A Hypothesis for the Natural Time History of Breast Cancer

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SUMMARY

A new method of analysis is developed for inferring the natural history of a disease using only the information available on a patient at time of treatment. The technique is applied to the study of breast cancer and has resulted in a coherent theory of breast cancer which accounts for many biologic variables simultaneously. Among the findings are: (a) There are at least four distinct time histories. (b) The four histories divide into two pairs such that the onset of the disease in one pair precedes that of the other pair by eight years. This accounts for the break in age-incidence rate reported by other investigators. (c) Early diagnosis combined with radical mastectomy increases survival time for only one time history, whereas early diagnosis in the other time histories does not result in an appreciable increase in longevity. (d) Radical mastectomy does not appear to be effective in significantly prolonging survival for these latter time histories. (e) The first biological event in time which occurs in the four time histories is that the degree of sinus hyperplasia of the axillary lymph nodes changes from favorable to unfavorable status. (f) The nuclear grade of the primary tumor does not change with time.

INTRODUCTION

This paper outlines a new quantitative method for studying the natural history (untreated) of chronic diseases using only the information available at the time of treatment. This method is then applied to a series of treated breast cancer cases to obtain a model for the time history of untreated mammary carcinoma. Study of the natural history of a disease is important for prognosis, evaluation of therapy, and possibly to give leads for new forms of therapy. However, such studies are difficult, as once a disease is diagnosed and therapy given its natural course may be changed. Occasionally the study of the natural history of a disease is attempted by analyzing data on patients from an earlier epoch when the method of treatment was not effective. Studies of this kind are handicapped, since usually only fragmentary information is available on the biologic events preceding the diagnosis of the disease. The technique introduced in this paper is capable of many extensions and can be formulated more precisely as a mathematical model. However, such generalizations and mathematical developments are reserved for future papers.

The main purpose of this paper is to infer a hypothesis for the natural history of untreated mammary carcinoma and to use the natural history to evaluate the effect of surgery and early diagnosis in prolonging survival. This disease is the most prevalent of neoplastic diseases with respect to women and has motivated more studies than has any other single organ site of cancer. Despite such attention there is controversy about fundamental aspects of the disease. Recently Maedonald (17) has reopened the issue of biologic predeterminism. He has used observations on the growth of mammary tumor cells to reinforce the evidence that early diagnosis of breast cancer may not result in longer life. A controversy even exists about the preferred treatment. Although radical mastectomy is the operation of choice for over fifty years, there has arisen a difference of opinion whether a radical mastectomy with resection of internal mammary nodes (extended radical mastectomy) or a simple mastectomy (combined with radiation therapy) may possibly have the same therapeutic benefit. There is even doubt as to the therapeutic value of surgery at all! Park and Lees (23), in a very thoughtful article, conclude that surgery is palliative or, at best, increases the five-year survival rate by five to ten percent.

There are conflicting claims about the effect of age on prognosis. Bloom (6) summarizes the evidence with respect to age and finds no relationship between age and prognosis. On the other hand several investigators, cf. Geschichter (13), Small and Dutton (24), find that prognosis is poorer for younger women. The proponents of the age relationship maintain that breast cancers of younger patients tend to be more anaplastic than those of older patients. Investigations by Bloom have failed to confirm this theory. Several investigators have reported that the incidence rate levels off between the ages of 45 and 54; see Waggoner et al. (25) for a current literature review. This observation has led to a hypothesis that hormone changes at menopause might affect the incidence of the disease. However, MacMahon (18) has stated that this may be an epidemiologic artifact associated with changes of incidence for cohorts.

In a series of very careful papers, Bloom (5, 6), Bloom and Richardson (7), have shown that histologic grading of the tumor is an important prognostic variable. The grading is thought to reflect the potential malignancy of the tumor and indicates which patients are more likely to have distant metastases at time of treatment. Bloom concludes that neglect of the tumor histology may be responsible for the wide variation in survival.
in results reported by different investigators using identical methods of treatment.

A number of investigators [Black et al. (2, 4), Black and Speer (3), Wartman (26), Di Re and Lane (12)] have studied the prognostic value of the degree of sinus hyperplasia of the axillary lymph nodes (sinus histiocytosis). These authors claim that the degree of sinus histiocytosis is associated with host resistance to the tumor. However, Berg (1) and Moore et al. (19) disagree with the prognostic value of sinus histiocytosis.

It is clear that the natural history of breast cancer is complicated, depending on the biologic properties of the neoplasm, possible host resistance factors, and perhaps, the menopausal status of the patient. This paper is an attempt to incorporate these factors in a theory of the natural history of the disease.

METHOD

Analysis for Obtaining Time History of Breast Cancer. The progress or status of a disease may depend on one or more disease-related variables which can be evaluated at the time of diagnosis. For simplicity, the disease-related variables will be characterized as being “favorable” or “unfavorable” with respect to each variable. The disease-related variables for breast cancer which we shall consider are (A) axillary nodal involvement; (B) nuclear grade; (C) degree of sinus histiocytosis; and (D) tumor size. There are other variables which also may be important, but they are undoubtedly correlated with those mentioned above. Taking each variable to be either favorable or unfavorable results in $2^4 = 16$ distinct combinations. These 16 combinations are regarded as defining 16 disease states. It will be convenient to associate the letters $A, B, C, D$ with axillary nodal status, nuclear grade, sinus histiocytosis, and tumor size, respectively. Combinations of lowercase letters will be used to denote the disease states. The presence of a letter indicates favorable status; absence of a letter denotes unfavorable status with respect to the missing letter. For example, $abc$ is the state where all variables are favorable. The state $abd$ corresponds to unfavorable status for sinus histiocytosis ($C$) and favorable status for the other three disease variables. The state where all four variables are unfavorable will be denoted by $(U)$.

Note that the more letters in a disease state, the more favorable the disease status. If a woman has breast cancer, her disease status will place her in one of the sixteen disease groups. However, if the disease is not diagnosed, the disease status may change as time progresses with respect to at least one of the disease variables. This advance in the disease will place her in another disease state. A sequence of disease states forms a path which describes the history of the disease if the disease is not diagnosed. It is quite possible that there may be several distinct paths. The first state in each path corresponds to the earliest clinically detectable state of the disease for that path. The set of possible paths characterizes the time history of the disease, provided one can assign a time scale which relates how long it takes to go from one disease state to another along a possible path. We desire to infer these time histories for breast cancer.

In order to determine a theoretical model for the time history of breast cancer we shall make the following assumptions:

1. Each disease variable remains the same or changes from favorable to unfavorable status as time progresses and the disease is not diagnosed. The change is never from unfavorable to favorable.

2. As time progresses, the disease variables characterizing the disease states either do not change or change one at a time and not simultaneously.

3. The survival of a patient in a given state will tend to be greater than the survival associated with a state to which the patient may eventually enter at a later time.

4. The age of diagnosis in a state will tend to be younger compared to the possible transition states reached at a later time.

Assumptions 1 and 2 mean that a person in a particular disease state who is not diagnosed, either remains in that state or will have a transition to another state characterized by one less lowercase letter than the state from which she came. For example, a woman in state $abc$, who is not diagnosed, may remain in that state or enter one of the states $abe, abd, acd$, $abd$. A person in state $ad$ either remains in that state or enters either $a$ or $d$; etc.

Associated with each state will be a median survival time: i.e., the time which 50% of the women survive if the disease is diagnosed in that state and treated. Then Assumption 3 implies an ordering among the states with respect to median survival time. Hence a path consisting of a sequence of disease states is such that the earlier disease states have greater median survival times than the later states.

Assumption 4 enables one to place a time scale on the possible paths. In addition to survival time, there exists information on age at diagnosis. A woman with breast cancer, who is not diagnosed, may eventually be diagnosed in a more advanced state at a later time. Consequently her age at diagnosis in the later state will be older than if she had been diagnosed in an earlier state. Hence the sequence of states in a path is also ordered with respect to age at diagnosis. For this purpose it is convenient to order the disease states by the median age at diagnosis.

These four assumptions result in three operational rules for finding sequences of states which make a path. The first rule is a logical one which requires that the letter combinations of an entering state differ from the state from which the patient came by having one less lowercase letter. The second and third rules are used to find the biologically possible paths from among the set of all possible paths. These last two rules are based on data and require that a transition may only be made from one state to another if the entering state has poorer survival and older age at diagnosis than the exiting state.

We will also require an additional assumption which leads to another rule for finding the possible time histories. However, this rule is of a more complicated nature and we delay introducing it until later (Modified Time Histories).

Inconsistencies may be encountered in applying these rules because of the variability of the data. The rules must be applied taking into account the statistical fluctuations of the data. Another modification of the rules is required when a disease state has entries from several disease states. This situation is
likely to arise with disease states occurring at the end of a path. Then one must employ relatively sophisticated arguments to determine the states in a path.

Applying these rules enables one to infer time histories for chronic diseases, provided the rules are valid for the disease. These time histories should be regarded as the principal or typical time histories of the disease. Undoubtedly, individual patients may experience paths which differ from the typical paths.

RESULTS

Characteristics of the Breast Cancer Series. The method of analysis described in the preceding section will be applied to a series of breast cancer cases diagnosed and treated at the Yale-New Haven Medical Center during the years 1921-1953. The original series consisting of 1458 cases has been discussed by Goldenberg et al. (14). Cutler et al. (10) and Myers et al. (20) have discussed these cases in relation to the significance of prognostic factors. The work by Cutler et al. (10) used a sub-set of the original series which consisted of 777 cases. Patients were excluded from the original series who: were diagnosed less than 5 years prior to close of follow-up (January 1, 1959); had distant metastases at time of diagnosis; had no staging information; had only autopsy information; had bilateral cancer; had no usable slides. Myers et al. (20) used only cases with full information on nodal involvement, nuclear grade, sinus histiocytes, and tumor size using the same exclusions as Cutler et al. (10). This resulted in 375 cases, among whom 371 received a radical mastectomy; the remaining 4 patients received a simple mastectomy. Details of these three sets of cases are summarized in Table 1 with the associated median survival times.

Details of the criteria for evaluating nuclear grade and sinus histiocytes are summarized in Cutler et al. (10). The study by Myers et al. (20) divided the patients into sixteen disease states according to the status of the axillary lymph nodes, nuclear grade, sinus histiocytes, and tumor size at time of mastectomy. These disease variables were classified favorable or unfavorable as briefly summarized below:

<table>
<thead>
<tr>
<th>Factor</th>
<th>Favorable</th>
<th>Unfavorable</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Axillary lymph nodes</td>
<td>Not involved</td>
<td>Involved</td>
</tr>
<tr>
<td>B. Nuclear grade</td>
<td>Tumors having some degree of nuclear differentiation</td>
<td>Tumors having minimal nuclear differentiation</td>
</tr>
<tr>
<td>C. Sinus histiocytes</td>
<td>Lymph nodes with marked evidence of histiocytic cells</td>
<td>Lymph nodes with little or no evidence of histiocytic cells</td>
</tr>
<tr>
<td>D. Tumor size</td>
<td>Smaller than 5 cm</td>
<td>5 cm or larger</td>
</tr>
</tbody>
</table>

Myers et al. (20) reported that the empirical survival distributions for each state can be approximated by exponential distributions. That is, the probability of a patient dying is independent of how long the patient has lived from the time of mastectomy. Survival depends only on the status of the disease at time of mastectomy. A possible explanation for this phenomenon is that in many cases the diagnosis of the disease is a chance event. For example, if a patient is discovered to have breast cancer during the course of a routine physical examination, discovery would not have been made at that time unless the examination had been scheduled. Consequently the starting point of many survival times is random and varies from patient to patient. This would tend to make survival independent of how long a patient has already lived, dated from time of mastectomy, for patients having the same disease status at time of treatment.

Specifically, if $S(t)$ denotes the probability of surviving at least $t$ years (survival function), then $S(t)$ is of the form

$$S(t) = \exp (-\lambda t)$$

where the parameter $\lambda$ depends on the disease state and is termed the mortality rate. The parameter $\lambda$ can be estimated from the data by the formula.

<table>
<thead>
<tr>
<th>Table 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Series</td>
</tr>
<tr>
<td>Original (1458)</td>
</tr>
<tr>
<td>1210</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>777</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

Summary of subset of cases from original series with median survival times. SH, sinus histiocytes.

* Numbers in parentheses refer to number of cases.
Chart 1. Plot of median age of diagnosis versus estimated median survival for sixteen disease states. Lines joining states denote possible transitions. Numbers in parentheses refer to number of patients diagnosed in state. Presence of letter denotes favorable disease variable: (a) nodal involvement, (b) nuclear grade, (c) sinus histiocytosis, (d) tumor size.

Table 2

<table>
<thead>
<tr>
<th>Disease state</th>
<th>Number of patients</th>
<th>Number of breast cancer related deaths</th>
<th>Estimated median survival (years)</th>
<th>Median age at diagnosis (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>abcd</td>
<td>30</td>
<td>6</td>
<td>25.6</td>
<td>54</td>
</tr>
<tr>
<td>abc</td>
<td>10</td>
<td>3</td>
<td>16.5</td>
<td>57</td>
</tr>
<tr>
<td>acd</td>
<td>15</td>
<td>5</td>
<td>16.1</td>
<td>46</td>
</tr>
<tr>
<td>abd</td>
<td>61</td>
<td>20</td>
<td>15.4</td>
<td>57</td>
</tr>
<tr>
<td>ad</td>
<td>34</td>
<td>14</td>
<td>11.8</td>
<td>51</td>
</tr>
<tr>
<td>ab</td>
<td>21</td>
<td>8</td>
<td>10.5</td>
<td>59</td>
</tr>
<tr>
<td>a</td>
<td>23</td>
<td>10</td>
<td>10.5</td>
<td>53</td>
</tr>
<tr>
<td>ac</td>
<td>5</td>
<td>2</td>
<td>10.3</td>
<td>58</td>
</tr>
<tr>
<td>cd</td>
<td>12</td>
<td>6</td>
<td>10.0</td>
<td>46</td>
</tr>
<tr>
<td>bd</td>
<td>67</td>
<td>43</td>
<td>5.7</td>
<td>59</td>
</tr>
<tr>
<td>bcd</td>
<td>12</td>
<td>5</td>
<td>7.4</td>
<td>54</td>
</tr>
<tr>
<td>bc</td>
<td>7</td>
<td>4</td>
<td>6.7</td>
<td>53</td>
</tr>
<tr>
<td>d</td>
<td>48</td>
<td>34</td>
<td>5.2</td>
<td>57</td>
</tr>
<tr>
<td>b</td>
<td>55</td>
<td>45</td>
<td>3.4</td>
<td>56</td>
</tr>
<tr>
<td>c</td>
<td>5</td>
<td>4</td>
<td>3.4</td>
<td>59</td>
</tr>
<tr>
<td>U</td>
<td>62</td>
<td>51</td>
<td>2.6</td>
<td>54</td>
</tr>
</tbody>
</table>

Median survival time and median age at diagnosis for all disease states.

Table 3

<table>
<thead>
<tr>
<th>Disease state</th>
<th>Age at diagnosis (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>20-29</td>
</tr>
<tr>
<td>abcd</td>
<td>1</td>
</tr>
<tr>
<td>abc</td>
<td>0</td>
</tr>
<tr>
<td>acd</td>
<td>0</td>
</tr>
<tr>
<td>abd</td>
<td>0</td>
</tr>
<tr>
<td>ad</td>
<td>0</td>
</tr>
<tr>
<td>ab</td>
<td>0</td>
</tr>
<tr>
<td>a</td>
<td>0</td>
</tr>
<tr>
<td>ac</td>
<td>0</td>
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<tr>
<td>cd</td>
<td>1</td>
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<tr>
<td>bd</td>
<td>0</td>
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<tr>
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<td>bc</td>
<td>1</td>
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<td>d</td>
<td>1</td>
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<tr>
<td>b</td>
<td>1</td>
</tr>
<tr>
<td>c</td>
<td>0</td>
</tr>
<tr>
<td>U</td>
<td>2</td>
</tr>
</tbody>
</table>

Frequency classification of age of diagnosis for disease states.

a One case at 91 years of age.
A characteristic of the exponential survival distribution is that
the median survival is estimated by
\[ \text{Median survival} = \frac{0.69}{\text{estimated value of } \lambda} \]
Formula III enables one to extrapolate the median survival
time for survival distributions where the median (50% prob-
ability point) has not been directly observed.

We shall apply the method of the preceding section to a sub
set of the Goldenberger series. The study will use the same
criteria for favorable and unfavorable disease status as the
Myers et al. (20) study with the exception of the criteria for
unfavorable sinus histiocytosis. Unfavorable histiocytosis will
be defined by lymph nodes with little or no evidence of histo-
cytic cells or all available lymph nodes are extensively involved
by metastatic carcinoma. This allows 92 cases to be added to the
375 studied by Myers et al. (20) to make a total of 467 cases.
Among these, all received radical mastectomy except for four
women who had a simple mastectomy.

Table 2 summarizes the estimated median survival, median
age of diagnosis, and number diagnosed for each of the sixteen
disease groups. Table 3 is a summary of the number of pa-
tients in each disease group by age classification.

**Time Histories.** The most expedient way to examine poten-
tial time histories is to plot the estimated median survival time
against the median age of diagnosis for each of the sixteen
states. If the median survival time is the ordinate and median
age of diagnosis the abscissa, then possible time histories have
transitions between states where the later states must be loc-
ated “south-east” with respect to the earlier states, i.e., as
time goes on, the age of diagnosis advances and the survival
is reduced. Chart 1 is such a plot of the sixteen disease states.
Sequences of disease states are joined together to form four
time histories using the rules described above. There is one
minor exception to the rules, i.e., the path joining bed to bc.
This path violates the age rule by one year. The median age
of diagnosis for bed is 54 years compared to 53 years for bc.
Such an inversion could have arisen easily from statistical
fluctuations.

Chart 1 indicates that there are four distinct time histories.
The initial disease states of each of these are abed, bed, acd,
and cd. These states represent the earliest clinical diagnosed
disease for each path. Note that the median age of diagnosis for
abed and bed are each 54 years; whereas the median age of
diagnosis for acd and cd are each 46 years. Thus the time his-
tories beginning with abed or bed are associated with older
women who tend to be post menopausal. The time histories
beginning with acd and cd are associated with younger women
who are pre menopausal or are undergoing menopause. (It has
been estimated that 90% of American women undergo meno-
pause during the 40- to 50-year age period.) We thus conclude
that the four time histories generate a distribution of incidence
rates having starting points in time which are approximately
eight years apart. Consequently, if one adds the incidence rates
associated with the two pairs of time histories, we would expect
to find a discontinuity in the total incidence rate when appre-
ciable numbers of patients are diagnosed having the later es-
tablished diseases. This would show up as a “break” or “dip”
in the total incidence rate at 54 years of age. Furthermore,
since the time histories differ in their biologic characteristics,
this finding lends further support that the “break” in the in-
cidence rate is not a statistical artifact related to changes in
incidence rate among different cohorts.

We shall refer to the time histories beginning with the initial
states abed and bed as the late major and late minor histories,
respectively. The late refers to the initial state beginning at 54
years of age; major and minor refer to the relative number of
patients in each history. Similarly, the histories beginning with
acd and cd will be referred to as the early major and early
minor histories.

Table 4 summarizes the paths associated with the four time
histories. The states abc, ac, bc, and c have so few patients that
small reliance can be placed on the paths associated with these
states. Also, there may even be doubt as to whether the degree of
sinus histiocytosis has been properly evaluated. Each of
these states is in the large tumor category (unfavorable D).
If the degree of sinus histiocytosis is actually related to the
host resistance of the tumor, one would only expect to find
favorable sinus histiocytosis associated with small tumors.
Hence, these four states may possibly represent misclassified
states due, perhaps, to the slides being inadequate to properly
evaluate the patient with respect to sinus histiocytosis. Omit-
ting the paths associated with these four states leaves the
principal paths corresponding to the four time histories. These
are also summarized in Table 4. All further analyses and com-
ments will be directed at only these principal paths.

We have allowed states d and bd to have entries from two
states. That is, patients entering d may come from states ad
(early major) or cd (early minor); patients entering bd may
come from states abd (late major) or bed (late minor). The
internal consistency between the early and late paths is re-
markable! The sequences of biological events are exactly iden-
tical within the major and minor paths except for the nuclear
grade (B). The late major has favorable nuclear grade (B)
status throughout; the early major has unfavorable nuclear
grade. Similarly, the minor paths are differentiated in the same
way. Both late paths are favorable with respect to nuclear
grade (B), whereas both early paths are unfavorable. This
implies that women having an early established disease tend to
have higher potential malignancy than those where the disease
is established late. The failure of investigators to completely
corroborate this finding is due to the fact that an early estab-
lished disease may be diagnosed late. Further note that, as
time progresses, the favorable nuclear grade tends to remain
favorable and not change. This phenomenon must be closely
related to the findings of Bloom and Richardson (7) who re-
ported that the histologic grade of distant metastases tends to
be identical with the primary tumor.

All four initial states are favorable with respect to sinus
histiocytosis (C). The first change in a disease variable within
each of the time histories is a change from favorable to un-
favorable for sinus histiocytosis. Hence the change in the de-
gree of sinus histiocytosis is a biologic event which occurs early
relative to other biologic events that will occur subsequently.
This lends support to the theory that favorable sinus histiocytosis may be associated with host resistance to the tumor. Change in sinus histiocytosis precedes both axillary nodal involvement and larger tumors for the two major paths.

Another interesting observation is that both the early and late minor paths are characterized by having nodal involvement in the earliest clinically detectable state. One could assume that there exist only two time histories having initial states 1 and 3 such that very early in the disease some patients have nodal involvement. This implies an immediate transition of the form 1 ~ b and 3 ~ c. We have treated this situation as consisting of separate paths beginning with 1 and 3.

It might be worth noting that these time histories are not seriously changed with moderate changes in median survival or median age at diagnosis. This is mainly due to the fact that the time histories are constructed from the relative position of one state to another in the median survival vs. age of treatment plot. Substantial changes in both median survival and age at treatment may leave the relative position of one state to another unchanged.

Modified Time Histories. The principal paths summarized in Table 4 can be regarded as only an initial step for inferring the time histories. These still may be subject to further modifications. One modification is suggested by examining the relation between the degree of sinus histiocytosis and tumor size. Earlier we had reached the conclusion that the change in sinus histiocytosis from favorable to unfavorable status is the first biologic event occurring after a woman leaves the initial state of a path. Tumors become larger after this event. If the tumor is slow-growing this sequence of events will be distinguishable. However, if tumor growth is rapid, it would then appear that the change in sinus histiocytosis occurs simultaneously with tumor growth. This would imply the possible transitions: 4 ~ 1, 4 ~ b, and 4 ~ c. All of these transitions satisfy the rules for decreasing survival time and increasing age of diagnosis as time progresses. We shall permit the paths to be modified to include the possibility of such transitions. Note that with this inclusion, state b is now included in the principal paths, whereas before it was not.

Table 1 contains a line depicting the median survival (as a function of age) for females (Caucasian, New England) based on the 1960 Census of Population, cf. National Center for Health Statistics (22). Using the normal median survival one can calculate the number of years a woman has lost in survival due to having breast cancer. We shall term this loss in survival the "deficit survival," i.e., deficit survival = (normal survival) - (survival with disease). The calculation of the deficit survival will be illustrated for state 6, which has a median age of diagnosis of 57 years and a median survival of 15.4 years. The normal median survival of 57-year-old women is 22.5 years. Hence the deficit survival for state 6 is 22.5 - 15.4 = 7.1 years. Table 5 summarizes the deficit survivals for the states in the four principal paths.

At this point we introduce a fifth assumption, in addition to the other four discussed previously.

5. The deficit survival of a state will be smaller or equal to the deficit survival associated with a state to which the patient may eventually enter. The deficit survival never becomes smaller.

This last assumption means that survival does not improve with delay in diagnosis. Hence, the deficit survival of the states.
along a path will remain the same or increase as the disease advances. A way to use this rule is that an admissible path segment connecting two states is one where the slope of the connecting line is steeper than the slope of the median survival line for normal women. For example, the line connecting bed to bd violates this rule. Referring to Table 5, the deficit survival for bed is 18.9, whereas the value for bd is 15.1 which is significantly lower. Hence the path segment bed → bd violates this rule. A similar situation occurs for the path segment cd → d which violates the deficit survival rule. Chart 2 plots these modified time histories and Table 6 summarizes these adjusted principal paths for the four time histories. Each of the states (except abc, ac, be, c) is assigned to the principal time history in which it occurs. The only multiple entry state is U, which appears as a final state in both the early major and minor histories.

It should be emphasized that these four histories may not be the only time histories which may occur. Others certainly must exist. However, it is hypothesized that these are the principal time histories. Also women of any age can experience any of the four time histories. That is, young women may have a late history and older women can experience an early history. However, the tendency will be for women in the late time histories to be older than women in the early time histories. The ascissa in Chart 2 (age of diagnosis) should be regarded only as placing a time scale on the paths describing the median time to go from one state to another.

The paths are capable of still further modifications by taking account of possible multiple entries into a state. Although one would expect the survival data to depend only on the extent of the disease at diagnosis (survival only depending on the disease state), the median age of a state could be composed of mixtures of median ages. In other words, for the same ordinate (survival time) there may be multiple ordinates (age of diagnosis). However, in order to distinguish multiple modes with respect to the age of diagnosis in a state, it is necessary to have a much larger series of cases than that used here.

The Benefit of Early Diagnosis and Radical Mastectomy.

The characterization of the various time histories of breast cancer enables one to evaluate the advantage of early detection of breast cancer and possibly the benefit of therapy. Explicitly we wish to address ourselves to two questions: Are any women "cured" by the radical mastectomy? Does early diagnosis result in longer survival? We shall discuss these questions with regard to the adjusted principal paths summarized in Chart 2.

Note that the line depicting the median survival of normal women intersects (within the random error) the state abed. The median age and survival for this state are 54 and 25.6 years, respectively, whereas the median expected survival for 54-year-old women in the normal population is 25.3 years. If "cure" is defined as having the same median survival as the normal population, then the women in the disease state abed may be considered "cured."

The role of early diagnosis combined with surgery can be evaluated by studying the deficit survival associated with each state along a path. If the deficit survival increases as a woman advances along a path, this implies that early diagnosis (combined with surgery) results in shorter reduction in life due to having the disease. Alternately, if the deficit survival is constant for each state along a path, then the reduction in life is the same regardless of when the disease is diagnosed.

Referring to Chart 2, it is clear that the late-major time history is the only time history where the line joining the states intersects the median survival line. The longer a woman has the disease the farther away the path line is from the normal line. The other time histories have lines joining the states which are approximately parallel, with the exception of the path segment a → (U).

Table 5 summarizes the deficit survival calculations. Using the calculated values we find that women in the late major time

<table>
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<th>History</th>
<th>State</th>
<th>No. in state</th>
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<th>Median survival (years)</th>
<th>Normal median survival (years)</th>
<th>Delay in diagnosis from initial state (years)</th>
<th>Deficit survival (years)</th>
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</table>

Summary of deficit survival.

* Inadmissible path segment. Deficit survival is significantly low.
Table 6

<table>
<thead>
<tr>
<th>History</th>
<th>Number of patients</th>
<th>Median age of initial state (years)</th>
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<td>46</td>
<td>ad → d</td>
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<td></td>
<td></td>
<td></td>
<td>acd → a → U</td>
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<tr>
<td>Late minor</td>
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<td>54</td>
<td>bcd → b</td>
</tr>
<tr>
<td>Early minor</td>
<td>74</td>
<td>46</td>
<td>cd → U</td>
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Adjusted principal paths for the four time histories.

Chart 2. Plot of disease states omitting states with small numbers of patients. Lines joining disease states refer to transitions for the adjusted principal paths.

We have concluded that early diagnosis does not increase survival time for patients in the minor and early major time histories. Since almost all these patients had a radical mastectomy, this further suggests that surgery does not increase survival for these histories. Another way to study the benefit of surgery is to compare the survival of the final state in each time history with the survival of a comparable series of untreated cases. The rationale behind this comparison is that all series of untreated cases were collected at an earlier epoch, when the disease was brought to the attention of the physician only after an increase in deficit survival occurs if the disease is allowed to progress to the final state (U) where all disease variables are unfavorable. Consequently, a woman may benefit from earlier diagnosis in the early major history if she is diagnosed before reaching state (U). However, even this small potential gain by early diagnosis is ambiguous, as state (U) is a multiple-entry state having entries from the early minor history.

The two minor paths contain only two states each. The agreement of the deficit survival within each path is very close. Hence we conclude that delay in diagnosis for these two time histories does not alter survival.
it was well advanced. Most likely the survival statistics of these untreated cases correspond to the final states of the time histories.

The classic study by Greenwood (15) reported a median survival of 2.3 years for untreated cases. Other studies by Daland (11) and Nathanson and Welch (21) both resulted in a median survival of 2.5 years. A study by Bloom et al. (8) gave 2.7 years from onset of symptoms. The combined average median survival for all groups is 2.5 years. The latter investigation also was able to obtain histologic sections and to estimate survival of untreated breast cancer according to the histologic grade of malignancy. Women having favorable histology (55 cases, Grades I and II) had a median survival time from onset of symptoms of 3.3 years (figure obtained from graphic interpolation). Favorable nuclear grade may be considered “approximately” comparable to the favorable histology in the Bloom et al. series. Table 7 summarizes the comparisons of the untreated median survival times with the median survival times associated with the last states of the four time histories.

The close agreement between the final states of the two minor histories implies that women in these histories do not have different survival than the untreated series. Hence, not only is delay of small import in these histories, but surgery has not increased survival.

We had concluded earlier that survival is increased with early diagnosis in the late major history. However, the difference in survival for bd is disappointingly small compared to the untreated series. This suggests that by the time a woman reaches bd she is near the end of the period where early diagnosis combined with surgery increases survival. A similar apparent increase in survival over the untreated series appears in state d of the early major history. Again the gain is small.

Undoubtedly the subset used here of the Goldenberg series contains biases which make a comparison with the untreated series not strictly comparable. The original series excludes non-operable cases and was amassed during the years 1921-1953 when women were beginning to be influenced by “early detection” education. The median survival of the entire Goldenberg series (cf. Table 1) is 4.2 years, whereas the median survival of the subset of 467 cases is 5.6 years. Hence the survival for the radical mastectomy group analyzed in this paper is biased towards higher survival. The apparent small gain from surgery over the untreated series is approximately the same as the possible biases in the treated series. We conclude that if radical mastectomy is actually beneficial in increasing survival for the final states of the early and late major histories, the gain in survival is at best only a few years. Moreover this small apparent gain in survival could also be explained by biases in the radical mastectomy series. Furthermore, although early diagnosis combined with surgery generally results in an increase in survival for patients in the late major history, by the time these patients reach the final state bd, a radical mastectomy results in little or no gain in survival.

**DISCUSSION**

According to our findings, the benefit of surgery for increasing survival is clearly shown only in patients having a late major time history. Moreover this gain is only appreciable for the states where there is no nodal involvement. Hence a simple mastectomy would have the same therapeutic benefit as a radical mastectomy for this time history. Surgery appears to be only palliative in the remaining time histories. Recently, Kaee and Johansen (10) have reported results of a trial comparing extended radical mastectomy with a simple mastectomy plus postoperative radiation therapy. They reported little difference between the two therapies. Another clinical trial has been reported recently by Brinkley and Haybittle (9) comparing simple mastectomy with a radical mastectomy, where both groups also received radiation therapy. They reported no significant difference between the two therapies. These results are in conformity with our conclusions that only in the late major history will surgery be beneficial, and then only in the states where there is no nodal involvement. In all other time histories surgery appears to be palliative. Most likely the disease is systemic by the time it is diagnosed in these histories. Thus any comparison of radical versus simple mastectomy will show no significant difference between the two therapies with regard to survival.

**CONCLUSION**

The present study was undertaken in an attempt to construct a hypothetical model of breast cancer. The method of investigation was to develop a new technique for inferring the natural history of a chronic disease using only the information available at treatment. Application of this new method to data on breast cancer resulted in the following findings:

There exist at least four principal histories which describe the progress of the disease if it is not diagnosed. These four histories are characterized by the earliest detectable clinical states. The earliest detectable clinical state for all histories is characterized by a small tumor and favorable sinus histiocytosis. The differences among the initial states are due to the nuclear grade and possible nodal involvement. These four histories are termed late major (no nodal involvement, favorable nuclear grade), late minor (nodal involvement, favorable nuclear grade), early major (no nodal involvement, unfavorable nuclear grade), and early minor (nodal involvement, unfavorable nuclear grade).

The first clinically detectable state for the early disease histories has a median of 46 years for age at diagnosis compared to 54 years for the late disease histories. This leads to a possible explanation for the break in incidence rate reported by some investigators.

<table>
<thead>
<tr>
<th>History</th>
<th>Final state</th>
<th>Median survival (years)</th>
<th>Untreated median survival (years)</th>
<th>Difference (years)</th>
</tr>
</thead>
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<td>bd</td>
<td>5.7</td>
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<tr>
<td></td>
<td>ab</td>
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Comparison of median survival of final states with untreated cases.
The hypothetical model implies that the nuclear grade of the primary tumor does not change with time. Furthermore, younger women tend to have disease with less favorable nuclear grade and hence more potential malignancy.

The initial state in each time history has favorable sinus histiocytosis. If a woman is not detected in this state, the next state has the same disease characteristics of the initial state except that sinus histiocytosis has changed to unfavorable status. Hence the earliest biologic event which occurs in each time history is a change in the degree of sinus histiocytosis.

Early diagnosis combined with surgery appreciably increases survival for the late major history for those states without nodal involvement. The decrease in life is 2.5 years for every year of delay in diagnosis dating from the first clinically detectable state. The median survival with radical mastectomy for the first clinically detectable state is the same as the normal population. We infer that a similar gain could be made with simple mastectomy.

Early diagnosis combined with radical mastectomy does not appear to prolong survival in the late minor, early major, and early minor histories.

Radical mastectomy appears to have minimal effect in increasing survival for the late minor, early major, and early minor histories.

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A Hypothesis for the Natural Time History of Breast Cancer

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