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The relation of breast cancer staging to screening protocol compliance: a computer simulation study

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Abstract

A computer model based on relational database techniques was used to analyze the relationship between staging and population compliance to a breast cancer screening protocol. Stage distribution data permitted estimates of compliance to the protocol. This relationship followed the equation $y = 5.83e^{-2.44x}$ where y was compliance and x was disease stage. Application of this equation to SEER and NCDB data estimated that the levels of compliance never exceeded 16 percent. Results indicated increasing clinical Stage IV disease as population compliance decreased. As the clinical staging increased there was increased sub-clinical Stage IV disease. With regular screening, simulation suggested that mortality would decrease.

Keywords: Breast cancer screening; Compliance; Computer simulation; Sub-clinical disease; Thresholds; TNM staging

1. Introduction

Several organizations have emphasized that screening procedures for breast cancer should be carried out by defined protocols [1]. These include the American Cancer Society (ACS), the American College of Physicians (ACP), the American College of Radiology (ACR), and the United States Preventive Services Task Force (USPSTF) among others [2,3].

In theory following, a protocol should lead to earlier detection, less advanced stage of disease and decreased mortality. The screening recommendations are put forth with the expectation that women will adhere to a protocol with a high level of compliance. Among the various reported studies on

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the efficacy of screening there was sizeable variation in the techniques used [4–6]. Some reports have had age limitations. The intervals between screens have varied from 18–24 months [7] to 24–33 months [8,9]. Sickles and Kopans [10] have analyzed the deficiencies in the studies of breast cancer screening data. Among the deficiencies they cite the effects of dilution from noncompliance. This is evident in the meta-analyses performed by several groups wherein the data indicate a decrease in participation or is not considered after the first round of screening in virtually all studies [11–13]. Given the extensive time consumed by clinical studies and the decreased participation with time, it appears reasonable to question whether another approach could be employed to obtain useful information. Several models have been published that used mathematical computation or simulation to screen for disease [4,14–17]. Habbema and co-workers developed a simulation program to study screening for disease [18] which they later applied to screening for breast cancer [19]. In these studies the simulations were based on the time of clinical diagnosis, and in some instances sojourn time was extrapolated [20–22]. Mortality rates were estimated from the growth rates of the tumors. In none of these studies were the effects of compliance with a defined protocol evaluated.

Breast cancer conventionally is staged to indicate the severity of disease based on the extensiveness of the disease process. Based on the stage of disease several questions can be raised. Is there a relation between compliance with a screening protocol over a lifetime and the staging of breast cancer at the time of clinical diagnosis? If there is a relationship, does compliance with a screening protocol influence staging such that Stage IV disease, a marker for mortality, can be reduced or perhaps eliminated?

Using the hypothesis of Gould and co-workers [23] that cancer may originate from a single cell, the model employed in the present study permits determination of when the first malignant cell appears, when tumor growth is diagnosable and when it spreads to the axilla and/or to distant sites [24]. The model's computer program permits the simulation of a cohort to examine a variety of questions, but this study was directed at examining the questions posed above.

2. Methods

The present study employs computer simulation based on a model structured in Microsoft ACCESS 2000, a relational database system. Data were collected on forms that defined cohort characteristics and controlled data processing. Compliance in this study was based on a uniform application of the recommendations of the ACS. In this investigation, cohorts of 10,000 individuals were simulated from birth to death using discrete event analysis, representing a longitudinal study over time.

The events, including breast cancer, were analyzed and stored over the lifetime of the individual. The constraints of software and hardware limited cohort size to 10,000 individuals. Each simulation was repeated a minimum of five times for each level of compliance. Compliance was studied at 100, 75, 50, 25, 20, 15, 10, 5 and 0 percent over the lifetime of each individual in the cohort. The data obtained from each simulation was recorded in a spreadsheet program, EXCEL (Microsoft Corporation, Roselle, IL, 1998).

The TNM staging method published by the American Joint Cancer Committee (AJCC) was used to classify the stage of disease for each simulated case. As specified by the AJCC five stages exist from Stages 0 to IV. For the analysis, each of the five stages, 0–IV, was assigned a corresponding numeric value from 0 to 4 and treated as a random variable. Each individual with breast cancer was

Table 1
Basic input values used by the model in simulation

Model components	Data source	Value or median (cm^3)	95% range
Cell size	Constant	1.00E-9	None
Maximum tumor volume	Constant	1.00E+3	None
Primary tumor growth rate	Lognormal distribution	1.52E-2	(4.23E-3–5.49E-2)
Invasive threshold	Lognormal distribution	1.11E-2	(2.25E-5–47E+0)
Axillary node threshold	Lognormal distribution	1.16E-1	(5.57E-4–2.39E+1)
Metastatic threshold	Lognormal distribution	2.36E+1	(1.20E-1–4.45E+3)
Axillary node diagnostic threshold	Constant	1.00E-6	None
Metastatic diagnostic threshold	Constant	6.54E-2	None

then staged. The fractional distribution of stages was then calculated by dividing the total number of individuals in a stage by the total number of individuals with breast cancer. The mean of this distribution was determined by multiplying the numeric value of each stage by its corresponding fraction and summed. The results of the summation represent the weighted mean of the stage distribution. The mean stage was used to describe a relationship to the level of compliance and was not considered a measure of the severity of disease.

Using Excel, linear, exponential, and logarithmic curve fitting was used to investigate the mean clinical stage and patient compliance. An exponential relation provided the best fit. The effect of increasing patient compliance on disease stage and the prediction of Stage IV breast cancer was then studied. The model permitted staging based both on clinical disease and co-existing sub-clinical disease when present. Differences between staging based on the clinical and sub-clinical information were determined.

The basic data used by the model are illustrated in Table 1. These data are used as thresholds that define transitions from one tumor state to another. Growth of tumor starts with the first malignant cell and follows Gompertzian growth over the duration of the tumor's existence. The Gompertzian functional aspects of the model were validated by comparing a clinical survival curve with the results of simulations [24]. Data sources include general mortality statistics, breast cancer incidence, and distributions of tumor growth rates. In Table 2 sensitivity and specificity data are presented which were used for self, clinical and mammographic examinations. These data are used as thresholds that vary with the size of the tumor and define levels of detectability. The screening protocol employed in this study was that of the ACS prior to 1997. Details of the ACS protocol are presented in Table 3. The complete details of the model used in this study are presented in a previous paper [24].

Some events in the model were determined using the Monte Carlo process. Non-Monte Carlo events were determined by a method dependent upon changes in tumor volume. When the first

Table 2
Screening tests characteristics

Test	Sensitivity (%)	Specificity (%)
Self breast exam[a]	80	75
Professional breast exam[b]	90	80
Mammography[c]	71/89[d]	93
Fine needle biopsy	95	95
Open biopsy	100	100

[a]Tumor volume dependent, maximum at 33.5 cm^3
[b]Tumor volume dependent, maximum at 33.5 cm^3
[c]Tumor volume dependent, maximum a 1 cm^3
[d]Premenopause/menopause

Table 3
ACS guidelines for breast cancer screening prior to year 1997

	Self-exam	Professional-exam	Mammogram
ACS	>Age 20, monthly	Ages 20–40, q 36 months; >Age 40, q12 months	Ages 40–49, q12 or 24 months; >Age 50, q12 months

malignant cell is introduced the thresholds related to tumor progression are assigned using the individual thresholds chosen from distributions using the Box and Muller equation for simulating continuous random variables. These thresholds for progression are based on tumor growth. Since the thresholds are randomly assigned the events related to spread of tumor are not necessarily sequential. When the tumor volume exceeds the threshold a new disease phase exists.

The data obtained reflect the growth and spread of a tumor over its existence. Importantly the staging of breast cancer is possible from the clinical standpoint. But also, it is possible to identify disease in a phase that is below threshold of detectability of a screening test, referred to as sub-clinical disease.

3. Results

The simulation uncovered a relationship between compliance to a screening protocol and the clinical stage of disease at the time of detection. Changes in the distributions of stages in relation to levels of compliance based on the ACS protocol are shown in Table 4. As compliance decreased, there was a reduction in the percent of cases in lower stages and an increase in higher stages, most notable in clinically diagnosed Stage IV. Conversely, with greater compliance there are more individuals at lower stages and fewer in the higher stages. The mean stage increased progressively as the level of compliance decreased. The relationship between the mean stage and the percent compliance is depicted in Fig. 1. The equation selected to demonstrate this relationship was obtained

Table 4
Changes in the distribution of clinical stages as influenced by differing levels of compliance to the ACS protocol

Percent compliance	Stage 0	Stage I	Stage II	Stage III	Stage IV	Mean stage
100	305 (20.6%)	922 (62.4%)	251 (17.0%)	0 (0%)	0(0%)	0.96
75	249.6 (17.9%)	811 (58.3%)	327 (23.5%)	0 (0%)	4.4 (0.3%)	1.07
50	215.1 (14.9%)	829 (57.5%)	394 (27.3%)	0 (0%)	2.9 (0.2%)	1.13
25	168 (11.6%)	710 (48.8%)	558 (38.4%)	6 (0.4%)	12 (0.8%)	1.30
20	120 (9.1%)	602 (45.6%)	569 (43.1%)	8 (0.6%)	20 (1.5%)	1.40
15	112 (9.3%)	489 (40.5%)	565 (46.8%)	8 (0.7%)	33 (2.7%)	1.47
10	69 (5.2%)	446 (33.4%)	731 (54.7%)	24 (1.8%)	67 (5.0%)	1.68
5	56 (4.3%)	297 (22.6%)	747 (56.7%)	76 (5.8%)	141 (10.7%)	1.96
0	7 (0.6%)	2 (0.2%)	627 (52.9%)	237 (20%)	312 (26.3%)	2.71

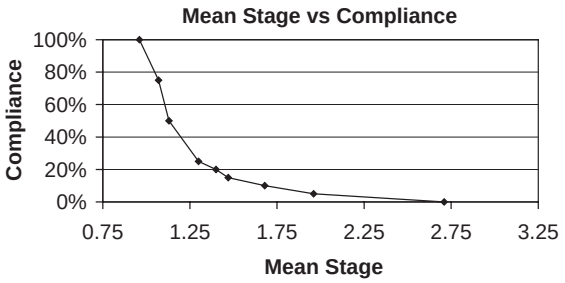


Fig. 1. Depicts the relationship between mean stage and compliance using the ACS protocol. The curve between the mean stage interval of 1.25 and 1.75 was fit with the equation $y = 5.83e^{-2.44x}$.

with the exponential fit $y = 5.83e^{-2.44x}$, $R^2 = 0.9814$, where y represents compliance and x represents clinical mean stage. This equation was fitted with data points between the mean stage interval 1.25 –1.75 and corresponded to compliance of approximately 30–10 percent.

Since compliance influences the mean stage of a population, then conversely the mean stage was used to estimate the level of compliance. The data for mean stage were obtained from published information from two national breast cancer databases [25,26]. Table 5, shows the relationships of mean stage obtained from SEER and NCDB data to calculate percent compliance from the exponential fit. This use of the mean stage is applicable within the limits of the exponential equation previously given and indicates that the level of compliance did not exceed 16 percent.

Even with 100 percent compliance with the ACS protocol there are limitations. Data presented in Fig. 2 illustrates one limitation with annual mammography. This individual was studied by simulation monthly to the time the first malignant cell appeared at 589 months (age 49). Although tumor was growing she did not begin annual mammography until about 604 months (age 50.3). The next four annual mammograms were negative, and by time the fifth mammogram was positive there was already spread to the axilla. From the time the first malignant cell appeared to the time a mammogram was positive 5.4 years had elapsed. Staging at this time indicates she has Stage II disease.

Table 5
Relationships of mean stage determined from national data to calculated percent compliance based on the exponential equation

	Mean stage	Compliance (%)
SEER[a] 1983–1987	1.70	9.3
SEER 1989–1995	1.48	15.9
NCDB[b] 1989	1.56	13.5

[a]Surveillance, epidemiology, and end-results.
[b]National Cancer Data Base.

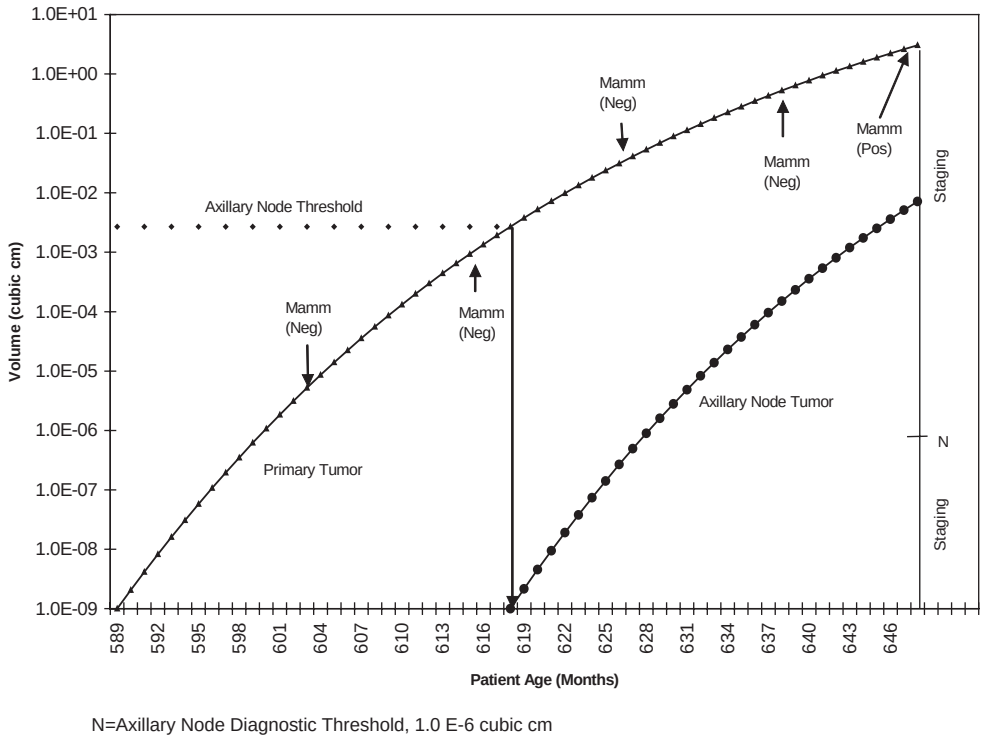
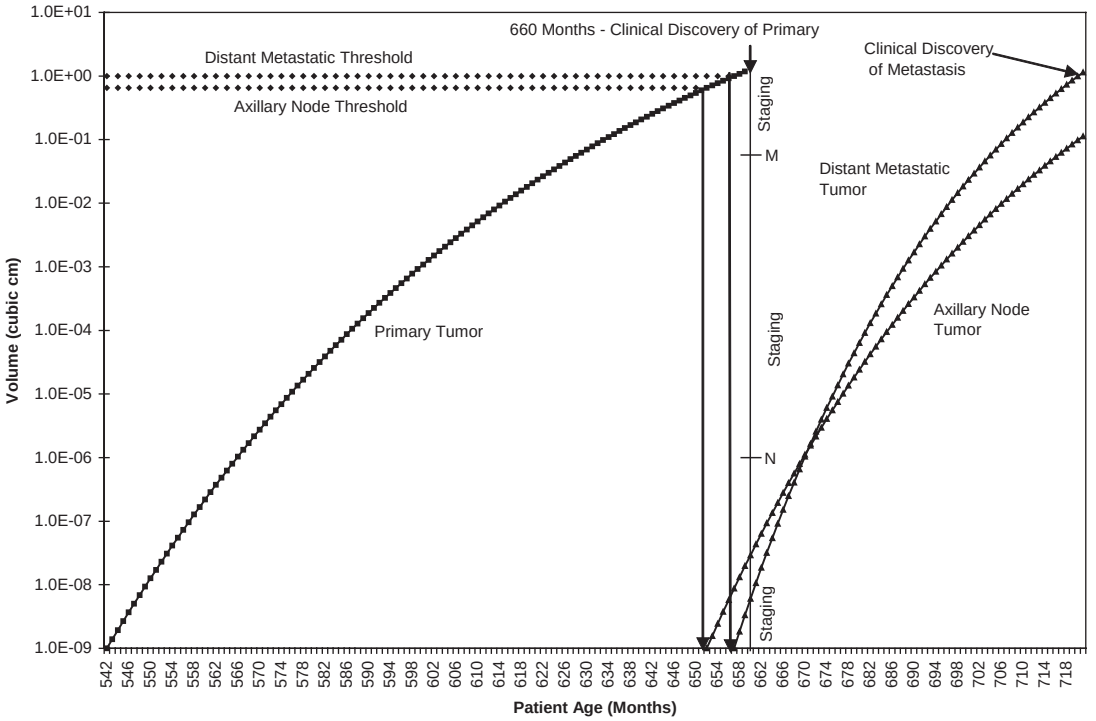


Fig. 2. Illustrates the limitations of 100 percent compliance with annual mammographic screening. Although a breast cancer was already growing, mammography fails to detect its presence because of the imperfections of this examination. By the time a positive mammogram was obtained the tumor had already spread to the axilla.

Fig. 3 illustrates another problem in staging for disease. This woman was staged at the time of clinical diagnosis and she was categorized as having Stage 1 disease. The reality is that the tumor was not only present in the axilla but had spread to a distant site. However, the distal metastasis would not become clinically apparent for another 5 years. The model assigns an estimated 2 years of life after distant metastasis is clinically diagnosed, so in this individual the total course of her disease to death was approximately 17 years. This example raises the new question regarding the



N = Axillary Node Diagnostic Threshold, 1.0 E-6 cubic cm
M = Metastatic Diagnostic Threshold, 1.0 E-1 cubic cm

Fig. 3. Demonstrates a pitfall in staging based on clinical findings. Almost 10 years after the appearance of the first malignant cell the clinical diagnosis was made. At this time the primary tumor had already spread to the axilla and a distant site. Staging based on finding the primary tumor would classify the individual as Stage I since the spread had not been detected. The fact was that the individual was actually a Stage IV but the distant metastasis would not become clinically apparent for another 5 years.

relation of staging to the distribution of clinical disease. When a cohort of 10,000 is simulated, Table 6 depicts the relation of clinical staging and the frequency of sub-clinical disease. As each clinical stage increases from Stages I to III, the amount of sub-clinical Stage IV disease increases.

4. Discussion

Prior to the present study other investigators have concentrated on estimating tumor growth from clinical observation. The study of Walter and Day is a case in point [22]. They developed a method for estimating the duration of the pre-clinical state. They took this period to be the time the disease became detectable by screening to the time it became symptomatically invasive, indicating at this point the tumor is diagnosed. This interval is considered to be the sojourn time. Similar definitions of sojourn time have been used by Spratt et al. [20] and Shen and Zelen [21]. Walter and Day note that prior to screening detectability there is the biological onset of disease that is manifested at an earlier

Table 6
The effect on clinical staging with inclusion of sub-clinical disease in a cohort of 10,000. Note that as clinical staging increases the amount of sub-clinical disease also increases

Staging based on clinical diagnosis (number)	Staging distribution including sub-clinical disease (number)	Percent of actual Stage IV in each category
I (598)	I (371) II (220) IV (7)	1.2
II (580)	II (474) III (21) IV (85)	14.7
III (78)	III (24) IV (54)	69.2
Total (1256)	(146)	11.6

time, but they do not study the growth period from this earlier time to screening detectability nor did they study the point in time at which metastasis occurred [22]. In the period when screening could detect tumor, if screening was performed, the result might be negative. This result was considered a false negative.

The present study uses a different approach. The onset of disease is defined by the appearance of the first malignant cell. From this point, the tumor is growing at a rate that may be different among different individuals. But current technology does not permit its detection because the tumor has not reached its assigned threshold for detectability, and this is referred to as sub-clinical disease. When the tumor growth has exceeded the assigned threshold, it is potentially detectable. Whether it actually is found may depend on the sensitivity of the screening test used. This is illustrated in Fig. 2, where several annual mammograms were negative before one was positive. Since the simulation indicated the presence of tumor, the negatives tests were all false negatives.

Based on the AJCC protocol for clinical staging of tumor the data in Table 4 indicates that as the level of compliance with the ACS screening protocol decreases the amount of clinical Stage IV disease increases. It should be emphasized that Table 4 indicates a lack of clinical Stage IV disease only when there is 100 percent compliance with the defined protocol. Given 100 percent compliance, 83 percent of tumors would be classified no greater than clinical Stage I. It is generally recognized that there may be fatalities even among individuals who are Stage I at the time of clinical diagnosis. The model demonstrates that there may be sub-clinical metastatic disease even at the level of Stage I clinical disease. This underscores the presence of fatalities when one might anticipate a cure. This observation that there may be ultimate mortality with clinically small tumors is in agreement with the findings of Tabar et al. [27] and Paci and coworkers [28].

The staging method of the AJCC has been used as a standard since 1977 [25]. In this standard staging is carried out at the time of clinical diagnosis. Similarly the model also stages at the time

of clinical diagnosis. The equation, $y = 5.83e^{-2.44x}$ where y represents compliance and x represents mean stage based on the AJCC standard, was applied to other data that also used the AJCC standard. From the stage distribution the mean stage was determined. Given the mean stage the level of compliance was calculated. Applying these concepts to recent SEER and NCDB data it was found that compliance in these sets of data was low.

A number of studies report decreased mortality in a screened population [12,13,29], although others have not found such benefit [5,30–32]. The data in the present study are consistent with previous reports that screening can reduce mortality. Considering the potential for reducing mortality with adherence to screening, efforts should be directed at improving compliance, at least until more efficient screening techniques are developed.

5. Summary

The present study was designed to examine the relation of breast cancer staging to compliance with a defined protocol using simulation, employing a model previously published. The technique used was based on a relational database system, and involved simulating cohorts of 10,000 women over a lifetime. Based on the incidence of breast cancer a Monte Carlo process determined which women and at what time women would develop cancer originating with the first cell. When the first malignant cell is introduced the thresholds related to tumor progression are assigned using the individual thresholds chosen from distributions using the Box and Muller equation for simulating continuous random variables. When the thresholds were exceeded, a new disease status emerged. This was based on tumor growth and defined spread to the axilla and to distant sites. Using this approach an equation was developed that expressed a relationship between staging of a tumor at the time of clinical diagnosis and adherence to a screening protocol. Staging was performed according to the definitions of the AJCC and ranged from Stages 0 to IV.

The results indicated that as the level of compliance with the protocol decreased the amount of clinical Stage IV disease, which was a marker for mortality, increased. In addition it was found that the amount of sub-clinical Stage IV disease, which could not be diagnosed by any available tests, rose progressively as the clinical stage rose from Stages I to III. The presence of sub-clinical Stage IV disease helps explain why some women with small tumors may already have distant spread that will result in a fatality. Problems with clinical staging are illustrated by specific examples. Considering the potential for reducing mortality with adherence to screening, efforts should be directed at improving compliance, at least until more efficient screening techniques are developed.

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