7	0.2–2.0
Cessation before index year (p-value for test of homogeneity = 0.47)					
< 5 years or current	121/291	1.4	0.9–2.2	1.0	0.6–1.7
5–15 years	9/14	2.2	0.9–5.6	1.8	0.6–5.5
> 15 years	7/16	1.5	0.6–4.0	1.5	0.5–4.2

[c] Adjusted only for age, the frequency matched variable.

* All measures of effect were adjusted for age, history of medical radiation therapy, body mass index, history of mother or sister with breast cancer, history of breast cancer, parity, history of benign breast disease, ever-active smoking, and passive-only smoking.

Table 5: Measured relative risks of breast cancer associated with estrogen replacement therapy (ERT)

Exposure Condition	Case/Control Ratio	RR[c]	95% CI	RR*	95% CI
Never ERT	120/343	1.		1.	
Ever ERT	42/69	1.5	0.9–2.4	2.0	1.2–3.3
ERT cessation before index year (p-value for test of homogeneity = 0.94)					
< 5 years or current	14/21	1.2	0.6–2.7	1.9	0.9–4.4
5–15 years	9/17	1.5	0.6–3.6	1.9	0.7–4.7
> 15 years	19/30	1.7	0.9–3.2	2.2	1.1–4.5
ERT duration (p-value for test of homogeneity = 0.03)					
≤ 5 years	33/41	2.3	1.4–3.9	2.8	1.6–4.9
> 5 years	9/27	0.9	0.4–2.0	0.9	0.4–2.3

Table 5: Measured relative risks of breast cancer associated with estrogen replacement therapy (ERT)

Exposure Condition	Case/Control Ratio	RR[c]	95% CI	RR*	95% CI
ERT within strata of alcohol (Relative excess risk due to interaction among ever ERT, ever alcohol equals –4.8 (95 percent confidence interval –14, 4.1))					
never ERT, never alcohol	18/81	1.		1.	
ever ERT, never alcohol	6/7	3.4	0.8–14	6.8	1.8–26
never ERT, ever alcohol	102/261	1.5	0.8–3.0	1.6	0.8–3.1
ever ERT, ever alcohol	36/62	2.0	0.9–4.3	2.6	1.2–5.7

[c] Adjusted only for age, the frequency matched variable.

* Adjusted for age, history of medical radiation therapy, body mass index, history of mother or sister with breast cancer, history of breast cancer, parity, history of benign breast disease, ever-active smoking, and passive-only smoking.

Table 6: Measured relative risks of breast cancer associated with smoking cessation and change in body weight among living respondents

Exposure Condition	Change in body weight among controls mean ± SE (kilograms)	Case / Control Ratio	RR*	95% CI
Never-active, Never Passive	-1.1 ± 1.1	8/41	1.	
Cessation before index year, without adjustment for change in body weight†				
< 5 years or current	4.5 ± 1.0	17/42	3.6	0.9–14
5–15 years	3.9 ± 1.0	22/32	5.1	1.5–18
> 15 years	2.6 ± 0.7	60/125	2.6	0.9–7.8

Table 6: Measured relative risks of breast cancer associated with smoking cessation and change in body weight among living respondents

Exposure Condition	Change in body weight among controls mean ± SE (kilograms)	Case / Control Ratio	RR*	95% CI
Cessation before index year, with adjustment for change in body weight†				
< 5 years or current		17/42	3.7	0.9–15
5–15 years		22/32	5.3	1.5–19
> 15 years		61/125	2.6	0.9–7.8
Relative risk associated with a 10 kg increase in body weight				
With adjustment for smoking cessation			0.87	0.6–1.3
Without adjustment for smoking cessation			1.04	0.8–1.4

* All measures of effect were adjusted for age, history of medical radiation therapy, body mass index, history of mother or sister with breast cancer, history of breast cancer, parity, and history of benign breast disease.

† Also adjusted for duration of active smoking and number of cigarettes per day.

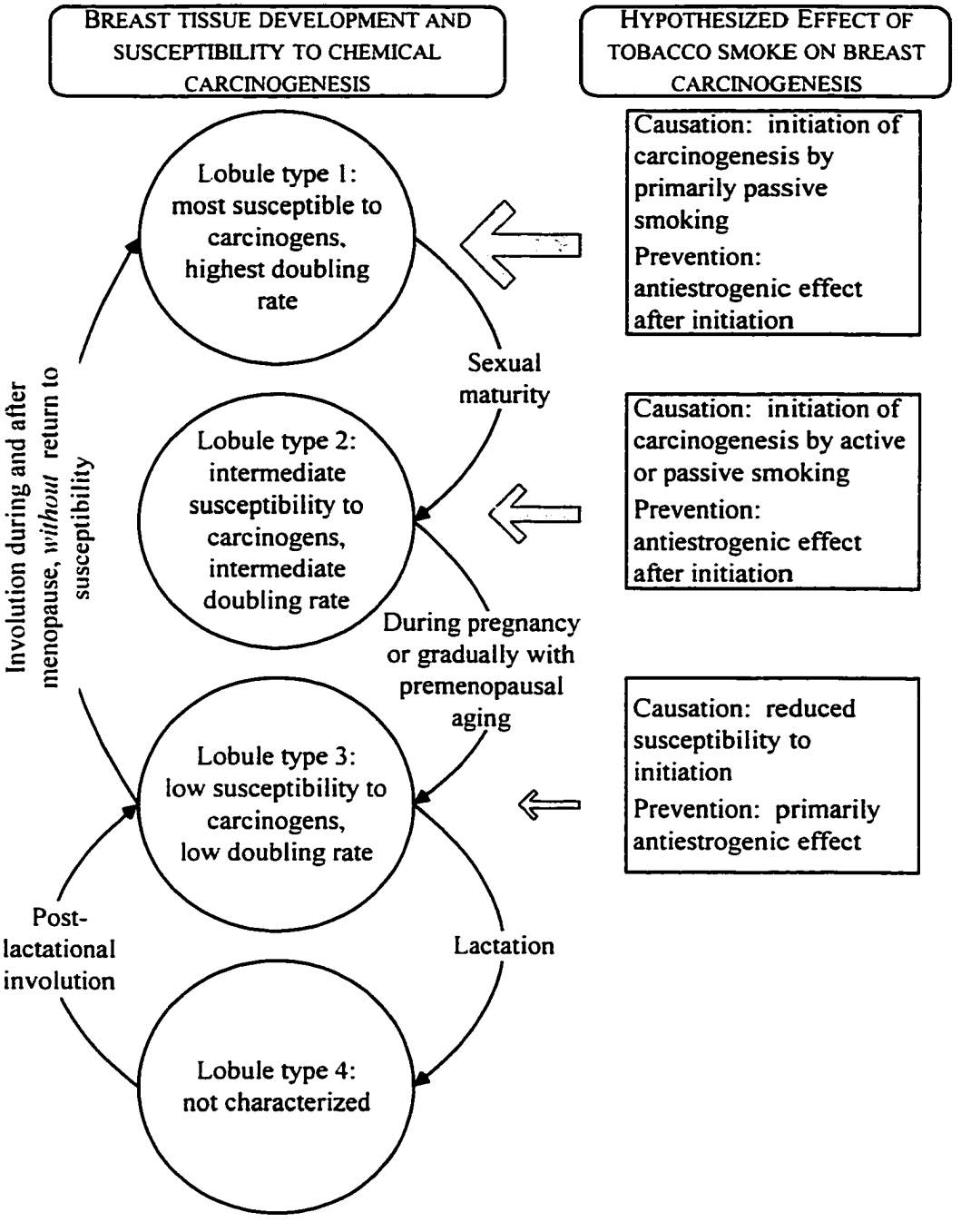

Figure 1: Diagrammatic representation of the susceptibility of breast tissue to tobacco smoke during the reproductive cycle.

3. Upper-Body Dysfunction After Breast Cancer Treatment

3.1. Introduction

Breast cancer is an important cause of morbidity and mortality among women. The American Cancer Society estimated that 178,700 women were diagnosed with breast cancer in 1998 and that 43,500 women died from the disease (1). The large number of breast cancer cases diagnosed each year, in combination with the relatively favorable survival rates for treated patients, yields the largest group of cancer survivors in the U.S. population. Nearly two million living U.S. women have been diagnosed with breast cancer (2). This sizeable pool of prevalent survivors suggests that the quality of life after breast cancer therapy is an important issue (3). Quality of life strongly depends on physical function, both of which decline on average following breast cancer therapy (4).

While it is reasonable to expect that patients' upper-body function will decline following breast cancer therapy, studies have only recently characterized the nature, determinants, and duration of impairment (3–6). An accurate understanding of the patient characteristics and therapy options that predispose towards upper-body dysfunction and discomfort is essential. Such an understanding would allow physicians to include consideration of the potential for these sequelae in their treatment

recommendations and to prescribe exercise interventions that can be initiated before surgery.

Gerber and colleagues found that women who received modified radical mastectomy recovered their pre-operative range of motion more slowly than women who received local excision and radiation therapy (5). The difference in recovery time for functional range of motion was not as large as the difference in recovery time for pre-operative range of motion. Sneeuw and colleagues examined functional outcomes four years after treatment among women who received breast conserving surgery, axillary dissection, and radiation therapy (6). Nearly half of the subjects reported a little (34 percent) or moderate (13 percent) limitation of movement in the arm and shoulder on the treatment side.

The present study assessed the effect of patient characteristics and therapy on self-reported upper-body function and discomfort approximately five months and approximately twenty-one months after primary breast cancer therapy. The study provides some guidance as to the identification of patients likely to suffer upper-body sequelae and the treatments that may induce these adverse effects.

3.2. METHODS

3.2.1. Sampling

We studied women ≥ 55 years of age, newly diagnosed with histologically confirmed stage I or stage II invasive breast carcinoma, and treated at one of five hospitals in Boston, Massachusetts. We sent an introductory letter and a consent form to 388 potential study participants whose surgeons permitted contact. The letters were sent two to three months after the patient's definitive surgical treatment. An interviewer followed-up with a telephone call to explain the study further, to answer questions, and to obtain informed consent. The average time from definitive surgery to baseline interview was 136 days (range 66 days to 458 days). We completed 90 percent of the baseline interviews by 185 days after definitive surgery. We attempted to contact all respondents for a follow-up interview. The average time from definitive surgery to the follow-up interview was 625 days, with a minimum of 473 days and a maximum of 1092 days. We completed 90 percent of the follow-up interviews by 694 days after definitive surgery.

3.2.2. Data collection

We reviewed patients' surgical records and conducted two 35-minute computer-assisted telephone interviews with consenting eligible patients. Data collected from medical records included: tumor size,

axillary node status, breast surgery or surgeries performed (mastectomy or breast conserving surgery, with or without axillary dissection), side of surgery, and whether or not the patient received a course of post-operative radiation therapy.

Both the baseline and followup telephone interviews included three questions about tasks that required upper-body function: 1) pushing or pulling large objects, such as a living room chair, 2) lifting objects weighing more than 10 pounds, such as a heavy bag of groceries, and 3) reaching or extending arms above shoulder level. We asked subjects to characterize the difficulty of each task as very difficult, somewhat difficult, or not difficult — or to say they did not do the task — during the four weeks preceding the interviews. We also asked subjects to characterize the difficulty of the tasks prior to their breast cancer treatment. We assumed that subjects who said they did not do a task had the most difficulty with that task, although we recognize that subjects might not do a task for reasons other than difficulty performing it. When we assumed that subjects who said they did not do a task had the least difficulty with that task, the results presented herein did not change substantially.

We selected these tasks to measure upper-body function from the items used by Satariano and colleagues (3), fielded previously in the Framingham Disability Study (7) and originally developed by Nagi (8).

We also asked subjects at the follow-up interview whether they were bothered by numbness and/or pain in their armpit as a result of surgery and whether they were bothered by swelling or problems with their arm as a result of surgery.

To characterize potential covariates, we asked questions about cardiopulmonary comorbidities that were part of the Total Illness Burden Index (9) and about patients' age, race, marital status, education, number of people in the household, height, and weight.

3.2.3.Major analytic variables

Our primary dependent variable was a decline in upper-body function. Patients were classified as having an early decline in upper-body function for any task if they responded that any of the three tasks was more difficult at baseline interview than it was before breast cancer treatment. Patients were classified as having a late decline in upper-body function for any task if (1) they responded that any of the three tasks was more difficult at baseline interview than it was before breast cancer treatment and they did not recover to at least the prediagnosis level of difficulty by the follow-up interview, or (2) they responded that

any of the three tasks was more difficult at follow-up interview than it was at baseline interview.

Secondary dependent variables included two characterizations of upper-body discomfort. The first was a self-report at the follow-up interview of numbness or pain in the armpit because of surgery. The second was a self-report at the follow-up interview of swelling or problems with an arm because of surgery.

For our independent variables we considered: age (categories of 55-64, 65-74, 75+ years); education (< high school or ≥ high school); number of residents in the household (lives alone or lives with somebody else); and marital status (married or other). We also considered body mass index (categorized as ≤23 kg/m^2, >23 to 27.5 kg/m^2, or >27.5 kg/); cardiopulmonary comorbidity (categorized as a score of 0, 1 to 3, or 4 or more — based on patients' reports of diagnoses of chronic obstructive pulmonary disease, congestive heart failure, and ischemic heart disease and related symptoms — with a higher score reflecting greater comorbidity); tumor stage (stage I or stage II); side of surgery (categorized as right or both sides versus left side); and breast cancer treatments received.

For the breast cancer treatments variables, we considered each of the two primary treatments (breast conserving surgery followed by

radiation therapy versus modified radical mastectomy) and whether or not subjects had an axillary dissection.

3.2.4.Analytic Strategy

We performed a series of bivariate analyses, examining the relationships between independent variables and the dependent variables. Next, we developed a multiple logistic regression model for each outcome: early decline in upper-body function, late decline in upper-body function, and each measure of upper-body discomfort. Because of the substantial range of times between definitive surgery and the interviews, we included days between definitive surgery and the interviews in the applicable multivariable regression models. We did not perform survival analyses because the time to decline was determined by the date of interview, so does not correspond to the true time to the event.

3.3. RESULTS

We interviewed three hundred and three women at the baseline interview following their definitive surgery. The 303 patients represent 78 percent of the 388 women whose surgeon permitted contact. Two hundred and fifty of these women then completed the follow-up interview. Of the 53 women lost to follow-up, 5 died, 16 refused to participate in the follow-up interview, 2 were unable to participate

because of poor health, and 30 could not be contacted. The women lost to follow-up were older, less likely to be married, and had lower body mass index, though these differences were not substantial. The risk of upper-body function decline did not depend on time to baseline or follow-up interview.

Of the women interviewed at baseline, 59 percent were ≥ 65 years of age. Most were white (93 percent) and had a high school education or greater (83 percent). Half were married; most of the remainder were widowed. The average body mass index was 26.0 ± 0.3 kg/m^2 and the average comorbidity score was 1.5 ± 0.1. Most patients had small tumors (77 percent ≤ 2 cm) and were node negative (80 percent). The majority (65 percent) had undergone breast-conserving surgery followed by radiation therapy; 23 percent had undergone modified radical mastectomy. Almost all (85 percent) had undergone axillary dissection.

At the baseline interview, 36 percent of subjects reported some decline in upper-body function and 7 percent reported a decline in all three of the upper-body function tasks. At the follow-up interview, 36 percent of subjects reported some decline in upper-body function and 4 percent reported a decline in all three of the upper-body function tasks. Two-thirds of the women who reported some decline in upper-body function at follow-up interview also reported a decline in upper-body

function decline at the baseline interview. Among the women who completed both interviews, 36% reported any early decline in upper-body function and among the women who completed only the baseline interview, 34% reported any early decline in upper-body function.

The only patient characteristic associated with any early decline in upper-body function was cardiopulmonary comorbidity (see Table 7 for measures of the effect of patient characteristics on upper-body function decline). Women with a cardiopulmonary comorbidity score of 1, 2, or 3 had an odds ratio for any early upper-body function decline of 1.4 (95 percent confidence interval 0.7–2.7), relative to women with a score of 0. Women with a cardiopulmonary comorbidity score of 4 or more had an odds ratio for any early upper-body function decline of 3.6 (95 percent confidence interval 1.6–7.8), relative to women with a score of 0. The association was attenuated for any late decline in upper-body function. Women with a cardiopulmonary comorbidity score of 1, 2, or 3 had an odds ratio for any late upper-body function decline of 1.0 (95 percent confidence interval 0.5–2.2), relative to women with a score of 0. Women with a cardiopulmonary comorbidity score of 4 or more had an odds ratio for any late upper-body function decline of 1.7 (95 percent confidence interval 0.7–3.9), relative to women with a score of 0.

The odds of any early upper-body function decline among women who had breast conserving surgery and radiation therapy, relative to women who had mastectomy, was 0.8 (95 percent confidence interval 0.4–1.5; see Table 7 for measures of the effect of treatment on upper-body function decline). The odds of any late upper-body function decline among women who had breast conserving surgery and radiation therapy, relative to women who had mastectomy, was 0.9 (95 percent confidence interval 0.4–2.0).

Axillary dissection was associated with any early decline in upper-body function, although the association did not hold for any late decline in upper-body function. The odds of any early upper-body function decline among women who underwent axillary dissection, relative to women who did not, was 3.7 (95 percent confidence interval 1.2–11). The odds of any late upper-body function decline among women who had axillary dissection, relative to women who did not, was 1.0 (95 percent confidence interval 0.3–2.9).

At the follow-up interview, 37 percent of women reported numbness or pain in the armpit and 17 percent reported swelling or other problems with an arm. Older women were less likely than younger women to report numbness or pain in the armpit and the oldest women were less likely than younger women to report swelling or other arm

problems (see Table 8 for measures of the effect of patient characteristics on upper-body discomfort). In addition, women who lived alone were more likely to have swelling or other arm problems than women who did not live alone (OR = 4.6; 95 percent confidence interval 1.3–16) and women with stage II disease were more likely to report swelling or other arm problems than women with stage I disease (OR = 2.2; 95 percent confidence interval 1.0–4.7).

Although the effect of axillary dissection on decline in upper-body function did not persist to the follow-up interview, axillary dissection did affect upper-body discomfort at the follow-up interview (see Table 8 for measures of the effect of patient characteristics on upper-body discomfort). Women who had axillary dissection were more likely to report numbness or pain in the armpit (OR = 13; 95 percent confidence interval 1.5–117) and swelling or other arm problems (OR = 4.3; 95 percent confidence interval 0.5–37) than women who did not have axillary dissection. While these associations are strong, and they agree with *a priori* expectation, they are imprecise.

3.4. Discussion

Among older women with early stage breast cancer, axillary node dissection and self-reported cardiopulmonary comorbidity are risk factors for decline in upper-body function during the early months

following primary breast cancer therapy. By approximately 21 months, upper-body function decline was only marginally related to cardiopulmonary comorbidity. Age, body mass index, marital status, living alone, education, and side of surgery were not related to decline in upper-body function either in the early months following definitive surgery or at the 21-month follow-up.

Axillary dissection remained an important cause of upper-body discomfort at the follow-up interview. Approximately 40 percent of women who had axillary dissection reported pain in their armpit at the follow-up interview, compared with 7 percent of those who did not have axillary dissection. Approximately 20 percent of women who had axillary dissection reported swelling or other arm problems at the follow-up interview, compared with 3 percent of women who did not have axillary dissection. Younger women were more likely than older women to report upper-body discomfort. Women who had Stage II disease were more likely to report swelling or other arm problems than women who had Stage I disease; and women who lived alone were more likely to report swelling or other arm problems than women who did not live alone. Marital status, education, side of surgery, and cardiopulmonary comorbidity were not related to upper-body discomfort at the follow-up interview.

Axillary node dissection appears to increase the risk of decline in upper-body function in the months after treatment, but not the risk of persistent decline or delayed onset of decline 21 months after definitive surgery. In addition, axillary dissection appears to increase the risk of swelling or other arm problems and numbness or pain in the armpit, even two years after diagnosis.

Our findings are consistent with previous investigations of upper-body function after treatment for early stage breast cancer. Liljegren and colleagues found that older patients and patients who underwent less extensive axillary dissection were at lower risk for arm symptoms at both 3–12 months and 13–36 months after treatment (10). Three other investigations also found that the prevalence of upper-body sequelae depended on the extent of axillary dissection (11, 12, 13). Ganz and colleagues found that measures of quality of life after treatment did not depend on receipt of breast conserving surgery versus modified radical mastectomy, except that patients who received the latter primary therapy were more likely to report problems with clothing and body image (14). Tasmuth and colleagues found that the occurrence of arm sequelae did not depend on whether the patient received breast conserving surgery or modified radical mastectomy and that reaching out, carrying heavy objects, working with the ipsilateral arm, and housework aggravated the arm symptoms (15). These aggravating factors may be among the

influences captured in our finding that women who live alone were more likely to report swelling or other arm problems.

Axillary node dissection is an important prognostic indicator for women with early stage breast cancer (16). Removal of level 1 and level 2 nodes is currently recommended for accurate staging and to reduce the risk of recurrence in the axilla, unless the risk of axillary metastasis is very low or when knowledge of node status will have no influence on therapy (17). Reliable indicators of node status to stage disease accurately when no axillary dissection is performed, however, have been difficult to identify (18).

Although there is a consensus regarding the current need for axillary dissection to facilitate staging and to avoid axillary metastases, the extent of dissection remains controversial (17). The axillary lymph nodes reside in three levels that are defined by their relationship with the pectoralis minor muscle (17). Level I nodes lie beside or below the lateral border of the muscle and receive most of the lymphatic drainage from the breast. Level II nodes lie beneath the muscle and receive lymph from the level I nodes and some lymphatic drainage directly from the breast. Level III nodes lie medial to the muscle in the infraclavicular fossa and receive lymph from the levels I and II nodes and directly from the superior part of the breast.

Axillary sampling of 3 to 5 nodes, which had shown some promise (19), has largely been abandoned in favor of dissection of only level I and level II nodes (17, 20, 21). Levels I and II dissection yields 10 or more nodes, which are usually sufficient to determine the breast cancer stage (17). The advent of lymphatic mapping and sentinel lymph node biopsy may further reduce the extent of recommended axillary dissection (22). In one recent series of T1–T2 N0 breast cancer patients, sentinel lymph node biopsy detected 44 of 45 patients with positive nodes by level I-III axillary dissection and all 59 patients with negative nodes by level I-III axillary dissection had a negative sentinel lymph node biopsy (23). In a second recent series of clinically node negative patients with invasive breast cancer, sentinel lymph node biopsy detected 101 of 114 patients with positive nodes by level I-II or I-III axillary dissection. All 291 patients with negative nodes by axillary dissection had a negative sentinel lymph node biopsy (24). Although these results suggest that sentinel node biopsy may supplant axillary dissection for breast cancer staging, the most current recommendation concludes that it would be premature to abandon axillary dissection in favor of sentinel node biopsy (25).

Our findings must be considered with the study's major limitations in mind. First, we did not directly measure upper-body function, either before or after treatment. We asked women to recall their upper-body

function prior to their treatment, and then compared their current self-reported function to the prediagnosis function as a measure of upper-body function decline. While this method may misclassify decline in upper-body function, we do not expect the misclassification to depend on cardiopulmonary comorbidity status. Non-differential misclassification of upper-body function would bias the estimated effect of cardiopulmonary comorbidity towards the null on average. Differential recall is more likely associated with axillary dissection; a surgical intervention that women may expect will cause a decline in upper-body function. We would not, however, expect this differential recall to dissipate by the follow-up interview, and axillary dissection was only associated with upper-body function decline at the baseline interview. We conclude that differential misclassification is unlikely to account for the entire association between cardiopulmonary comorbidity, or axillary dissection, and upper-body function decline.

Furthermore, some earlier investigators have argued that patient's self-report of arm function is likely to be more accurate than objective measures (26, 27, 28). These investigators contend that objective measures of function do not adequately measure the patient's perception of their function. Patients with poor objective measures may report no impact on their upper-body function and patients with poor self-reported function may score in the normal range of objective measures.

Second, we did not gather side of surgery information in relation to handedness. One earlier investigation showed that grip strength declined more if surgery was performed on the side of the dominant hand (15). As a crude approximation, we measured the effect of side of surgery on the upper-body outcomes. If one assumes that all women in the cohort are right handed, then side of surgery crudely approximates the effect of surgery on the side of a woman's dominant hand. Approximately 6 percent of women in the study's age range are left-handed (29), so would be misclassified as right handed in this analysis. Side of surgery had no effect on upper-body function decline or discomfort. If surgery on the side of the dominant hand is more likely to result in upper-body function decline than surgery on the side of the less dominant hand, we would have expected to see some effect. It may be that the measures of upper-body function decline are too crude to detect a hand-dependent effect. Measures of fine motor control or sensation, for example, may be more dependent on whether surgery occurs on the side of the dominant hand.

Third, we did not collect information about prior recreational or occupational injuries involving the upper extremities. We do not expect these to depend on the variables included in the analysis, so the reported measures of effect should not be confounded by these prior conditions.

Fourth, we did not measure upper-body function decline in a control population that was not diagnosed with breast cancer. Thus, we cannot measure the effect of the diagnosis and/or receipt of any primary therapy on upper-body function and discomfort. Satariano and Ragland (30) did measure the prevalence of upper-body function limitation in both a control population and a population of breast cancer patients. They defined a limitation as any report of a lot of difficulty, or that the task was not performed on doctor's orders, for any of the upper-body tasks originally developed by Nagi (8). Using a similar definition for upper-body limitation at baseline interview, and stratifying our population into the age groups used by Satariano and Ragland (30), we found that the prevalence of upper-body limitation in our population of breast cancer patients more closely resembled the prevalence of upper-body limitation in the control population of Satariano and Ragland (30) than the prevalence in their population of breast cancer patients (data not shown). Satariano and Ragland asked subjects about limitations in lifting items that weigh less than ten pounds, and we did not. The difference in prevalence of upper-body limitation between our breast cancer patients and their breast cancer patients may be partly explained by their inquiry about this additional task.

Fifth, we were not able to investigate the effect of radiation therapy independent of its effect as a component of breast conserving surgery

and radiation therapy as a primary treatment option. Radiation therapy and breast conserving surgery were too strongly correlated. Several investigators have shown that upper-body dysfunction, particularly lymphedema, is related to the nature and extent of radiation therapy (12, 13, 27, 31, 32).

Given the critical importance of upper-body function in maintaining independent living (33), our findings suggest that clinicians should consider the functional consequences of treatment when discussing treatment options and post-operative care with older women who have early stage breast cancer. For example, women who have cardiopulmonary comorbidity, regardless of the primary therapy that they chose, are likely to benefit from a supervised rehabilitation program. Such a program might include instructions for accomplishing common tasks with minimum pain or discomfort. Strategies to prevent overcompensation for discomfort or weakness on the side of surgery by overusing the opposite side should also be outlined. Women who undergo axillary dissection may be another group likely to benefit from such a program, especially if they are relatively young (less than age 65 in this study) or have Stage II disease.

This study demonstrates that upper-body dysfunction can arise shortly after therapy and resolve, arise and persist for at least 21

months, or arise at some time distant from therapy. Therefore, the upper-body function of all breast cancer patients should be followed and appropriate interventions planned for at least two years after diagnosis.

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Table 7: Effect of patient characteristics and therapy on early and late upper-body function

	Early Decline			Late Decline		
	# declining/total	% declining	adjusted* OR (95% CI)	# declining/total	% declining	adjusted* OR (95% CI)
Age group						
55–64 years	45/126	36%	1.	36/107	34%	1.
65–74 years	40/110	36%	0.9 (0.5–1.6)	32/95	34%	0.7 (0.4–1.4)
75+ years	21/62	34%	1.2 (0.5–3.0)	23/48	48%	0.8 (0.3–2.0)
missing	5			7		

Table 7: Effect of patient characteristics and therapy on early and late upper-body function

	Early Decline			Late Decline		
	# declining/total	% declining	adjusted* OR (95% CI)	# declining/total	% declining	adjusted* OR (95% CI)
Race†						
White	100/276	36%		84/237	35%	
African American	5/13	38%		4/9	44%	
Hispanic	1/2	50%		1/1	100%	
Asian or Pacific Islander	0/2	0%		1/2	50%	
Other	0/2	0%				
Missing	7			2		

Table 7: Effect of patient characteristics and therapy on early and late upper-body function

	Early Decline			Late Decline		
	# declining/total	% declining	adjusted* OR (95% CI)	# declining/total	% declining	adjusted* OR (95% CI)
Education						
< High School	30/50	40%	1.	22/40	55%	1.
≥ High School	86/246	35%	0.8 (0.4–1.7)	68/209	33%	0.4 (0.2–1.0)
Missing	7			2		
Number in House						
Lives with someone	67/194	35%	1.	50/164	30%	1.
Lives alone	38/101	38%	1.0 (0.4–2.1)	39/84	46%	1.5 (0.6–3.6)
Missing	8			3		

Table 7: Effect of patient characteristics and therapy on early and late upper-body function

	Early Decline			Late Decline		
	# declining/total	% declining	adjusted* OR (95% CI)	# declining/total	% declining	adjusted* OR (95% CI)
Marital Status						
Other than married	58/148	39%	1.	55/121	45%	1.
Married	48/148	32%	0.7 (0.3–1.4)	35/128	35%	0.7 (0.3–1.6)
Missing	7			2		
Body Mass Index						
≤ 23 kg/m2	27/90	30%	1.	29/76	38%	1.
>23 to 27.5 kg/m2	47/118	40%	1.5 (0.8–2.9)	35/94	37%	0.8 (0.4–1.7)
≥27.5 kg/m2	32/87	37%	1.2 (0.5–2.5)	26/78	33%	0.7 (0.3–1.6)
missing	8			3		

Table 7: Effect of patient characteristics and therapy on early and late upper-body function

	Early Decline			Late Decline		
	# declining/total	% declining	adjusted* OR (95% CI)	# declining/total	% declining	adjusted* OR (95% CI)
Tumor Stage						
Stage 1	65/188	35%	1.	61/163	37%	1.
Stage 2	41/109	38%	0.8 (0.4–1.4)	30/87	34%	0.8 (0.4–1.6)
Missing	6			1		
Side of Surgery‡						
Left Only	42/123	34%	1.	45/120	38%	1.
Right or Both	46/125	37%	1.1 (0.6–2.0)	41/124	33%	0.8 (0.4–1.4)
Missing	55			7		

Table 7: Effect of patient characteristics and therapy on early and late upper-body function

	Early Decline			Late Decline		
	# declining/total	% declining	adjusted* OR (95% CI)	# declining/total	% declining	adjusted* OR (95% CI)
Cardiopulmonary						
Comorbidity Score						
Zero	53/177	30%	1.	46/145	68%	1.
One, two or three	27/72	38%	1.4 (0.7–2.7)	23/62	63%	1.0 (0.5–2.2)
Four to fifteen	26/49	53%	3.6 (1.6–7.8)	22/43	49%	1.7 (0.7–3.9)
Missing	5			1		
Primary therapy						
Mastectomy	30/69	43%	1.	21/55	38%	1.
BCS & Rad	69/194	36%	0.8 (0.4–1.5)	59/168	35%	0.9 (0.4–2.0)
Other	7/35	20%		11/27	41%	
Missing	5			1		

Table 7: Effect of patient characteristics and therapy on early and late upper-body function

	Early Decline			Late Decline		
	# declining/total	% declining	adjusted* OR (95% CI)	# declining/total	% declining	adjusted* OR (95% CI)
Axillary Dissection						
No	10/40	25%	1.	15/30	50%	1.
Yes	95/257	95/257	3.7 (1.2–11)	75/219	34%	1.0 (0.3–2.9)
Missing	6			2		

*Unless otherwise indicated, adjusted for the effects of the other listed variables, time to baseline interview, and time to follow-up interview (for dependent variables measured at the follow-up).

†Race was not included in the multivariable models because of the small number of nonwhite subjects.

‡The effect of side of surgery was adjusted for the other variables. Side of surgery was not included in the multivariable models to estimate the effects of the other variables because of the high proportion of subjects for whom side of surgery was unknown.

Table 8: Effect of patient characteristics and therapy on numbness, pain or swelling at follow-up interview

	Numbness or Pain in Armpit			Swelling or Other Arm Problems		
	# declining/total	% declining	adjusted* OR (95% CI)	# declining/total	% declining	adjusted* OR (95% CI)
Age group						
55–64 years	60/105	57%	1.	19/105	18%	1.
65–74 years	26/93	28%	0.2 (0.1–0.5)	19/94	20%	1.0 (0.5–2.4)
75+ years	6/48	13%	0.1 (0.03–0.4)	4/48	8%	0.2 (0.03–0.9)
missing	5			4		

Table 8: Effect of patient characteristics and therapy on numbness, pain or swelling at follow-up interview

	Numbness or Pain in Armpit			Swelling or Other Arm Problems		
	# declining/total	% declining	adjusted* OR (95% CI)	# declining/total	% declining	adjusted* OR (95% CI)
Race†						
White	85/234	36%		39/235	17%	
African American	5/8	63%		2/8	25%	
Hispanic	0/1	0%		0/1	0%	
Asian or Pacific Islander	1/2	50%		1/2	50%	
Other	7					
Missing				5		

Table 8: Effect of patient characteristics and therapy on numbness, pain or swelling at follow-up interview

	Numbness or Pain in Armpit			Swelling or Other Arm Problems		
	# declining/total	% declining	adjusted* OR (95% CI)	# declining/total	% declining	adjusted* OR (95% CI)
Education						
< High School	14/40	35%	1.	8/40	20%	1.
≥ High School	77/205	38%	0.6 (0.2–1.7)	34/206	17%	1.1 (0.3–3.5)
Missing	7			5		
Number in House						
Lives with someone	65/161	40%	1.	25/162	15%	1.
Lives alone	26/83	31%	1.6 (0.6–4.1)	17/83	20%	4.6 (1.3–16)
Missing	8			6		

Table 8: Effect of patient characteristics and therapy on numbness, pain or swelling at follow-up interview

	Numbness or Pain in Armpit			Swelling or Other Arm Problems		
	# declining/total	% declining	adjusted* OR (95% CI)	# declining/total	% declining	adjusted* OR (95% CI)
Marital Status						
Other than married	39/119	33%	1.	20/119	17%	1.
Married	52/126	41%	1.1 (0.5–2.6)	22/127	17%	2.4 (0.7–7.9)
Missing	7			5		

Table 8: Effect of patient characteristics and therapy on numbness, pain or swelling at follow-up interview

	Numbness or Pain in Armpit			Swelling or Other Arm Problems		
	# declining/total	% declining	adjusted* OR (95% CI)	# declining/total	% declining	adjusted* OR (95% CI)
Body Mass Index						
≤ 23 kg/m2	24/74	32%	1.	11/75	15%	1.
>23 to 27.5 kg/m2	37/93	40%	1.0 (0.5–2.2)	15/93	16%	1.0 (0.4–2.5)
≥27.5 kg/m2	30/77	39%	0.9 (0.4–2.1)	16/77	21%	1.3 (0.5–3.6)
missing	8			6		
Tumor Stage						
Stage 1	58/160	36%	1.	21/161	13%	1.
Stage 2	34/86	40%	0.9 (0.5–1.8)	21/86	24%	2.2 (1.0–4.7)
Missing	6			4		

Table 8: Effect of patient characteristics and therapy on numbness, pain or swelling at follow-up interview

	Numbness or Pain in Armpit			Swelling or Other Arm Problems		
	# declining/total	% declining	adjusted* OR (95% CI)	# declining/total	% declining	adjusted* OR (95% CI)
Side of Surgery						
Left Only	45/119	38%	1.	24/120	20%	1.
Right or Both	46/125	37%	1.0 (0.6–1.9)	18/125	14%	0.6 (0.3–1.3)
Missing	8			6		
Cardiopulmonary Comorbidity Score						
Zero	54/142	38%	1.	26/143	18%	1.
One, two or three	22/61	36%	1.4 (0.6–3.1)	10/61	16%	0.8 (0.3–2.0)
Four to fifteen	16/43	37%	2.4 (0.9–6.1)	6/43	14%	0.8 (0.3–2.4)
Missing	3			4		

Table 8: Effect of patient characteristics and therapy on numbness, pain or swelling at follow-up interview

	Numbness or Pain in Armpit			Swelling or Other Arm Problems		
	# declining/total	% declining	adjusted* OR (95% CI)	# declining/total	% declining	adjusted* OR (95% CI)
Primary therapy						
Mastectomy	19/53	36%	1.	13/53	25%	1.
BCS & Rad	66/166	40%	1.5 (0.7–3.2)	26/167	16%	0.6 (0.2–1.3)
Other	7/27	26%		3/27	11%	
Missing	5			4		
Axillary Dissection						
No	2/30	7%	1.	1/30	3%	1.
Yes	90/216	42%	13 (1.5–117)	41/217	19%	4.3 (0.5–37)
Missing	6			4		

*Unless otherwise indicated, adjusted for the effects of the other listed variables and time to follow-up interview.

†Race was not included in the multivariable models because of the small number of nonwhite subjects.

4. The Effect of Less Than Definitive Care on Breast Cancer Recurrence and Mortality

4.1. Introduction

Effective diagnostic evaluation, prognostic evaluation, and primary therapy for early stage breast cancer has been well characterized (1, 2). Although the standard of breast cancer care enjoys a broad consensus (3, 4), this standard has not fully penetrated medical practice.

For example, age-dependent variations in breast cancer care have been documented for nearly two decades (5). Recent evidence suggests older women who receive less than definitive therapy have both higher recurrence rates and higher mortality rates (6–8). Furthermore, breast cancer-specific mortality rates have declined among women less than 70 years old, but remain stable among 70-79 year olds and have increased among those 80 or more years old (9). Altogether, this evidence suggests that less than definitive care can adversely impact outcomes following a breast cancer diagnosis, at least among older women.

The present study advances the understanding of the consequences of receiving less than definitive care. We examined the effect of less than definitive prognostic evaluation and/or less than definitive primary therapy, whereas previous studies have examined only less than definitive therapy. We followed patients for longer than

previous studies and ascertained recurrence and cause-specific mortality, whereas previous studies have ascertained only recurrence and/or all cause mortality.

4.2. Methods

4.2.1. Study population

The study population comprised 494 female breast cancer patients diagnosed at eight Rhode Island hospitals between July 1984 and February 1986 and identified by Silliman *et al.* (10). All patients were Rhode Island residents between the ages of 45 and 90 at diagnosis who had histologically confirmed breast cancer and no previous cancer diagnosis. Patients were identified through hospital pathology records, and eligibility was confirmed by examining each patient's medical record.

The Brown University Institutional Review Board approved the study that originally enrolled the patients. The Boston University Medical Center's Institutional Review Board approved this follow-up study. The Brown University Institutional Review Board approval required that the investigators expunge the patients' identifying variables following the data analysis. We reidentified subjects for the follow-up study by matching unique patient characteristics to the Cancer Registry of the Hospital Association of Rhode Island. The patient characteristics used for reidentification were date of birth, date of diagnosis, hospital of

diagnosis, tumor type (all patients had breast cancer), and sex (all subjects were female). The Hospital Association of Rhode Island considered a subject to match a case in the registry (a) if the study's date of diagnosis was within one month of the registry's date of diagnosis and the date of birth and hospital of diagnosis matched exactly, or (b) if two of the three components of the date of birth matched exactly, the study's recorded year of birth was within five years of the registry's recorded year of birth, and the hospital, month, and year of diagnosis matched exactly. For each match, the Hospital Association reported to the present investigators the subject's first, middle and last name; social security number when available; and the registry's recorded date of birth.

The Hospital Association of Rhode Island reidentified 431 of the original 494 patients. The probability of reidentification did not depend on patients' age, breast cancer stage, comorbid disease index, or receipt of definitive care, as illustrated by the p-values for the tests for homogeneity shown in Table 9. However, the probability of reidentification did depend on the hospital of diagnosis. We expected this dependence because two affiliated hospitals (E and F) participated in the Hospital Association of Rhode Island Cancer Registry for only part of the enrollment. We limited our analyses to the 390 reidentified patients with local or regional disease. We excluded from the analyses the 41

reidentified patients who had metastatic disease at diagnosis because we know of no standard of care for advanced breast cancer.

4.2.2.Follow-up

Figure 1 illustrates the follow-up process that we used to ascertain breast cancer recurrence and mortality. The Hospital Association of Rhode Island reported the recurrence status of each subject, the date of any recurrence, and the date of last follow-up.

We ascertained the vital status of subjects by matching the identifying variables to three databases. First, the National Death Index matched each subject's first and last name, middle initial, social security number, date of birth, father's surname, sex, race, marital status, and state of residence against its database of death records collected through December 31, 1996. For potentially true matches, the National Death Index reported a probability score reflecting the quality of the match, a judgment of whether the match was a true match, the date and cause of death for the potential match, the state that holds the death certificate, and the death certificate number.

Second, the Social Security Administration matched each subject's first, middle, and last name; date of birth; sex; and social security number to its database of active social security transactions. For potentially true matches, the Social Security Administration reported

whether their database indicated that the subject was dead, living, or had unknown vital status. For subjects known to be dead, the Social Security Administration reported the date of death and death certificate number.

Third, ChoicePoint Corporation matched each subject's first and last name, middle initial, social security number, date of birth, father's surname, sex, race, marital status, and state of residence against its proprietary databases. For potentially true matches, ChoicePoint Corporation reported the date of last follow-up and vital status.

4.2.3.Outcomes

We ascertained four outcomes. The first outcome was recurrent breast cancer, which we defined as any type of breast cancer recurrence reported by the Hospital Association of Rhode Island or death from breast cancer reported by the National Death Index. Possible recurrence types reported by the Hospital Association of Rhode Island were local (n=12), regional (n=23), distant (n=69), and site unknown (n=7). We coded recurrences reported by the Hospital Association of Rhode Island in preference to recurrences ascertained from the death records. The date of recurrence was as reported by the Hospital Association of Rhode Island or the date of death as reported by the National Death Index for recurrences ascertained from death records. For subjects who met

neither recurrence definition, the last date of recurrence-free follow-up was the date of last follow-up reported by the Hospital Association of Rhode Island.

The second outcome was breast cancer-specific mortality, which we assigned to subjects with a death certificate containing the International Classification of Disease, ninth revision code 174 for breast cancer as the underlying cause of death or as one of the contributing causes of death reported in Part I of the death certificate. All women who died of breast cancer would also have been coded as having recurrent breast cancer, but not all cases of recurrent breast cancer died of breast cancer.

The third outcome was all but breast cancer-specific mortality, which we assigned to subjects who matched a National Death Index record but who did not meet the condition for breast cancer-specific mortality.

The fourth outcome was all cause mortality, which we assigned to all subjects who matched a National Death Index record.

For the mortality outcomes, we assigned the date of last follow-up as the date of death recorded on the death certificate for decedents. For subjects with no National Death Index match and confirmed by the Social Security Administration or Choice Point Corporation to be of living

or unknown status on or after 31 December 1996 we assigned 31 December 1996 as the date of last follow-up. For subjects with no matching death certificate and no confirmation of vital status by the Social Security Administration or the Choice Point Corporation, we assigned 31 December 1996 as the date of last follow-up. Analyses with the date of last follow-up for these 62 subjects assigned to be the date of last follow-up by the Hospital Association of Rhode Island yielded results equivalent to those with the date of last follow-up assumed to be 31 December 1996.

4.2.4.Primary Determinants

The two treatment-related predictors of outcomes in patients with local or regional breast cancer were definitive prognostic evaluation and definitive primary therapy. All evaluation and treatments — including surgery, adjuvant systemic therapy, and radiation therapy — actually received during the first year following diagnosis were documented for each patient. The documentation used information from hospital records and from the outpatient records of radiation therapy practices and medical oncology practices. We defined a definitive prognostic evaluation as including an axillary dissection and evaluation of estrogen receptor status. Current practice guidelines recommend removal and pathologic examination of axillary lymph nodes for patients with early, invasive breast cancer unless the risk of axillary metastasis is very low or

knowledge of node status will have no influence on therapy (11). The estrogen receptor status is an important prognostic indicator for women with node-negative (12) and node-positive disease (13). We classified women who did not receive this minimum evaluation as having had less than definitive prognostic evaluation. We considered histologic examination among the criteria for definitive prognostic evaluation (12), but all tumors in this population were examined histologically, so all patients met this criterion.

We defined definitive primary therapy for women with local disease as receiving a mastectomy or breast conserving surgery plus radiation therapy within five months of surgery (14). We similarly defined definitive primary therapy for women with regional disease and required systemic adjuvant therapy (chemotherapy, hormonal therapy, or both) (13). We classified women who did not receive this minimum primary therapy as having had less than definitive primary therapy.

We stratified subjects into four categories depending on the care they received: (1) those who received less than definitive prognostic evaluation and less than definitive therapy, (2) those who received less than definitive prognostic evaluation but definitive therapy, (3) those who received definitive prognostic evaluation but less than definitive therapy,

and (4) those who received definitive prognostic evaluation and definitive therapy. The last group served as the reference condition throughout.

4.2.5.Confounders

We adjusted for three potential confounders: (1) age at diagnosis — in categories of 45 to 64 years, 65 to 74 years, and 75 to 90 years; (2) extent of disease — categorized as local (tumor contained within the anatomic boundaries of the breast) or regional (spread to either tissues immediately adjacent to, or lymph nodes that drain the breast primarily), and (3) an ordinal scale of comorbid diseases, which we constructed as the sum of individual dichotomous variables assigned to notations (1 if present, 0 otherwise) of cardiac disease, respiratory disease, neurologic disease, diabetes mellitus, and renal disease in the medical record. Multivariable analyses with these conditions entered in the model as individual dichotomous variables yielded equivalent results.

4.2.6.Analytic Strategy

We used Kaplan-Meier survival analysis to prepare survival curves and complementary log-log survival curves. We used Cox's proportional hazards regression (15) to estimate the effects of less than definitive care on the four outcomes, adjusted for the three confounders. We examined the complementary log-log survival plots to assure that the assumption of proportional hazards was satisfied for each outcome.

To further adjust for potential confounding and bias (*e.g.*, due to selection of the subset of patients reidentified), we implemented the propensity score technique suggested by Rubin (16, 17). We calculated a score for each subject to reflect her propensity to receive less than definitive therapy. Receipt of less than definitive therapy was the dependent variable in a logistic regression model that included age, extent of disease, interaction between age and extent of disease, comorbidity index score, reidentification status (a dichotomous variable set equal to 1 if the Hospital Association of Rhode Island reidentified the patient or 0 if the patient was not reidentified), and hospital of diagnosis (categorized with dummy variables) as the independent variables. For each patient, we transformed the logit to the probability of receiving less than definitive therapy, which is the patient's propensity score. We then stratified subjects into quintiles by their propensity score. We used Cox's proportional hazards regression to assess the effect of less than definitive care on the outcomes, using four dummy variables to represent the quintiles of propensity to receive less than definitive therapy. This technique can reduce confounding and bias by 90 percent (17), assuming that there are no other significant residual confounders or sources of bias.

We also examined whether the effect of the less than definitive care categories on the outcomes depended on the time following diagnosis.

We first examined the effects in the follow-up period limited to five years after diagnosis. We then examined the effects in the follow-up period beyond five years, limiting the data set to subjects who had survived at least five years. In these models, we used the propensity score method applied to the whole data set to control for confounding and bias.

4.2.7.Stage misclassification

Less than definitive prognostic evaluation may yield an incorrect assessment of the extent of disease, particularly in women who did not undergo axillary dissection. These women might have had regional disease, but because they received less than definitive prognostic evaluation, they may have been misclassified as having local disease (*i.e.*, they have false negative node status). They then received less than definitive primary therapy for the underassessed disease. In this scenario, the effect of less than definitive primary therapy would be overestimated. It would reflect the combined effects of less than definitive therapy, stage misclassification, and less than definitive prognostic evaluation.

In this study, women who received less than definitive prognostic evaluation had worse outcomes than women who received definitive prognostic evaluation. In addition, these women were more likely to receive less than definitive therapy. Prognostic evaluation is therefore

also a potential confounder of the relation between less than definitive therapy and the outcomes in this study. To separate the effect of less than definitive primary therapy from the effects of stage misclassification and less than definitive prognostic evaluation, we undertook a sensitivity analysis.

First, we created a triangular probability density function to reflect the probability that a woman with local disease actually had regional disease (*i.e.*, the false-negative proportion among women with local disease), given that she received no axillary dissection and therefore a less than definitive prognostic evaluation (3). We used reports in the literature to approximate the probability that a woman whose clinical node status was negative would have been pathologically node positive. The minimum probability equals 15 percent (4), the maximum probability equals 44 percent (4), and the mode of the triangular distribution equals 28 percent, which we calculated as the weighted average of all the literature reports (4, 18–20).

Second, we created a triangular probability density function to reflect the probability that a woman with regional disease actually had local disease (*i.e.*, the false-positive proportion among women with regional disease), given that she received no axillary dissection and therefore a less than definitive prognostic evaluation (3). We used

reports in the literature to determine the probability that a woman whose clinical node status was positive would have been pathologically node negative. The minimum probability equals 8 percent (20), the maximum probability equals 55 percent (19), and the mode of the triangular distribution equals 34 percent, which we calculated as the weighted average of all the literature reports (4, 18–20).

To perform the sensitivity analysis we selected misclassification probabilities from the two triangular probability density functions. Then, for each of the 78 women classified as having local disease and who received less than definitive prognostic evaluation, we conducted a Bernoulli trial using the false-negative misclassification probability to determine whether she was correctly or incorrectly classified. Similarly, for each of the 18 women classified as having regional disease and who received less than definitive prognostic evaluation, we conducted a Bernoulli trial using the false-positive misclassification probability to determine whether she was correctly or incorrectly classified. We reclassified the extent of disease and receipt of definitive primary therapy for the women selected as having been misclassified and then subjected the modified data set to the multivariable analysis to estimate the effect of less than definitive care. We repeated the sensitivity analysis 2,000 times to generate a distribution of expected results. We plotted the cumulative frequency of results to judge the sensitivity of the results to

misclassification. Steep cumulative frequency curves indicated that the results were insensitive to misclassification. Shallow cumulative frequency curves indicated that the results were sensitive to misclassification.

4.3. RESULTS

4.3.1. Population characteristics

Table 10 shows the characteristics of the 390 women who had local or regional disease at diagnosis and who were reidentified by the Hospital Association of Rhode Island. These women constitute the study population followed for the analyses. As in the analysis of the entire population (10) patients 75 to 90 years old were more likely than patients 45 to 64 years old to receive less than definitive prognostic evaluation (OR = 2.2, 95 percent confidence interval 1.2–3.9) and less than definitive primary therapy (OR = 3.5, 95 percent confidence interval 1.8–6.8), after adjusting for stage and comorbid disease index by logistic regression.

4.3.2. Outcomes

Table 11 shows the unadjusted rates of breast cancer recurrence and the mortality outcomes within the therapy groups. Table 12 shows the adjusted relative hazard of breast cancer recurrence and the mortality outcomes associated with less than definitive care, regional breast cancer stage, older age groups, and the comorbid index. Women

who received less than definitive prognostic evaluation and less than definitive therapy had an adjusted relative hazard of breast cancer recurrence of 2.3 (95 percent confidence interval 1.3–4.0) and an adjusted relative hazard of breast cancer specific mortality of 3.0 (95 percent confidence interval 1.6–5.4), compared with women who received definitive prognostic evaluation and definitive therapy. Women who received less than definitive care had little excess hazard of death from causes other than breast cancer (relative hazard of 1.4; 95 percent confidence interval 0.7–2.7). Women who received only less than definitive prognostic evaluation had relative hazards of 1.0 for the adverse outcomes. Women who received only less than definitive primary therapy had a relative hazard of 1.1 for breast cancer recurrence (95 percent confidence interval 0.7–1.8) and a relative hazard of 1.1 for breast cancer-specific mortality (95 percent confidence interval 0.7–1.9).

As expected, women with regional disease had an excess hazard of breast cancer recurrence relative to women with local disease (adjusted relative hazard of 2.4; 95 percent confidence interval 1.6–3.5) and an excess hazard of breast cancer-specific mortality (adjusted relative hazard of 2.6; 95 percent confidence interval 1.6–4.1). Women with regional disease had no excess hazard of death from causes other than breast cancer relative to women with local disease (adjusted relative hazard of 0.7; 95 percent confidence interval 0.4–1.2).

Women ages 75 to 90 had a lower hazard of breast cancer recurrence relative to women ages 45 to 64 after adjustment for evaluation and therapy (relative hazard of 0.6; 95 percent confidence interval 0.4–0.9) and had a lower hazard of breast cancer-specific mortality (adjusted relative hazard of 0.6; 95 percent confidence interval 0.4–1.0). As expected, older women had a higher risk of death from causes other than breast cancer. The women ages 65–74 had an adjusted relative hazard of death from causes other than breast cancer of 3.5 (95 percent confidence interval 1.5–7.9) compared with women ages 45–64. Women ages 75 to 90 had an adjusted hazard of death from causes other than breast cancer of 13.4 (95 percent confidence interval 6.2–29) even after adjustment for comorbid conditions.

The preexisting comorbid conditions were marginally associated with breast cancer recurrence and mortality from breast cancer. A unit increase in the comorbidity index — which included medical record diagnoses of respiratory disease, cardiac disease, diabetes mellitus, neurologic disease, and renal disease — conferred an adjusted relative hazard for mortality from causes other than breast cancer of 1.7 (95 percent confidence interval 1.3–2.1).

4.3.3.Effects of treatment groups within age groups and follow-up periods

The effect of less than definitive care on breast cancer recurrence and breast cancer mortality showed some dependence on age at diagnosis (Table 13). Less than definitive therapy appeared to confer the greatest risk of recurrence and breast cancer-specific mortality among women 45 to 64 years old at diagnosis. Among women 65 to 90 years old at diagnosis, less than definitive prognostic evaluation combined with less than definitive therapy appeared to confer the greatest risk of recurrence and breast cancer-specific mortality. These data are sparse, however, so it is difficult to assess the age-therapy interaction with confidence.

We estimated relative hazards adjusted by each subject's propensity to receive definitive therapy as predicted by her age, extent of disease, interaction between age and extent of disease, comorbid disease index, hospital of diagnosis, and whether she was reidentified (Table 14). These adjusted relative hazards were similar to those adjusted for only age, extent of disease, and comorbid disease index in the Cox's proportional hazards regression. Compared with the estimates of effect obtained from this simpler model, the relative hazards estimated by the propensity score method that were associated with breast cancer recurrence and breast cancer-specific mortality generally migrated

towards the null. The relative hazards associated with all but breast cancer-specific mortality migrated away from the null. However, the magnitude, precision, and pattern of effects did not change substantially under the propensity hazard adjustment.

The propensity score adjustment allows preparation of Kaplan-Meier survival distribution curves that reflect primarily treatment differences, when the subjects are limited to those with similar propensity scores. Figures 2 to 5 show the survival distributions within treatment groups for the four outcomes, limited to subjects with a propensity score rank for receipt of definitive therapy between the 0 and 60th percentiles (31 patients who received less than definitive prognostic evaluation and less than definitive therapy, 25 patients who received only less than definitive therapy, 68 patients who received only less than definitive prognostic evaluation, and 118 patients who received definitive prognostic evaluation and definitive therapy).

The effects of less than definitive breast cancer care were largely confined to the first five years following diagnosis (Table 15). Within the first five years after diagnosis, the relative hazards of recurrence and breast cancer-specific mortality associated with less than definitive care exceeded the relative hazards measured over the entire follow-up period. The relative hazard of death from causes other than breast cancer

associated with receiving both less than definitive prognostic evaluation and less than definitive therapy persisted into the period beyond five years after diagnosis (relative hazard 2.8; 95 percent confidence interval 1.2–6.7). These findings, which are adjusted for confounding and bias by the propensity score method, suggest that women who received the least definitive breast cancer care were more likely to die of their breast cancer in the first five years and more likely to die of other causes over the whole follow-up period.

4.3.4.Sensitivity to misclassification

Women who received less than definitive prognostic evaluation were 6.0-fold (95 percent confidence interval 2.7–13) more likely to receive less than definitive primary therapy, after adjusting for age, extent of disease, and comorbid disease status. As described above, less than definitive prognostic evaluation may yield an incorrect assessment of the extent of disease if no axillary node evaluation is performed.

Figure 6 shows the cumulative frequency distribution of the adjusted relative hazard of breast cancer-specific mortality for each of the breast cancer care groups generated by application of the sensitivity analysis to 2,000 combinations of false-positive and false-negative misclassification probabilities. The adjusted relative hazards of only less than definitive prognostic evaluation and only less than definitive

therapy were insensitive to misclassification, as illustrated by their very steep cumulative frequency distributions. The adjusted relative hazard of receiving less than definitive prognostic evaluation and less than definitive therapy was more sensitive to misclassification, as illustrated by the more shallow cumulative distribution frequency. However, the adjusted relative hazard exceeded 1.16 in every combination and exceeded 1.7 in about 80 percent of the combinations, which suggests that the excess risk of breast cancer-specific mortality from receipt of this combination of care cannot be attributed entirely to misclassification.

4.4. Discussion

In this study, women who received less than definitive prognostic evaluation and less than definitive primary therapy were at excess risk of breast cancer recurrence and breast cancer-specific mortality. Before considering the implications of these findings, we first consider whether the observed association might have resulted from influences other than deficits in medical care.

4.4.1. Methodologic considerations

Observational studies of treatment related outcomes are susceptible to confounding by indication. That is, the patients most likely to have adverse outcomes may have indications that predispose

them towards receipt of less than definitive care. We do not attribute our findings to confounding by indication for two reasons. First, we analytically controlled for the confounding influence of a wide range of comorbid conditions that were reported in the patients' medical records. These conditions should be among the indicators for receipt of less than definitive care. Second, we used an alternative analytic technique to control for the propensity to receive less than definitive care as indicated by the confounding variables, by the hospital of diagnosis, and by whether the patient was reidentified by the Hospital Association of Rhode Island. This alternative technique should reduce the bias due to confounding by 90 percent or more (17), so long as there are no other significant residual confounders or sources of bias. The results of this alternative analysis were equivalent to the primary results described herein.

The Hospital Association of Rhode Island did not reidentify all of the women, possibly resulting in a bias. The only systematic influence was the lower probability of reidentification at the hospitals without operational cancer registries. Some of the cases treated at these hospitals were never reported to the Hospital Association of Rhode Island cancer registry, which would preclude reidentification. We see no resulting bias that would systematically influence the central findings of the present study. Furthermore, we included hospital of diagnosis and

reidentification status as predictors of propensity to receive less than definitive therapy in the propensity score analysis. That analysis yielded results equivalent to the primary analyses that we have presented.

Causes of death reported on death certificates are subject to error (21). The influence of such errors on the present results merits consideration. The first issue is whether breast cancer is more likely to be assigned as the cause of death to women who received less than definitive care than to women who received definitive care. For example, lung cancer may be more likely assigned as the underlying cause of death for smokers and as a contributing cause of death for nonsmokers (22), although alternative explanations for the disparity have been suggested (23). Such a bias is not possible in this investigation because we used both underlying and contributing cause of death to assign breast-cancer specific mortality. The second issue to consider is the likely nondifferential error rate in assigning breast cancer as the cause of death in this population. Although many studies have documented errors in assigning causes of death on death certificates, they have uniformly found that malignant neoplasms are coded in error less often than other causes of death (24) and that breast cancer is coded in error less often than the other neoplasms (25–29). Most of these studies have found an overall accuracy for attribution of breast cancer as the underlying cause of death of about 90 percent. Furthermore, our study

is unique because all subjects had a pathologically confirmed diagnosis of breast cancer and because both underlying and contributing causes of death attributed to breast cancer were assigned to breast-cancer specific mortality. These unique aspects should improve the accuracy of cause of death attribution (30, 31). In sum, both the methods applied in this study and a review of the relevant literature indicate that errors in assigning cause of death to breast cancer should be few. The error rate should not depend on the assignment of definitive evaluation or therapy. We expect a low rate of non-differential misclassification to exert a negligible bias towards the null.

The effect of less than definitive care on breast cancer recurrence and breast cancer-specific mortality arose primarily in the first five years after diagnosis. The diluted effect of less than definitive care in the subsequent years is probably best explained by a depletion of women susceptible to the less than definitive care in the early years of follow-up. Women who received the least definitive care were at excess risk of death from causes other than breast cancer throughout the follow-up, which deserves consideration. One might attribute the finding to confounding by indication — the women received less than definitive care because they had comorbid diseases that precluded definitive care and they died of these diseases. The estimates of effect are adjusted for the comorbid disease index, however, which should reduce confounding by indication.

The comorbid disease index may not have adequately measured the total illness burden and disease severity. A measure of physical function at diagnosis might have improved the ability to control for confounding by indication. A third explanation is that women who received less than definitive care for their breast cancer also were more likely to receive less than definitive care for other diseases. We favor this explanation because of the stability of the effect of less than definitive care on causes of death other than breast cancer throughout the follow-up period.

4.4.2.Interpretation

The source of less than definitive care likely resides in the complex interaction between the physician, the patient, her family, and their medical environment (32). The interaction contains elements of physician training, the physician's recommendation for the individual patient, and the patient's or her family's own preferences (33). While evidence from randomized clinical trials of treatment efficacy enters the process (34), it is not always the dominant influence (32, 35). In fact, physicians may reject this evidence when recommending therapy to patients if the physician considers the populations studied in clinical trials to have been highly selected (36).

Another important element in the interaction between patient and physician, at least for choosing breast cancer therapy, is the patient's

age. Age-dependent variations in breast cancer treatment have been observed in a number of geographic regions, at different calendar periods, in different health care settings, and encompass all aspects of initial treatment. These aspects include diagnostic evaluation (10, 37), prognostic evaluation (10, 37), primary tumor therapy (38–46), and systemic adjuvant therapy (10, 47). These variations occur despite long-standing recommendations to clinicians to avoid relying upon chronologic age when establishing breast cancer treatment plans (48).

The influence of these age-dependent variations on recurrence and survival have only recently been investigated (6–8, 49). These studies have all reported that patients who receive less definitive therapy are more likely to experience an adverse outcome related to their breast cancer. In the study most similar to ours, Goodwin and colleagues reported that breast cancer patients who received less than definitive therapy for local or regional disease were 2.2-fold (95 percent confidence interval 1.1–4.3) more likely to die of any cause within two to eight years than patients who received definitive therapy. We found a relative hazard for all cause mortality in the first five years after diagnosis of 3.1 (95 percent confidence interval 1.8–5.3) associated with receipt of the least definitive care.

Our study advances the validity of the methods applied to the investigation of the consequences of less than definitive care for early stage breast cancer. The duration of follow-up in our study exceeds the duration of follow-up in the other studies. We were able to examine cause-specific mortality, whereas the other studies examined only all cause mortality. Finally, only one other study (7) controlled for confounding by comorbid diseases.

4.4.3.Conclusions

The predictors of receipt of less than definitive care thus include — alone or in combination — patient preferences, physician preferences, the patient's age, the patient's comorbid disease status, the geographic region (50), and the hospital size (51). While the interaction of these predictors is no doubt complex, the result of receipt of less than definitive care is straightforward. In this study, patients who received less than definitive prognostic evaluation and less than definitive primary therapy were at excess risk of breast cancer recurrence and breast cancer-specific mortality.

The well-established risk factors for breast cancer offer few opportunities for intervention and account for less than half of breast cancer cases (52). Most involve aspects of a woman's reproductive course that are intimately related to her lifestyle and culture — so are

difficult to predict and thus to change — or are currently immutable (*e.g.*, genotype). Most of the risk factors that have been identified confer excess risks of incident disease well below the excess risks of breast cancer mortality observed within the first five years of follow-up among women who received less than definitive care. The reduction of morbidity and mortality among women diagnosed with breast cancer must therefore remain a priority. One strategy is to assure that women with early stage breast cancer are treated in accordance with existing guidelines (2, 3).

Future studies of the effect of less then definitive care for early stage breast cancer should focus on control of confounding by physical function as well as comorbid disease status, resolution of the survival period over which less than definitive care exerts an influence, and the identification of the factors that result in less than definitive care and their individual impact on breast cancer recurrence and mortality.

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Table 9: Percent of 494 patients reidentified by the Hospital Association of Rhode Island within strata of patient characteristics

Characteristic (p-value for test of homogeneity)	Number reidentified/ Total	Percent Reidentified
Age Group (p=0.63)		
45 to 64 years	190/220	86%
65 to 74	128/143	90
75 to 90	113/131	86
Breast Cancer Stage (p=0.79)		
local	242/280	86%
regional	148/169	88
metastatic	41/45	91

Table 9: Percent of 494 patients reidentified by the Hospital Association of Rhode Island within strata of patient characteristics

Characteristic (p-value for test of homogeneity)	Number reidentified/ Total	Percent Reidentified
Comorbidity index (p=0.76)		
0	282/326	87%
1	108/122	89
2	31/36	86
3	7/7	100
4	3/3	100
Prognostic Evaluation and Therapy (p=0.76)		
both less than definitive	35/39	90%
only evaluation less than definitive	61/73	84
only therapy less than definitive	69/78	88
both definitive	225/259	87

Table 9: Percent of 494 patients reidentified by the Hospital Association of Rhode Island within strata of patient characteristics

Characteristic (p-value for test of homogeneity)	Number reidentified/ Total	Percent Reidentified
Hospital (p=0.001)		
A	184/187	98%
B	40/44	91
C	63/44	98
D	39/41	95
E	3/19	16
F	18/51	35
G	64/68	94
H	20/20	100

Table 10: Population characteristics within strata of therapy (number, %)

	Both less than Definitive (n=35)	Prognostic less than Definitive (n=61)	Therapy less than Definitive (n=69)	Both Definitive (n=225)
Age (years)				
45–64	8 (23%)	25 (41%)	26 (38%)	109 (48%)
64–74	6 (17%)	20 (33%)	18 (26%)	73 (32%)
75–90	21 (60%)	16 (26%)	25 (36%)	43 (19%)
Extent				
Local	22 (63%)	56 (92%)	5 (7%)	159 (71%)
Regional	13 (37%)	5 (8%)	64 (93%)	66 (29%)

Table 10: Population characteristics within strata of therapy (number, %)

	Both less than Definitive (n=35)	Prognostic less than Definitive (n=61)	Therapy less than Definitive (n=69)	Both Definitive (n=225)
Comorbidity Index				
0	15 (43%)	41 (67%)	41 (59%)	155 (69%)
1	13 (37%)	14 (23%)	16 (23%)	57 (25%)
2	4 (11%)	4 (7%)	11 (16%)	10 (4%)
3	2 (6%)	2 (3%)	0 (0%)	2 (1%)
4	1 (3%)	0 (0%)	1 (1%)	1 (0.4%)

Table 11: Unadjusted rates of breast cancer recurrence and mortality outcomes within therapy groups (number of outcomes / person-years; rate (PY^{-1}))

	Both less than Definitive	Prognostic less than Definitive	Therapy less than Definitive	Both Definitive
Breast Cancer Recurrence	17/161	15/411	32/368	74/1531
	0.106	0.037	0.087	0.048
Breast Cancer-Specific	15/193	11/551	25/499	54/2009
Mortality	0.078	0.020	0.050	0.027
All but Breast Cancer	13/193	15/551	16/499	41/2009
Mortality	0.067	0.027	0.032	0.020
All Cause Mortality	28/193	26/551	41/499	95/2009
	0.145	0.047	0.082	0.047

Table 12: Adjusted relative hazard† of breast cancer recurrence and mortality outcomes associated with the predictors of outcomes (95 percent Confidence Interval)

	Breast Cancer Recurrence	Breast cancer mortality	All but breast cancer mortality	All cause mortality
Prognostic Evaluation and Therapy				
Both Definitive	1.	1.	1.	1.
Prognostic Evaluation less than definitive	1.0 (0.6–1.8)	1.0 (0.5–2.0)	1.0 (0.5–1.8)	1.0 (0.7–1.6)
Therapy less than definitive	1.1 (0.7–1.8)	1.1 (0.7–1.9)	1.0 (0.5–2.1)	1.1 (0.7–1.6)
Both less than definitive	2.3 (1.3–4.0)	3.0 (1.6–5.4)	1.4 (0.7–2.7)	1.9 (1.2–3.0)

Table 12: Adjusted relative hazard† of breast cancer recurrence and mortality outcomes associated with the predictors of outcomes (95 percent Confidence Interval)

	Breast Cancer Recurrence	Breast cancer mortality	All but breast cancer mortality	All cause mortality
Extent of breast cancer				
local	1.	1.	1.	1.
regional	2.4	2.6	0.7	1.5
	(1.6–3.5)	(1.6–4.1)	(0.4–1.2)	(1.1–2.1)
Age group (years)				
45–64	1.	1.	1.	1.
65–74	0.8	0.7	3.5	1.1
	(0.5–1.1)	(0.4–1.1)	(1.5–7.9)	(0.7–1.5)
75–90	0.6	0.6	13.4	2.1
	(0.4–0.9)	(0.4–1.0)	(6.2–29)	(1.4–2.9)

Table 12: Adjusted relative hazard† of breast cancer recurrence and mortality outcomes associated with the predictors of outcomes (95 percent Confidence Interval)

	Breast Cancer Recurrence	Breast cancer mortality	All but breast cancer mortality	All cause mortality
Comorbid disease index (per unit increase)	1.2 (1.0–1.5)	1.2 (0.9–1.6)	1.7 (1.3–2.1)	1.4 (1.2–1.7)

† Each estimate of effect is adjusted for all of the other variables using Cox's proportional hazards regression.

Table 13: Modification of the adjusted breast cancer care relative hazards† by age at diagnosis (95 percent Confidence Interval)

	45 to 64 years at diagnosis	65 to 74 years at diagnosis	75 to 90 years at diagnosis
		Breast Cancer Recurrence	
Both Definitive	1.	0.8	0.7
		(0.4–1.3)	(0.3–1.3)
Prognostic Evaluation less	0.9	1.0	0.5
than definitive	(0.4–2.1)	(0.4–2.3)	(0.1–1.9)
Therapy less than definitive	1.5	0.9	0.5
	(0.8–2.7)	(0.4–1.9)	(0.2–1.0)
Both less than definitive	1.3	1.7	1.8
	(0.4–4.1)	(0.5–5.4)	(0.9–3.6)

Table 13: Modification of the adjusted breast cancer care relative hazards† by age at diagnosis (95 percent Confidence Interval)

	45 to 64 years at diagnosis	65 to 74 years at diagnosis	75 to 90 years at diagnosis
	Breast Cancer-Specific Mortality		
Both Definitive	1.	0.7	0.6
		(0.4–1.3)	(0.2–1.3)
Prognostic Evaluation less	0.9	0.8	0.7
than definitive	(0.3–2.4)	(0.3–2.2)	(0.2–2.8)
Therapy less than definitive	1.4	0.7	0.5
	(0.7–2.8)	(0.3–1.8)	(0.2–1.3)
Both less than definitive	1.7	1.7	2.6
	(0.5–5.4)	(0.4–6.9)	(1.2–5.5)

† Adjusted for confounding by age, breast cancer stage, and comorbid disease index using Cox's proportional hazards regression.

Table 14: Relative hazards associated with breast cancer care, adjusted using propensity score technique

	Breast Cancer Recurrence	Breast cancer mortality	All but breast cancer mortality	All cause mortality
Both Definitive	1.	1.	1.	1.
Prognostic Evaluation less than definitive	0.8 (0.5–1.5)	0.8 (0.4–1.6)	1.4 (0.8–2.6)	1.1 (0.7–1.7)
Therapy less than definitive	1.2 (0.7–1.9)	1.2 (0.7–2.1)	1.1 (0.6–2.1)	1.2 (0.8–1.8)
Both less than definitive	1.7 (1.0–3.0)	2.3 (1.3–4.1)	2.2 (1.1–4.1)	2.2 (1.4–3.4)

† Adjusted using quintiles of a score assigned to each subject to measure the propensity to receive definitive therapy — given the subject's age, extent of disease, comorbid disease index, hospital of diagnosis, and whether they were reidentified.

Table 15: Modification of the adjusted breast cancer care relative hazards† by period of follow-up (95 percent Confidence Interval).

	Breast Cancer Recurrence	Breast cancer mortality	All but breast cancer mortality	All cause mortality
	Relative hazards in the first five years			
Both Definitive	1.	1.	1.	1.
Prognostic Evaluation less than definitive	1.2 (0.6–2.2)	1.3 (0.6–2.9)	1.0 (0.4–2.8)	1.2 (0.6–2.3)
Therapy less than definitive	1.3 (0.8–2.3)	1.5 (0.8–2.9)	0.8 (0.3–2.2)	1.3 (0.8–2.1)
Both less than definitive	2.6 (1.4–4.9)	3.4 (1.7–6.8)	2.5 (1.0–6.5)	3.1 (1.8–5.3)

Table 15: Modification of the adjusted breast cancer care relative hazards† by period of follow-up (95 percent Confidence Interval).

	Breast Cancer Recurrence	Breast cancer mortality	All but breast cancer mortality	All cause mortality
	Relative hazards after the first five years			
Both Definitive	1.	1.	1.	1.
Prognostic Evaluation less than definitive	0.6 (0.3–1.4)	0.4 (0.1–1.4)	1.8 (0.8–4.0)	1.0 (0.6–2.0)
Therapy less than definitive	1.0 (0.5–2.2)	1.0 (0.3–2.9)	1.0 (0.4–2.4)	1.0 (0.5–1.9)
Both less than definitive	1.3 (0.5–3.3)	1.3 (0.4–4.5)	2.8 (1.2–6.7)	2.1 (1.0–4.1)

† Adjusted using quintiles of a score assigned to each subject to measure the propensity to receive definitive therapy — given the subject's age, extent of disease, comorbid disease index, hospital of diagnosis, and whether they were reidentified.

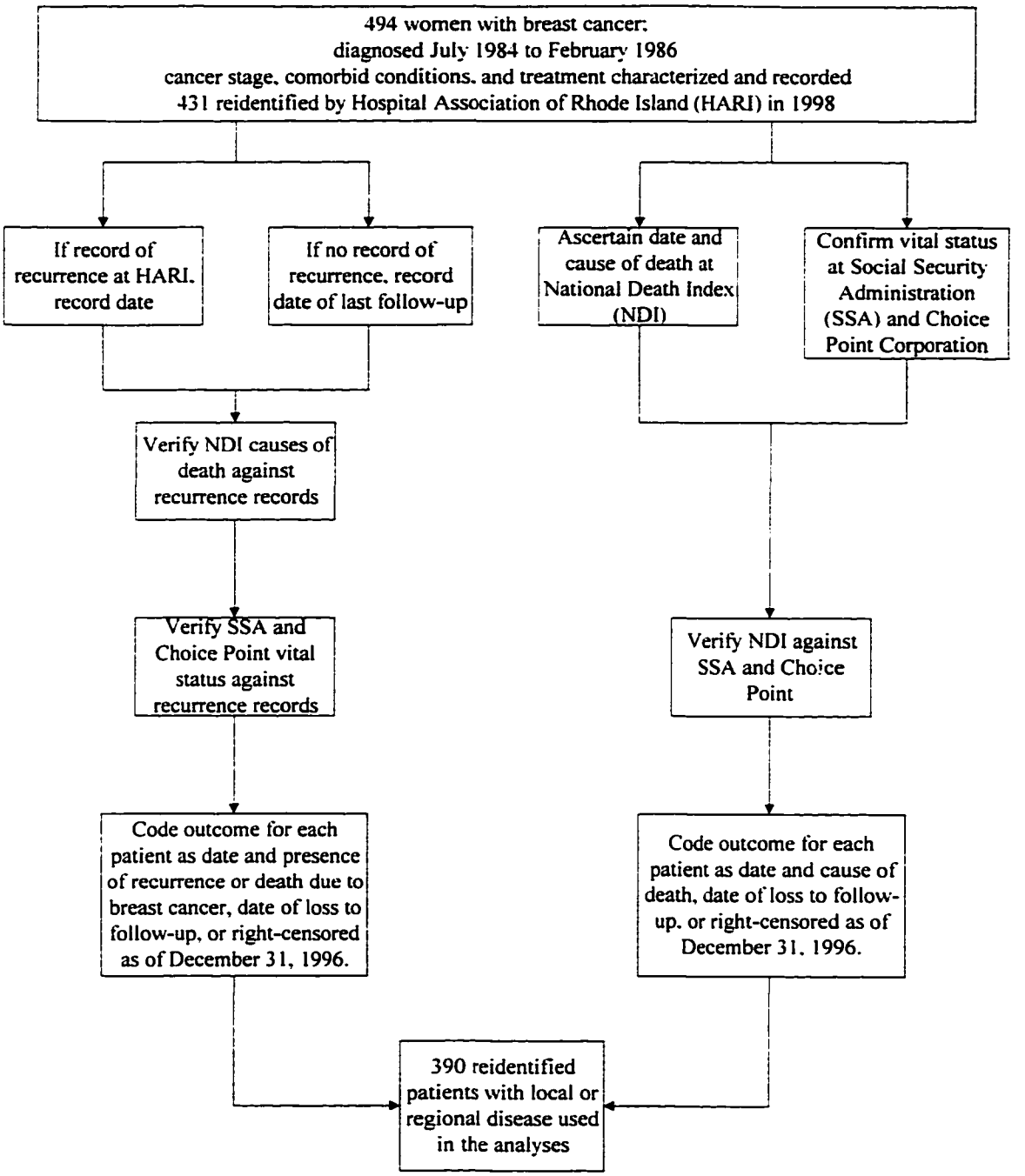

Figure 2: Diagram of population identification and follow-up

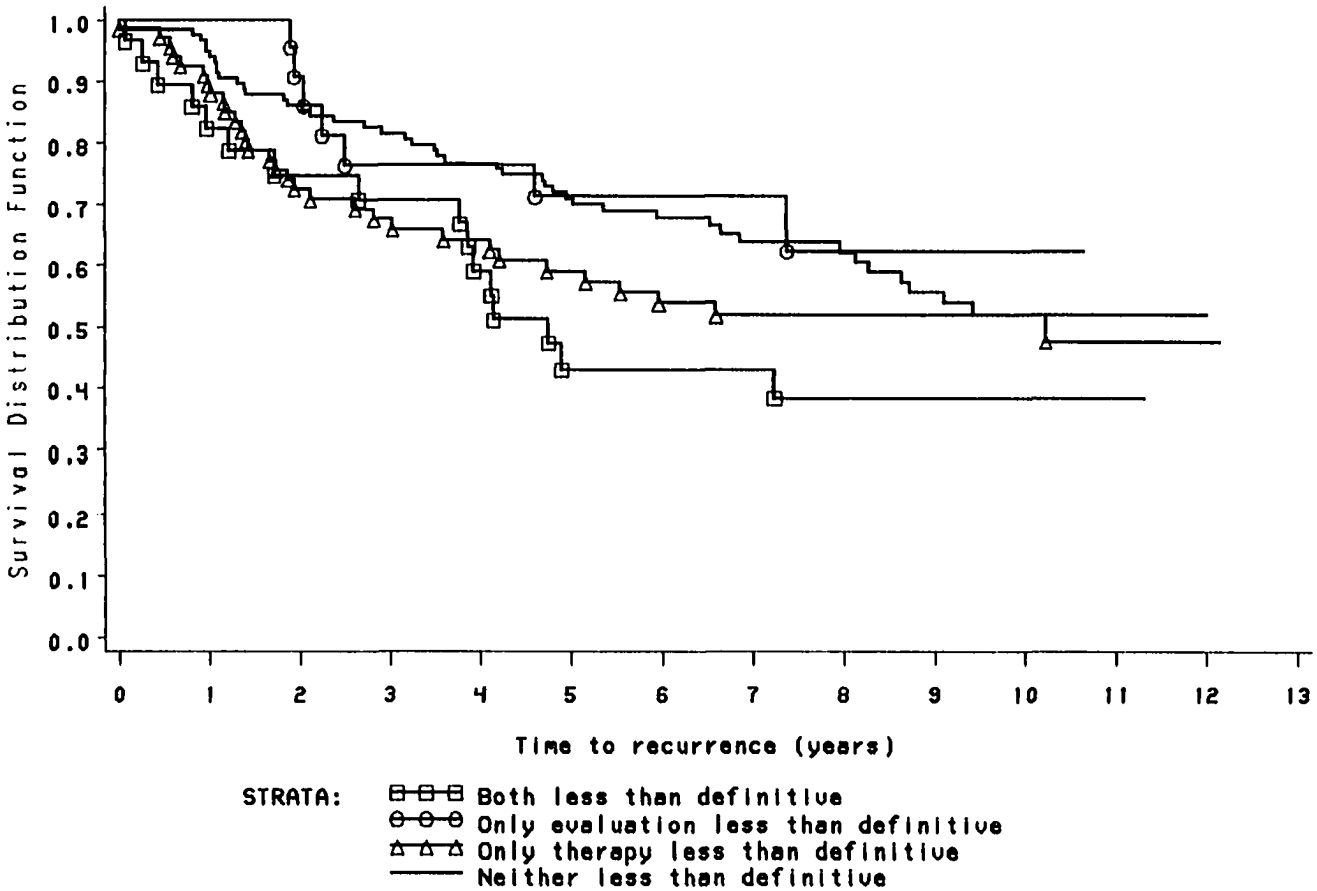

Figure 3: Time to breast cancer recurrence within therapy groups; limited to subjects with propensity scores below the 60th percentile

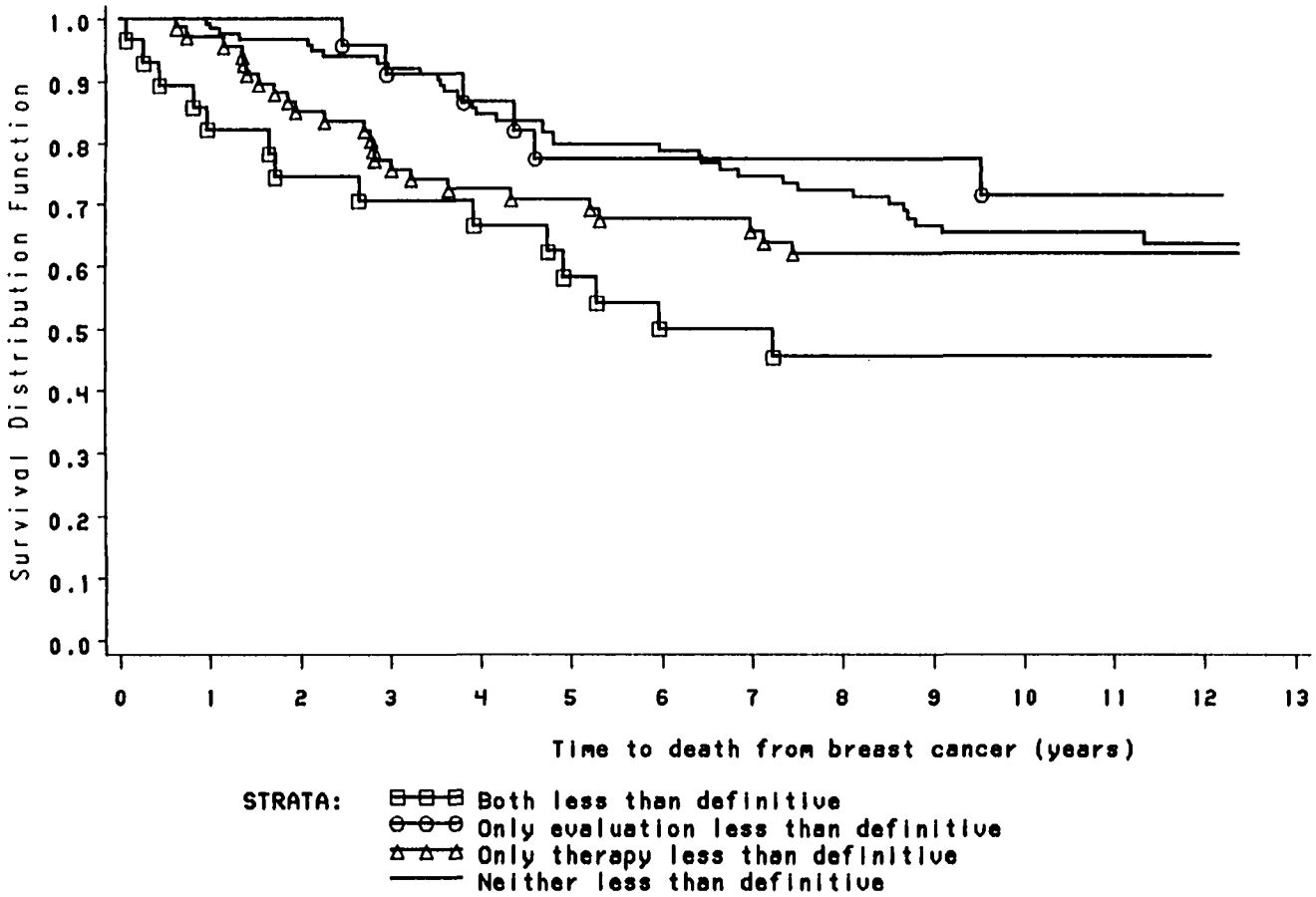

Figure 4: Time to death from breast cancer within therapy groups; limited to subjects with propensity scores below the 60th percentile

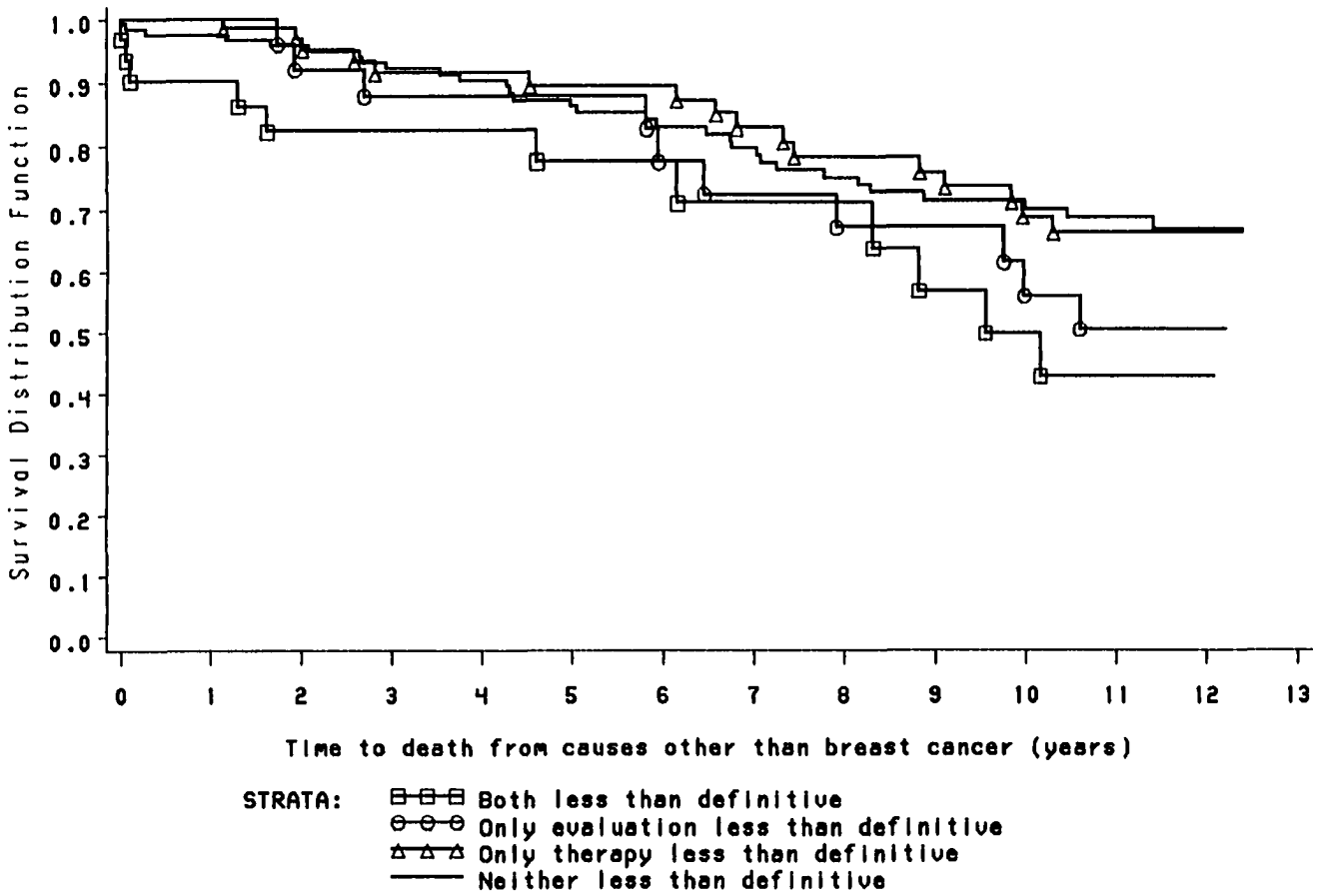

Figure 5: Time to death from causes other than breast cancer within therapy groups; limited to subjects with propensity scores below the 60th percentile

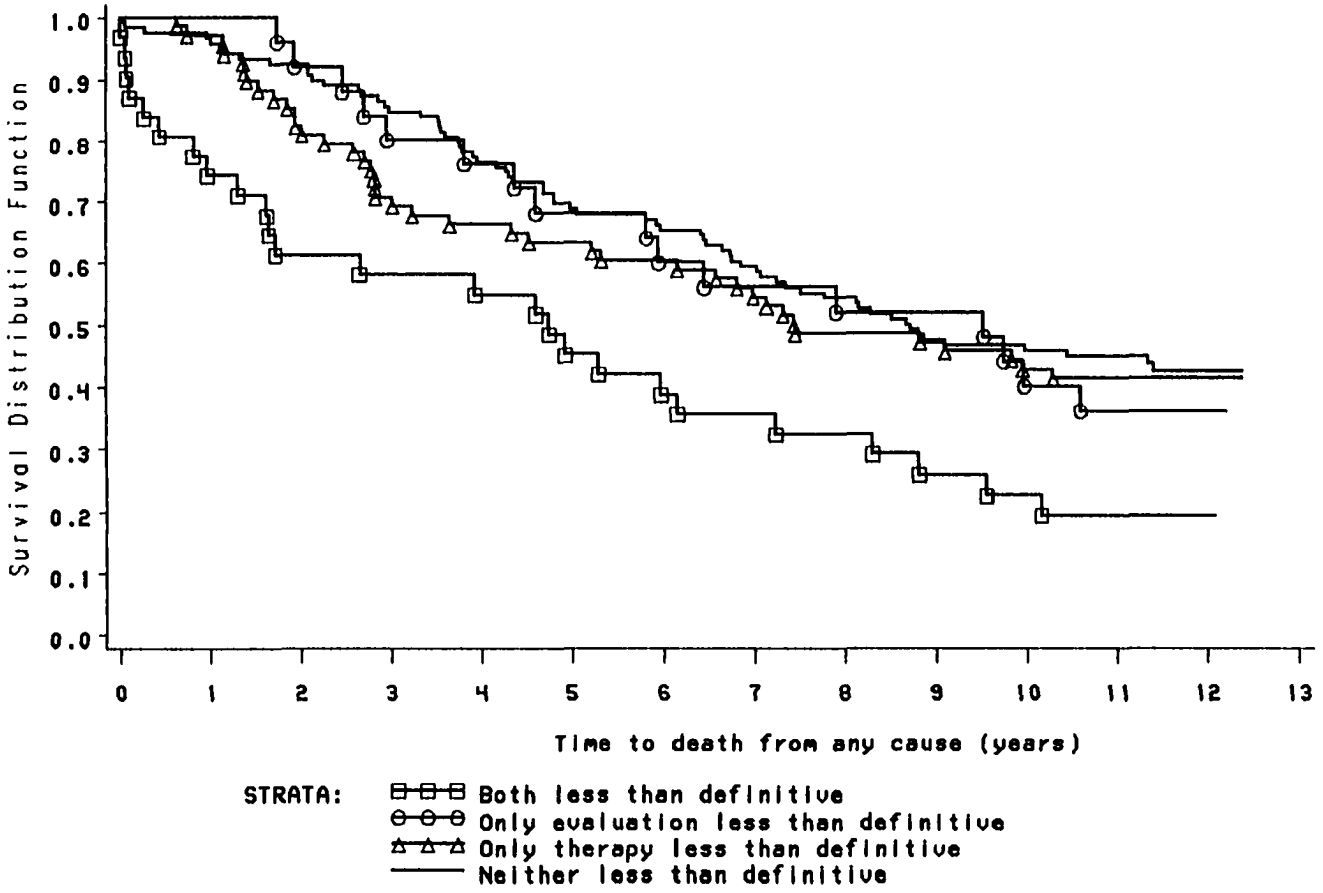

Figure 6: Time to death from any cause within therapy groups; limited to subjects with propensity scores below the 60th percentile

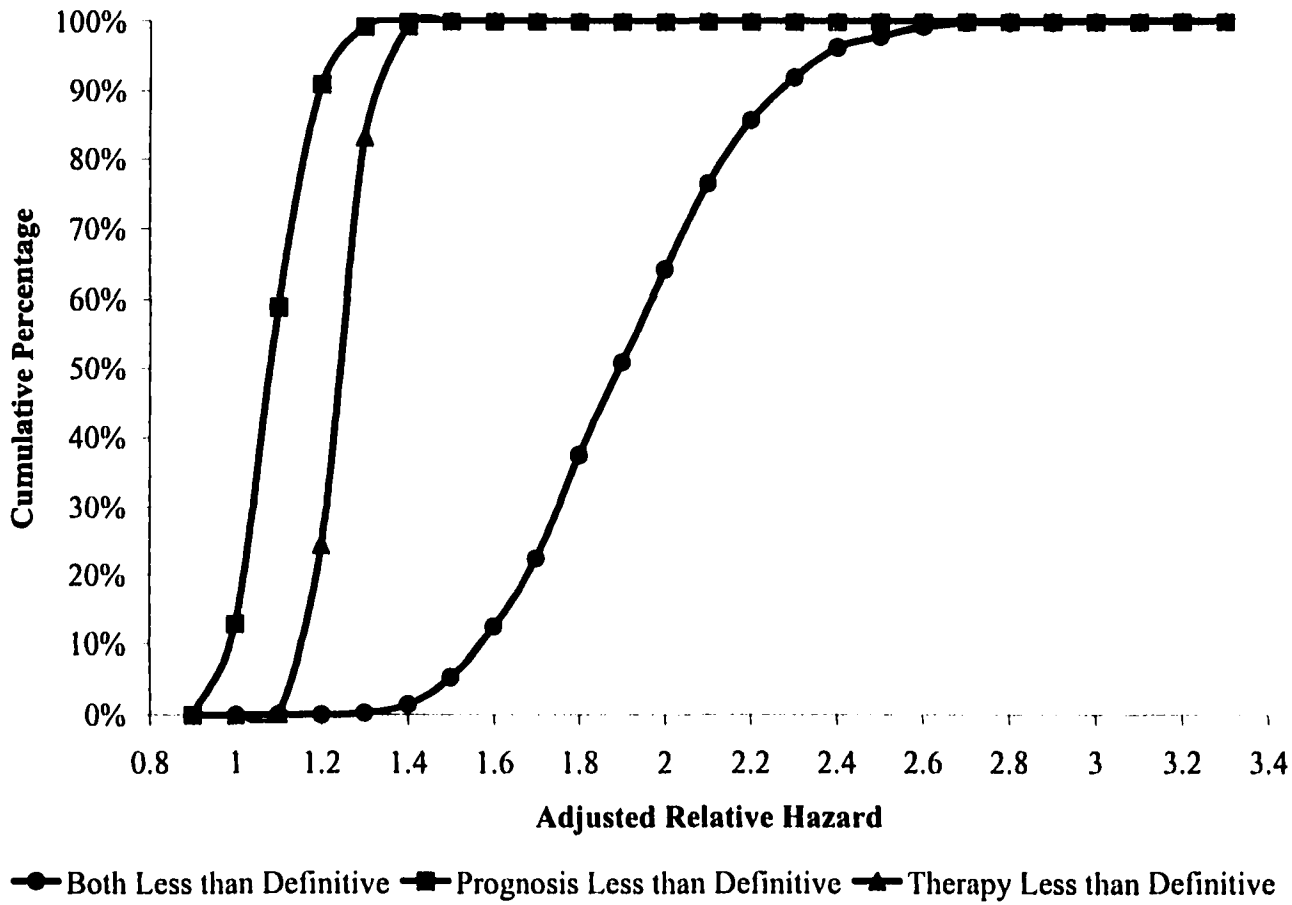

Figure 7: Sensitivity of relative hazards to misclassification of stage

5. Conclusions

Breast cancer is an important cause of morbidity and mortality among women. The American Cancer Society estimated that 178,700 women were diagnosed with breast cancer in 1998, and that 43,500 women died from the disease (1). Those women who survive the disease face short- and long-term consequences of their therapy that affect their quality of life. The preceding studies described three important aspects of public health efforts to reduce the impact of breast cancer.

The first study measured the effect of exposure to active and passive cigarette smoke on breast cancer occurrence using a case-control design. Ever-active smokers had an odds ratio of 2.0 (95 percent confidence interval 1.1–3.6) and passive-only smokers had an odds ratio of 2.0 (95 percent confidence interval 1.1–3.7) compared with never-active, never-passive smokers. Women who smoked only before their first pregnancy (OR of 5.6; 95 percent CI 1.5–21) and women who quit smoking 5 to 15 years before their index year (OR of 3.9; 95 percent CI 1.4–10) were at highest risk. Women exposed to passive smoke before age 12 years had an odds ratio of 4.5 (95 percent CI 1.2–16) among passive-only smokers and 7.5 (95 percent CI 1.6–36) among ever-active smokers. Women first exposed to passive smoke after age 12 had lower, though still elevated, odds ratios.

The measurements of relative risk in this study comport with an underlying biologic model of breast carcinogenesis. The model suggests that exposure to carcinogens before first pregnancy ought to have the largest impact on breast cancer risk. Cigarette smoking causes cancer in organs that are not in direct contact with smoke (2), but it is also anti-estrogenic (3,4). Exposure to cigarette smoke before first pregnancy should therefore increase the risk of breast cancer, while exposure after first pregnancy may reduce the risk of breast cancer. These observations suggest the need for further examination of the relation between exposure to cigarette smoke and the occurrence of breast cancer. Future studies might focus on the segregation of the effects of passive smoking and active smoking, the minimum duration and intensity of active and passive smoking necessary to initiate breast carcinogenesis, the interaction between time of exposure and milestones of breast tissue development, or the precise interval of susceptibility to smoking cessation.

The second study assessed the effect of patient characteristics and therapy on self-reported upper-body function and discomfort five months after and twenty-one months after primary breast cancer therapy. Women with a cardiopulmonary comorbidity score of four or more had an odds ratio for any early upper-body function decline of 3.6 (95 percent confidence interval 1.6–7.8) relative to women with a score of zero. The

odds of any early upper-body function decline among women who underwent axillary dissection, relative to women who did not, was 3.7 (95 percent confidence interval 1.2–11). Women who had axillary dissection were also more likely to report numbness or pain in the armpit (OR = 13; 95 percent confidence interval 1.5–117) and swelling or other arm problems (OR = 4.3; 95 percent confidence interval 0.5–37) than women who did not have axillary dissection. Finally, women who lived alone were more likely to have swelling or other arm problems than women who did not live alone (OR = 4.6; 95 percent confidence interval 1.3–16) and women with stage II disease were more likely to report swelling or other arm problems than women with stage I disease (OR = 2.2; 95 percent confidence interval 1.0–4.7).

Upper-body function is critical to maintaining independent living (5). This study suggests that clinicians should consider the functional consequences of treatment when discussing treatment options and post-operative care with older women who have early stage breast cancer. For example, women who have preexisting cardiopulmonary diseases, who live alone, or who have advanced stage breast cancer are likely to benefit from a supervised rehabilitation program. Such a program might include instructions for accomplishing common tasks with minimum pain or discomfort. Strategies to prevent overcompensation for discomfort or weakness on the side of surgery by overusing the opposite side should

also be outlined. Women who undergo axillary dissection may be another group likely to benefit from such a program, especially if they are relatively young (less than age 65 in this study) or have Stage II disease.

The third study measured the effect of less than definitive care for early stage breast cancer on recurrence and survival. Patients were diagnosed between 1984 and 1986 and were treated at one of eight Rhode Island hospitals. Three hundred and ninety women ages 45 to 90 with local or regional disease were followed through 31 December 1996. Patients who received less than definitive prognostic evaluation and less than definitive treatment had an adjusted relative hazard of breast cancer recurrence of 2.3 (95 percent confidence interval 1.3–4.0) and an adjusted relative hazard of breast cancer-specific mortality of 3.0 (95 percent confidence interval 1.6–5.4) compared with patients who received definitive care.

Effective diagnostic evaluation, prognostic evaluation, and primary therapy for early stage breast cancer has been well characterized (6, 7). Although the standard of breast cancer care enjoys a broad consensus (8, 9), this standard has not fully penetrated medical practice. The predictors of receipt of less than definitive care include — alone or in combination — patient preferences, physician preferences, the patient's age, the patient's comorbid disease status, the geographic region, and

the hospital size. While the interaction of these predictors is no doubt complex, the result of receipt of less than definitive care is straightforward. In this study, patients who received less than definitive prognostic evaluation and less than definitive primary therapy were at excess risk of breast cancer recurrence and breast cancer-specific mortality.

Most of the risk factors for breast cancer that have been identified confer excess risks of incident disease well below the excess risks of breast cancer mortality observed within the first five years of follow-up among women who received less than definitive care. The reduction of morbidity and mortality among women diagnosed with breast cancer must therefore remain a priority. One strategy is to assure that women with early stage breast cancer are treated in accordance with existing guidelines.

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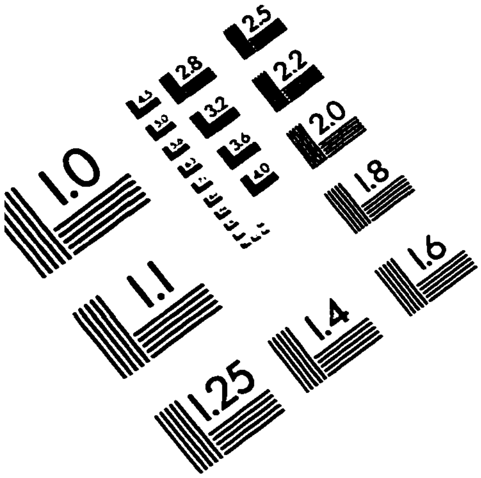
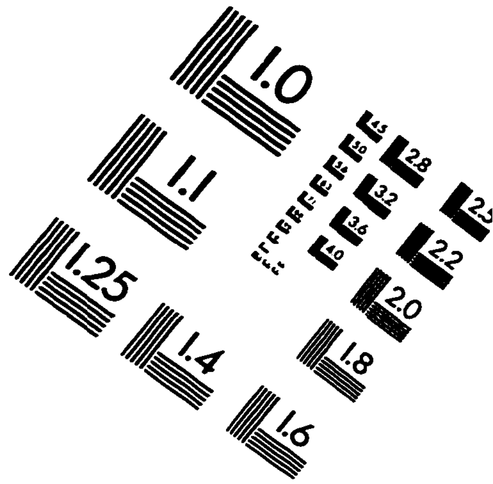
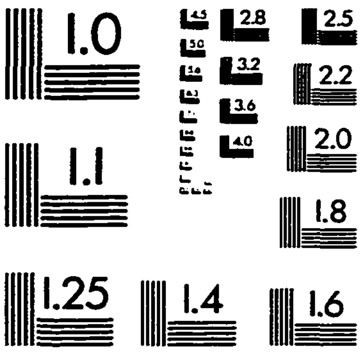
IMAGE EVALUATION TEST TARGET (QA-3)







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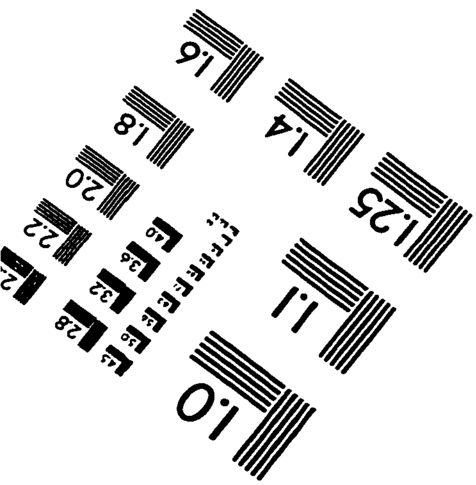

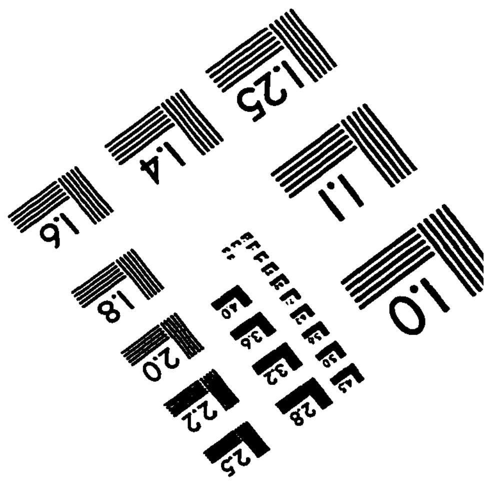

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