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Report

Reduced rates of cancer-related worries and mortality associated with guideline surveillance after breast cancer therapy

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Summary

Objective. Guidelines have been developed for appropriate post-therapy surveillance for breast cancer recurrence. Two objectives of post-therapy surveillance are to support and counsel patients and to detect potentially curable local recurrences and new cancers in the opposite breast. The objective of this investigation was to assess the impact of guideline surveillance (history, physical examination, and annual mammography) on cancer-related worries and all-cause mortality.

Study design and setting. We collected data on a cohort of 303 Massachusetts women with stages I or II breast cancer diagnosed between 1992 and 1994. Cases were women with increasing cancer-related worries or decedents. We used risk-set sampling to match five controls to each case on follow-up time. Cases and members of their matched risk set were characterized with respect to receipt of guideline surveillance and covariates preceding the date of their outcomes.

Results. The adjusted odds ratio associating guideline surveillance in the preceding year with an increase in cancer-related worries equaled 0.37 (95% CI = 0.14–0.99). The adjusted odds ratio associating continuous guideline surveillance with all-cause mortality equaled 0.66 (95% CI = 0.51–0.86).

Conclusion. The results are consistent with the stated objectives of surveillance follow-up of breast cancer patients after the completion of their primary therapy.

Introduction

Advances in the early detection and treatment of breast cancer have yielded a population of about 2 million breast cancer survivors in the United States [1]. Guidelines for their care recommend history, physical examination and annual mammography (guideline surveillance), but no surveillance with blood chemistry tests or X-rays for distant metastases unless symptoms warrant [2–5].

Post-therapy surveillance has four primary objectives [3]: (a) to provide patients with support and counseling, (b) to detect potentially curable conditions such as local recurrence of cancer in the breast following breast-conserving surgery and new cancers in the contralateral breast, (c) to provide care for patients in whom metastatic disease develops, and (d) to determine outcomes for patients enrolled in trials or for population registries.

The first objective – to provide support and counseling to patients [3, 6] – responds to patients' fear of recurrence. Breast cancer patients often report that they are reassured and less anxious after receipt of surveillance examinations [7, 8], although they may have a transient increase in anxiety in the days preceding their appointment [7, 9].

The second objective – to detect potentially curable conditions – responds to the potential for cure of local recurrence or new cancers in the contralateral breast [3, 6, 10]. Physical examination and mammography have complementary test properties for the detection of local recurrence in the ipsilateral breast among women who have been treated with breast conserving surgery [11, 12].

Asymptomatic surveillance is also aimed at detecting new primary cancers in the contralateral breast. The lifetime cumulative incidence of contralateral breast cancer among primary breast cancer patients is at least 7%, and the second primary reduces survival rates by approximately 50% [13]. Screening breast cancer survivors with mammography and clinical examination results in a significant shift toward earlier stage of diagnosis of second primaries [13].

The guideline recommendations are not based on clinical trial evidence [3, 14–16]. Moreover, in the presence of the guidelines reviewed above, new randomized clinical trials that would assign women to less than guideline surveillance are unlikely to be conducted. Measures of the effectiveness of guideline surveillance must, therefore, come from observational research – such as the findings we present here. In an earlier study [17], we characterized the tests ordered and received for

surveillance of breast cancer recurrence in this cohort, as well as the proportion of the cohort receiving guideline surveillance through their follow-up time. The objective of this investigation is to estimate the effects of guideline surveillance on the rate of cancer-related worries and mortality.

Methods

Study sample

The enrollment and data collection procedures have been described elsewhere [17, 18]. Briefly, we enrolled women 55 years old or older with stages I or II breast carcinoma [19] diagnosed at 1 of 5 hospitals in Boston, Massachusetts between 1992 and 1994. We excluded women diagnosed with any other cancer in the preceding 5 years or ever previously diagnosed with breast cancer. Eligible women were sent an introductory letter signed by their surgeon and a consent form 2–3 months after definitive surgical treatment. Shortly thereafter a trained interviewer contacted the potential participant by telephone to further explain the study, answer questions, and obtain informed consent. The Boston University Medical Center Institutional Review Board approved the study protocol.

Data collection

Data were collected for consenting participants through four telephone interviews and by reviewing patients' medical records. Data collected initially from medical records included: tumor size, axillary node status, breast surgery performed (mastectomy or breast conserving surgery, with or without axillary dissection), receipt of radiation therapy, and the presence of comorbid diseases. Verification of medical record data by one of us (RAS) re-abstracting a sample showed replicability of ≥95% for all items.

The patient telephone interviews occurred three months after diagnosis, 21 months after diagnosis, and annually thereafter. The interviews ascertained demographic variables, the Medical Outcomes Study 36-item short form (MOS SF-36) [20], and the presence of comorbid conditions. The mental health index 5 (MHI5) is a subscale of the MOS SF-36 [20] that measures general mental health. It is scaled from 0 to 100 with higher scores reflecting better mental health. The interviews also included four questions specific to patients' abilities to cope with their breast cancer diagnoses. Respondents were asked how well they were 'doing with each of the following: (a) dealing with feelings such as anger, fear, grief, and anxiety; (b) worries about your family's ability to manage if you get sicker, (c) worries about who will take care of you if you get sicker, and (d) worries about recurrence of the cancer.' Available responses were 'excellent, very good, good, fair, and poor.' From these responses, a single score standardized to a scale of 0–100 was derived to reflect how well the respondent was dealing with cancer-specific worries (Cronbach's $\alpha = 0.78$, as described by Silliman et al. [21]). Interviews began before two more well-known measures of breast cancer-related worries had been established [22, 23]. However, in a second cohort of breast cancer patients 65 years old and older, our scale correlated well ($p < 0.0001$ for all correlations) with both the MHI5 [20] and the psychosocial subscale of the CARES-SF [22]. The correlation between our cancer-related worries scale and the psychosocial subscale of the CARES-SF was stronger, as would be expected, than our scale's correlation with the general measure of mental health, the MHI5 (unpublished data).

We reviewed patients' medical records to record medical visits for breast cancer surveillance after primary therapy. The follow-up period began 90 days after the completion of primary therapy (surgery, radiation therapy, and chemotherapy, but not including hormonal therapy) because the symptoms related to initial therapy should have resolved by then. The date of completion of primary therapy ranged from October 1992 to March 1994. The medical records of each patient's surgeon, medical oncologist, and radiation oncologist – and medical notes received by these physicians from a patient's gynecologist – were reviewed through December 1999.

For each test received, we recorded the date, nature (asymptomatic surveillance or symptomatic of suspected recurrence), and specialist ordering the test. Medical record abstractors were instructed to assume that tests were ordered for asymptomatic surveillance unless the record included a specific note that the patient presented with symptoms suggesting breast cancer recurrence or second primary breast cancer. In such cases, tests were ordered with an indication to rule out recurrence, metastases, or second primary breast cancer. A note of a patient's symptoms, worries, or complaints – unaccompanied by comments reflecting the physician's concern about them being suggestive of recurrence, metastases, or second primary breast cancer – was not sufficient to code surveillance testing as symptomatic. Only tests ordered for asymptomatic surveillance were included in the exposure definitions.

Surveillance tests included in the medical record review were patient history and physical examination, mammography, liver function studies, complete blood count, carcinoembryonic antigen, chest X-ray, skeletal survey, bone scan, and liver scan. Medical record reviewers were blind to patients' interview data and vital status. It is unlikely that the medical record review affected physician surveillance practices, because the reviews occurred at irregular intervals among only a small portion of each physician's patients.

Mortality status was ascertained by matching participants' identifying information to the records of the National Death Index through 31 December 2001. Breast cancer was assigned as the cause of death to any

decedent with ICD9 code 174 appearing in the underlying cause of death field or in any line of Part I of the death certificate, as reported by the National Death Index.

Analytic variables

Dependent variables

Cancer-related worries. Women who had a MHI5 score of 60 or greater and a cancer-related worries score of 50 or greater were considered mentally healthy at baseline, so at risk for an increase in cancer-related worries over the follow-up period. We chose the MHI5 score of 60 for a cutpoint because patients with symptomatic depression [24] and women ≥65 years old cared for by mental health providers [20] both have scores below 60. The odds of a woman having a cancer-related worries score below 50 was 11-fold higher among those with a MHI5 score below 60 than among those with a MHI5 score of 60 or more.

Of the 303 women, 221 satisfied the baseline criteria, with a mean MHI5 score of 81.4. Women whose cancer-related worries score declined below 50 at one of the three follow-up interviews were classified as cases of cancer-related worry. 37 women met this case definition. For each of the 37, a set of five controls was sampled with replacement from the cohort of women who (a) satisfied the baseline mental health criteria, (b) completed at least as many of the follow-up interviews as the corresponding case, and (c) had not satisfied the case criteria by the time of the follow-up interview at which the matched case was ascertained. The study design allowed for a minimum of 12-months of follow-up for the cancer-related worries outcome. The median follow-up equaled 2.8 years with a minimum of 1.1 years and a maximum of 4.5 years.

Mortality. The primary analysis focused on all-cause mortality. Secondary analyses focused on categories of breast cancer-specific mortality and all-but breast cancer mortality. For each of the 63 decedents, a set of five controls was sampled with replacement from the cohort of women at risk of dying at the same time in their follow-up period. These controls were therefore women who enrolled in the original cohort of 303 breast cancer patients and survived at least as long as the case after completion of primary therapy. The time of follow-up began 90 days after completion of primary therapy and terminated at the date of death or completion of the follow-up period on 31 December 2001. The study design allowed for a minimum of 7.5 years of follow-up for the mortality outcome. The median follow-up equaled 7.4 years with a minimum follow-up of 10 months and a maximum follow-up of 9.5 years.

Independent variables. Guideline surveillance, versus less than guideline surveillance, was the independent variable whose effect on cancer-related worry and all-cause mortality was of primary interest. We defined guideline surveillance as an examination with asymptomatic history, physical examination, and mammography. Women who received greater than guideline surveillance, primarily additional laboratory tests, were categorized as receiving guideline surveillance since we were particularly interested in the effect of less than guideline surveillance.

Surveillance tests soon before an interview should be most protective against the cancer-related worries outcome, so we defined receipt of guideline surveillance in the year preceding the interview as the exposure variable for this outcome. Women who did not receive guideline surveillance in the year preceding the interview were the reference group.

In contrast, continuous surveillance beginning in the year after completion of therapy should be most protective against mortality, so we defined the number of consecutive years of receipt of guideline surveillance as the exposure variable for this outcome. Women who received no consecutive years of guideline surveillance were categorized in the reference group.

Covariates. Candidate covariates were patient's age at diagnosis (categories of 55–64 years, 65–74 years, and 75–90 years), primary therapy (categories of breast conserving surgery plus radiation therapy, mastectomy, or breast conserving surgery without radiation therapy), body mass index (categories of <25 kg/m^2, 25–<30 kg/m^2, and ≥ 30 kg/m^2), cardiopulmonary comorbidity index [25] (categories of 0, 1–3, or ≥4), education (<high school versus ≥high school graduate), marital status (married or living with someone versus other marital status), number of people living in the household (lives alone versus lives with others), employment status (working for pay versus other), breast cancer stage at diagnosis (stage I versus stage II), and receipt of systemic adjuvant therapy (first as any chemotherapy or hormonal therapy versus no systemic adjuvant therapy, then with categories of no tamoxifen therapy, tamoxifen therapy not completed, and completed tamoxifen therapy).

Analytic strategy

Crude

We calculated the frequency of cases and controls within the exposure variable categories. The crude estimates of effect were calculated as odds ratios using conditional logistic regression, conditioned only on the risk-set strata. Because controls were selected by risk-set sampling – which matches controls to cases on follow-up time – the conditional odds ratios estimate the relative rates of the outcomes among those who received guideline surveillance versus those who received less than guideline surveillance [26].

Multivariate modeling. Adjusted estimates of effect were obtained from a conditional logistic regression model [27], with guideline surveillance as the variable of

primary interest and the vector of candidate covariates as adjustment variables. After controlling for age group, candidate confounders were added to the conditional logistic regression model one at a time in descending order of impact on the estimate of effect of guideline surveillance until the estimate of effect changed by less than ten percent [28].

Results

Study population

Of the 388 eligible patients whose surgeons gave permission for contact, we enrolled 303 during the study period. The 85 non-participants were not enrolled because they declined to participate ($n = 39$), could not be contacted ($n = 25$), were in ill health ($n = 13$), or were non-English speaking without a translator available ($n = 8$). Nonparticipants were an average of 3 years older than participants (71.2 versus 68.4 years, $p = 0.01$), but had similar proportions of stages I and II disease as participants.

Among the 303 participants (Table 1), two-thirds of the women had stage I breast cancer and the rest had stage II disease. The majority of the women received breast conserving surgery (76%), radiation therapy (68%), and systemic adjuvant therapy (67%). Most of the women were white (93%), had at least a high school education (83%), and were not working for pay (72%).

Of the 221 women with a MHI5 score of 60 or greater and a cancer-related worries score of 50 or greater at baseline, 37 (17%) had an increase in cancer-related worries during the follow-up period. Of the 303 study participants, 63 (21%) died during the follow-up period and 27 of the deaths (43%) were attributed to breast cancer.

Table 1. Characteristics of the cohort of 303 Massachusetts breast cancer patients

Characteristic	Number	Percent
Age group		
55–64 years	126	42%
65–74 years	111	37%
75+ years	66	22%
Race		
White	281	93%
African American	13	4%
Hispanic	2	0.7%
Asian or Pacific Islander	3	1%
Other	2	0.7%
Missing	2	
Education		
<High school	51	17%
≥High school	249	83%
Missing	3	
Working full or part time for pay		
No	218	72%
Yes	83	28%
Missing	3	
Number in house		
Lives with someone	197	66%
Lives alone	103	34%
Missing	3	
Marital status		
Other than married	153	51%
Married or living with someone	148	49%
Missing	2	
Tumor stage		
Stage I	193	64%
Stage II	109	36%
Missing	1	
Cardiopulmonary comorbidity score		
0	180	59%
1, 2, or 3	73	24%
4–15	50	17%
Primary surgical therapy		
Mastectomy	71	24%
Breast conserving surgery	228	76%
Missing	4	
Radiation therapy		
No	97	32%
Yes	206	68%
Systemic adjuvant therapy (chemotherapy or hormonal therapy)		
No	99	33%
Yes	204	67%

Cancer-related worries

Table 2 shows the distribution of cases of increased cancer-related worries and risk-set controls within the guideline surveillance groups, collapsed across risk-set strata. The crude estimate of the effect of guideline surveillance in the year before interview, compared with receipt of less than guideline surveillance, equaled an odds ratio of 0.50 (95% CI = 0.20–1.27, Table 2). The age-adjusted estimate of effect equaled 0.37 (95% CI = 0.14–0.99, Table 2). None of the candidate covariates confounded the estimate of effect after control for age group.

Mortality

Table 3 shows the distribution of decedents and risk-set controls within the guideline surveillance groups, collapsed across risk-set strata. The crude estimate of the effect of a consecutive year of guideline surveillance, compared with receipt of no consecutive years of guideline surveillance, equaled an odds ratio of 0.62 (95% CI = 0.48–0.80, Table 3). The age-adjusted estimate of effect equaled 0.66 (95% CI = 0.51–0.86, Table 3). None of the candidate covariates confounded the estimate of effect after analytic control for age group. The adjusted estimates of effect on breast cancer-specific mortality (OR = 0.76; 95% CI = 0.52–1.1) and

Table 2. Crude distribution of cases of increased cancer-related worries and their matched controls and odds ratio estimates of effect [OR (95% CI)]

	Guideline surveillance in the year before interview	Less than guideline surveillance in the year before interview
Cases/controls	5/48	32/137
Crude conditional OR	0.50 (0.20, 1.3)	1
Conditional OR adjusted for age	0.37 (0.14, 0.99)	1

Table 3. Crude distribution of all decedents and their matched controls and odds ratio estimates of effect [OR (95% CI)]

Consecutive years of guideline surveillance	All cause mortality cases/controls
Zero (reference)	43/134
1 year	7/57
2 years	8/39
3 years	3/48
4 or more years	2/37
Crude conditional OR (per consecutive year of guideline surveillance)	0.63 (0.51, 0.79)
Conditional OR adjusted for age (per consecutive year of guideline surveillance)	0.66 (0.53, 0.83)

all-but breast cancer mortality (OR = 0.69; 95% CI = 0.48–0.99) were similar to the effect on all cause mortality. The distributions among breast cancer decedents of consecutive years of guideline surveillance were equivalent in strata of stage and primary therapy type (data not shown). Neither the baseline MHI5 score (OR for 10 point increase = 0.93; 95% CI = 0.80–1.1) nor the baseline cancer-related worries score (OR for 10 point increase = 0.98; 95% CI = 0.84–1.1) were associated with all-cause mortality.

Discussion

The crude and adjusted estimates of effect differ little in their magnitude and precision. All suggest that breast cancer patients who received guideline surveillance had reduced rates of cancer-related worries and mortality over the follow-up period compared with breast cancer patients who did not. The absence of confounding effects is consistent with the absence of predictors of guideline surveillance previously observed in this cohort [17]. That is, while there may be other important influences on these outcomes – such as stage, therapy, and demographic factors – these influences do not affect receipt of guideline surveillance; so do not confound the relations. The absence of confounding by stage held true when stage was analyzed with its separate components of tumor size and node status (data not shown).

The reduced rate of cancer-related worries associated with guideline surveillance testing agrees with earlier work by Kiebert and colleagues [29]. They reported that cancer patients had a positive attitude toward cancer surveillance one month before a scheduled appointment, at the appointment, and two weeks after the appointment. Furthermore, patients reported less fear of recurrence two weeks after their appointment than on the day of their appointment. There was no difference in overall quality of life at the three time periods. The specificity of the anxiety in this study, and in ours, suggests that cancer-specific worries may be decreased by surveillance visits and testing [30].

The observed reduction in mortality may be viewed with some skepticism. Despite the guideline's objective of detecting local recurrences and second primary breast cancers at a treatable stage, it is often held that surveillance testing affords no survival benefit [7, 31–34]. This sentiment likely derives from three sources: (a) the notion that recurrent breast cancer is incurable, (b) the perception that clinical trials of surveillance testing have had null results, and (c) the observation that comparisons of survival among women with local, regional, or distant metastases detected asymptomatically versus symptomatically have failed to demonstrate a difference. None of these sources directly refutes the potential protective effect of guideline surveillance on survival.

First, local recurrences of breast cancer can be effectively treated. The 5-year survival rate for breast cancer patients following local recurrence is approximately 75% [35–37]. Second, clinical trials of the effectiveness of post-therapy surveillance have compared intensive surveillance (e.g., bone scan, liver sonography, chest X-ray, and laboratory tests) with less intensive surveillance (e.g., physical examination and annual mammogram) [38]. No substantial difference in all-cause mortality was observed for these two regimens over 6-years of follow-up, nor were there differences in self-reported quality of life. Another trial of intensive surveillance versus clinical surveillance observed that recurrences were detected earlier among women with intensive surveillance, but that the mortality rates were equivalent [39]. Neither of these trials was designed to

assess whether current guideline surveillance confers benefits compared with less than guideline surveillance [38, 39], and a recent systematic review pointed out that no such trials have been conducted [16].

Last, it is true that comparisons of breast cancer patients with local/regional recurrences or distant metastases detected asymptomatically by intensive surveillance, versus those diagnosed symptomatically, have observed no substantial differences in survival [33, 40–45]. These comparisons are directed at assessing the effect of surveillance procedures such as chest X-ray on metastatic disease. They do not address the effect of guideline surveillance on local recurrences and their outcomes.

Our findings must be considered with the following limitations in mind. First, the study population was restricted by age, geography, and calendar period, and was limited to patients treated at five Boston hospitals. Although these hospitals included a community hospital, a city hospital, and major academic hospitals, the study findings may not generalize to other settings.

More importantly, we were unable to review the medical records of patients' primary care physicians. Tests ordered by primary care physicians were not, therefore, included in the ascertainment of receipt of guideline surveillance. In a 5-year Canadian cohort study of 183 stage I breast cancer patients, medical oncologists and surgeons accounted for a total of 82.5% of surveillance tests [46]. Primary care physicians accounted for only 17.5% of surveillance tests. Multidisciplinary cancer teams seldom include family physicians, particularly in cities, perhaps reflecting patient preference for follow-up by cancer specialists [6, 7, 47]. We expect that few of the women classified as receiving less than guideline surveillance received guideline surveillance from their general practitioner, and it is unlikely that this misclassification of guideline surveillance status depended on the outcomes. The non-differential underascertainment of guideline surveillance examinations may have biased the estimates of effect toward the null.

Next, restricting our cancer-related worries population to women who had a MHI5 score of 60 or greater at baseline lead to a study sample whose average mental health was higher (mean MHI5 81.4) than those reported by other investigators (range of mean MHI5 73.4–79.5) [20, 21]. In addition, the majority of the women who reported cancer-related worries did so within the first 24 months after primary therapy. Fifty percent of the cases occurred within the first 12 months and 75% by the second year of follow-up. Women may be at lower risk for a decline in cancer-related worries the longer they survive asymptomatically. Whether this is because women's cancer-related worries decrease naturally as they move further away from diagnosis and primary therapy or because they received guideline surveillance testing cannot be resolved by the findings of this study.

Finally, we ascertained vital status by matching identifying characteristics with the National Death Index. The National Death Index has consistently been shown to have high sensitivity and specificity for death ascertainment. The accuracy of ascertaining mortality outcomes should be independent of guideline surveillance classification, since those who matched participants to the mortality databases were blinded to the surveillance history of the participants. We expect to have few, if any, false-positive decedents and non-differential sensitivity of mortality ascertainment, the combination of which is expected to yield an unbiased estimate of relative effects [48].

Our findings are consistent with the stated objectives of the published guidelines for follow-up care of breast cancer survivors [2, 3]. That is, breast cancer patients who receive regular follow-up care receive support, counseling and reassurance that stabilize or improve their quality of life, particularly regarding cancer-related worries. Their reduction in cancer-related worries is borne out by the reduced rate of mortality. The lower mortality rate of women who receive continuous guideline surveillance may derive, in part, from detection of local recurrences or second primary breast cancer at an earlier stage with better prognosis. It may also derive, in part, from preventive medical care, which is received more regularly by breast cancer survivors than by matched controls [49]. The expected impact of guideline breast cancer surveillance – in conjunction with preventive care for other diseases – would be to reduce the rate of mortality from both breast cancer and other causes of death, just as we observed.

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