Abstract: Survival following treatment of breast cancer may be estimated through the recognition of various prognostic factors. The Case Study presented here calls attention to several of these factors. The reliability and relative value of these prognosticators are discussed. Recommendations are offered for the practical application of prognostic information in the determination of expected mortality.

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Case Presentation
A forty-three year old woman, applying for $300,000 of term life insurance in November 1996, admitted a history of cancer of the left breast with excision of the tumor and removal of axillary lymph nodes in February 1994. She reported spread of the tumor to some of her lymph nodes. Radiation treatment was administered, followed by a six month course of chemotherapy, concluding late in 1994. The applicant had been followed regularly by her oncologist and was free of symptoms. At the time of application, she was taking Nolvadex daily. Her surgeon and oncologist provided Attending Physician Statements.

The APS’s corroborated the applicant’s history. The patient had first noted a left breast nodule in December 1993, but did not seek medical attention until two months later. Mammmography revealed dense fibrocystic disease of both breasts and an area of increased density corresponding to the palpable nodule at the 7:00 position in the left breast. She then had ultrasonography which revealed a hypoechoic area measuring approximately 1.9 cm in diameter. A needle biopsy yielded tissue consistent with adenocarcinoma. On February 8, 1994, a lumpectomy and axillary lymph node dissection were carried out.

The pathologic report indicated an infiltrating ductal carcinoma, less than 2 cm in diameter, with no significant intraductal component and no involvement of the operative margins. Histopathologically, the tumor was described as grade 2. There was no blood vessel invasion, but the pathologist equivocated with regard to lymphatic invasion. Axillary dissection yielded 23 lymph nodes, two of which were positive for malignancy.

Tissue assay of the resected tumor revealed the following:

- Estrogen receptor ..................Positive
- Progesterone receptor .............Positive
- S-phase faction ....................3.4% (Low)
- DNA index ................1.89 (Aneuploid)
Postoperatively the patient received radiotherapy to the chest wall and axillary regions. This was followed by a six month course of triple chemotherapy (cyclophosphamide, methotrexate and 5-fluorouracil), concluding in October 1994. She was then placed on tamoxifen, 10 mg daily. Her last oncologic follow-up was on October 11, 1996, at which time she was feeling well. No evidence of recurrence was detected, and it was noted that she should remain on tamoxifen for a total of at least five years.

Discussion
Given the fact that breast cancer is the most common female malignancy in the USA, medical directors and underwriters are frequently called upon to assess expected extra mortality among proposed insureds following treatment for this malignancy. The task involved in making this assessment may be simply defined as a determination of the probability of residual occult micrometastatic disease after completion of therapy. In pursuing this task, the risk classifier has the benefit (or, depending upon one's viewpoint, the dilemma) of considering several well-established (and other numerous obscure and perplexing) prognostic factors.

The importance of identifying factors which foretell the likelihood of survival from breast cancer ensues from the reality that clinically undetectable micrometastases not infrequently subsist following primary and adjuvant treatment of this malignancy. This circumstance relates to the relatively slow growth of most breast cancers—commonly requiring a ten year period for progressing from one cell to a diameter of 1 centimeter (the minimum size at which most breast cancers are detected). Metastases may occur at any time during this lengthy preclinical period, particularly during the final three to four years prior to detection—meaning that the preoperative clinical staging of all breast cancers should be suspected of being inaccurately low, compared to the ultimate true pathologic stage.

It, therefore, becomes important to make an attempt to classify all treated breast cancer patients according to their probability of suffering recurrence and death from residual micrometastatic disease. Hence, the current extraordinary interest in identifying prognostic/predictive factors in breast cancer. The clinical expectation of such enhanced information is an improved selection and delivery of adjunctive systemic therapy; the underwriting expectation is an improved identification of breast cancer subsets with differing expectations of mortality, leading to increased accuracy in the equitable determination of insurability.

The oncologic community emphasizes the distinction between prognostic factors and predictive factors, using the following definitions:

**Prognostic Factor:** a biologic or clinical measurement associated with disease-free or overall survival in the absence of adjuvant systemic therapy.

**Predictive Factor:** any measurement associated with response or lack of response to a particular therapy.

As will be shown, some factors meet both these definitions. From an underwriting viewpoint, the distinction is often of little consequence, for if a factor points to responsiveness to treatment, it must also impact mortality. The case at hand provides an opportunity to examine the various prognostic factors in breast cancer. The following discussion will address the differing materiality of these factors in assessing the expectation of future extra mortality.

**Epidemiologic/Demographic Factors**

**Age.** Younger age is well-known to be a poor prognostic indicator of both overall and relapse-free survival. Patients under age 35 are usually considered to have the most unfavorable outlook. Age is usually said to be an independently significant factor, but it has
been suggested that the outlook for younger patients is influenced by the higher proportion of poorly differentiated cancers in this age group. Hormonal status is likely another confounding variable (below). At age 43, the subject of this Case Study would be expected to have an intermediate age-related prognosis.

**Menopausal Status.** Numerous studies have shown women over age 50 years to have a better prognosis. There is less agreement on whether this relates mainly to age, hormonal status or both. More importantly, the menopausal status is a very helpful means of determining the most efficacious form of adjuvant systemic therapy (generally, chemotherapy in premenopausal women and anti-estrogen in postmenopausal or castrated women). In the present Case Study, the patient was late premenopausal and estrogen receptor-positive (below) and appropriately treated with chemotherapy, followed by long-term anti-estrogen therapy.

**Race.** Most studies suggest that white women have a better prognosis than black women. However, at least one study indicated that race had no independent significance for survival from stage II cancer in women treated with adjuvant triple chemotherapy.

**Anatomic/Morphologic Factors**

The histologic findings in this case (T1, N1, M0) establish the pathologic stage IIA (American Joint Committee on Cancer). Medical directors and underwriters are accustomed to using cancer stage as the primary indicator of extra mortality. However, in assessing prognosis in breast cancer, it has long been the practice to separately consider primary tumor characteristics (T) and regional lymph status (N) as independently significant prognostic factors, with the presence or absence of distant spread (M) having obvious implications.

**Axillary Lymph Nodes.** The number of axillary lymph nodes positive for metastatic disease is generally accepted as the most meaningful indicator of both disease-free and overall survival in breast cancer, if the dissection includes at least 10 nodes and if these nodes are serially sectioned. The risk of both recurrence and death has been shown to increase directly with an increasing number of positive nodes (Table 1). Using this table, patients having the same nodal status as the subject in this Case Study would have an expected 5-year survival of 62% (based on this variable alone).

It is generally conceded that most patients with node-positive breast cancer will benefit from systemic adjuvant therapy. In the past such adjuvant therapy was not felt necessary for node-negative tumors, but it has been pointed out that even these women have a 20-30% ten-year relapse rate. Therefore, node-negative patients are increasingly receiving adjuvant systemic therapy.

**Tumor size.** Numerous studies view tumor size as the second best prognosticator in breast cancer. Most are in agreement with a strong correlation between primary tumor size and the risk of both recurrence and death. This prognostic factor is especially helpful in node-negative cancers. It is generally held that tumors less than 1 cm in diameter are associated with a 5-year survival of about 90%. The linear relationship between tumor size and survival is quite apparent from the follow-up of 24,740 patients by Carter, et al. (Table 2). Additionally, one study correlated tumor size to the median time from primary therapy to the development of metastatic disease, observing the following relationships: 1.0-2.5 cm (42 months); >8.5 cm (4 months). It should be noted that the accuracy of tumor size measurement may be limited by tumor multicentricity and multifocality and by the extent of noninvasive components around the tumor.

Referring to Table 2, it can be seen that the patient presented in this Case Study should have a favorable prognosis based on tumor size (a 5-year survival of approximately 85%).
presence of two pathologically positive lymph nodes, one might be justified in predicting a 5-year survival of about 74%—a sort of “hybrid” of the two separate probabilities.

**Histopathologic Grade.** Breast cancers are graded on the degree of cellular differentiation, with grades 1-3 representing well-, moderately- and poorly differentiated tumors, respectively. Lower grade tumors exhibit relatively lower recurrence and death rates, and these tumors respond more favorably to endocrine therapy. The determination of grade is rather subjective and influenced by intra- and inter-observer variability. Because of this problem, greater objectivity and reproducibility is being attempted by measurement of S-phase fraction (below) as a correlate of nuclear grade. The subject in this Case Study exhibited intermediate cellular differentiation (G-2)—meaning that this prognostic factor should neither detract from nor augment the expected mortality as determined by other prognostic factors.

**Histologic Subtype.** In contrast to invasive ductal and lobular breast carcinomas, several less common histologic types have been observed to have a relatively good prognosis. These subtypes include tubular, mucinous, medullary and papillary carcinomas (representing only 15-20% of all breast cancers). Because of the more common ductal carcinoma encountered in this Case Study, the histologic consideration posed no mitigation of the evidence provided by the major prognostic factors.

**Lymphatic and Vascular Invasion.** It is quite elementary that the prognosis should be adversely affected by the entry of malignant cells into potential conduits of dissemination. In the Case Study presented here, blood vessel invasion was not observed, while the pathologist hedged on the question of lymphatic invasion—perhaps as a defensive position prompted by his awareness of the pervasive interobserver variation in assessing the histologic variable. These findings provide little reason to modify risk classification of the present case, as determined by the major prognostic factors.

**Tumor Angiogenesis.** The extent of intratumoral microvessel density (MVD) has been assessed by immunohistochemical assay of breast cancer tissue. Various investigators have reported MVD to be a significant prognostic factor in breast cancer for both disease-free and overall survival. However, this technique remains investigational at the present time.

**Hormonal/Cellular Factors**

Various technologies are being used in assaying tumor tissue for the presence or absence and concentration of several substances purported to have prognostic significance in breast cancer. Some of these likely have prognostic significance, while many of them receive conflicting reviews, but none of them appear to have the prognostic capability of the anatomic/morphologic factors. Only those factors commonly used in clinical practice will be discussed. Their favorable ranges are summarized in Table 3.

**Hormone Receptor (HR) Positivity.** A commanding consensus points to a relatively good prognosis among breast cancer patients with high concentrations of estrogen receptor and progesterone receptor. However, after 5 years there is little difference in the recurrence rates of HR-positive and HR-negative patients—leading Harris, et al to conclude that HR status correlates with prognosis “to a weak degree.” On the other hand HR positivity is a very important predictive factor in identifying tumors responsive to anti-estrogen therapy. It has been said that progesterone receptor status is a better prognostic factor, while estrogen receptor status is, more accurately, a predictive factor. The patient in this Case Study has a favorable HR status, probably indicating a slightly better prediction of survival than would otherwise be warranted, particularly considering her long-term tamoxifen therapy.
DNA Index for Determining Ploidy. This flow cytometric measurement of the DNA content of tumor cells distinguishes cancer cells as to whether they are diploid (the normal chromosome content of normal somatic cells) or aneuploid (abnormal chromosome content). It has been observed that aneuploidy has a much greater relative risk for cancer death compared to diploid tumors. However, owing to poor reproducibility, the National Institutes of Health has recommended that ploidy not be used in making clinical decisions. Moreover, since aneuploidy correlates with poor histopathologic differentiation, it may not qualify as an independent prognosticator. The subject of this Case Study had a DNA index of 1.89 (aneuploidy) suggesting a relatively poor prognosis, but the interpretation of this must be tempered by the above reservations.

S-phase Fraction (SPF). This proliferative index is also measured by flow cytometry. It measures the percentage of tumor cells preparing for mitosis by actively synthesizing DNA. As such it is an indicator of tumor aggressiveness. High levels correlate with poor histologic differentiation, larger tumors and hormone receptor negativity. Because of technical difficulties, Harris, et al believe the SPF should not be used in clinical practice. The Case Study patient’s SPF was low (3.4%) and, therefore, a favorable prognosticator. Additionally, this finding offers a counterstatement to the more subjective histopathologic grade which was less favorable (Grade 2) in this case.

Cathepsin D. This protease is estrogen-induced and has been considered capable of promoting cancerous invasion of stroma. Various studies have produced inconsistent conclusions, and this factor is generally not considered to have major prognostic significance. Nevertheless, clinical laboratories continue to offer this measurement. It was not reported on the subject of our Case Study.

Other Cellular and Genetic Factors
No attempt will be made to discuss these investigational and/or controversial attempts to further establish prognosis in breast cancer. These factors include other proliferative indices (e.g. mitotic index); several growth factors (e.g. epidermal growth factor receptor); tumor associated antigens (e.g. carcinoembryonic antigen); indicators of impaired immune responsiveness (e.g. cytokine underproduction); and genetic factors, including erbB-2 amplification and suppressor gene p53 mutation. It should be apparent that some of these factors may be both carcinogenic and prognostic. For further information on these factors, the reader is referred to the reviews by von Kleist and Kaufman.

Adequacy of Treatment
It should not be assumed that all breast cancer patients are treated in a manner most likely to produce a cure. Occasionally, therapeutic decisions are modified by patient preference, intolerance of certain procedures or drugs and noncompliance with follow-up. In the case at hand, the relatively small unicentric tumor justified the decision to perform breast conservation surgery (lumpectomy). This was properly followed by radiation therapy. The patient’s age and menopausal status justified the triple chemotherapy she received. Finally, her hormone receptor positivity was appropriately addressed by the institution of long-term anti-estrogen therapy. The adequacy of breast cancer treatment should be considered an indicator of long term outcome, and this patient’s particular management may be viewed as a favorable prognostic factor.

Conclusion
Disease-free and total survival following treatment of breast cancer is related to the presence or absence of occult micrometastatic disease. The accurate prediction of the existence of this residual can be enhanced by considering various prognostic factors. Age and menopausal status are helpful indicators of survival, although these variables are more important in guiding treatment. Anatomic and morphologic factors continue to provide the most
meaningful prognostic information. Among these, lymph node status and tumor size are most strongly associated with outcome. Histopathologic grade and subtype, lymphatic and vascular invasion and tumor angiogenesis can add further discrimination in estimating expected mortality. An increasing number of tumor tissue assays appear to qualify as lesser prognosticators. Those assays having greater promise are hormone receptor status, DNA ploidy and S-phase fraction. Others are largely investigational and/or controversial. The assessment of prognosis following treatment of breast cancer continues to be most reliant on conventional histopathologic observations.

References
TABLE 1
Five Year Survival Following Primary Treatment of Breast Cancer
Based on Axillary Node Positivity in 19,933 Patients

<table>
<thead>
<tr>
<th>Positive Nodes</th>
<th>Survival (%)</th>
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<tbody>
<tr>
<td>0</td>
<td>71.8</td>
</tr>
<tr>
<td>1</td>
<td>63.1</td>
</tr>
<tr>
<td>2</td>
<td>62.2</td>
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<tr>
<td>3</td>
<td>58.8</td>
</tr>
<tr>
<td>4</td>
<td>51.9</td>
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<tr>
<td>5</td>
<td>46.9</td>
</tr>
<tr>
<td>6-10</td>
<td>40.7</td>
</tr>
<tr>
<td>11-15</td>
<td>29.4</td>
</tr>
<tr>
<td>16-20</td>
<td>28.9</td>
</tr>
<tr>
<td>&gt;20</td>
<td>22.2</td>
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</tbody>
</table>


TABLE 2
Five Year Survival Following Primary Treatment of Breast Cancer
Based on Tumor Size in 24,740 Patients

<table>
<thead>
<tr>
<th>Tumor Size (cm)</th>
<th>Survival (%)</th>
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<tbody>
<tr>
<td>&lt; 0.5</td>
<td>96.2</td>
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<tr>
<td>0.5-0.9</td>
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<tr>
<td>1.0-1.9</td>
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<td>84.3</td>
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<tr>
<td>3.0-3.9</td>
<td>77.0</td>
</tr>
<tr>
<td>4.0-4.9</td>
<td>70.3</td>
</tr>
<tr>
<td>5.0 +</td>
<td>62.7</td>
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</table>


TABLE 3
Tumor Tissue Assays

<table>
<thead>
<tr>
<th>Prognostic Factor</th>
<th>Favorable Range*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estrogen Receptor</td>
<td>≥ 3 fmol/mg</td>
</tr>
<tr>
<td>Progesterone Receptor</td>
<td>≥ 5 fmol/mg</td>
</tr>
<tr>
<td>DNA Index</td>
<td>1.0 (Diploid)</td>
</tr>
<tr>
<td>S-Phase Fraction</td>
<td>&lt; 6%</td>
</tr>
<tr>
<td>Cathepsin D</td>
<td>&lt; 51 pmol/mg</td>
</tr>
</tbody>
</table>

* Reference ranges specified by Nichols Institute, 33608 Ortega Highway, San Juan Capistrano, CA 92690. Favorable ranges will vary by laboratory and methodology.