1991

Efficacy and Cost Effectiveness of Adjuvant Chemotherapy in Women with Node-Negative Breast Cancer — A Decision-Analysis Model

Bruce E. Hillner , M.D.
Virginia Commonwealth University

Thomas J. Smith , M.D.
Medical College of Virginia, Massey Cancer Center

10. Brodie BB, Axelrod J. The estimation of acetanilide and its metabolic products, aniline, N-acetyl p-aminophenol and p-aminophenol (free and total conjugated) in biological fluids and tissues. J Pharmacol Exp Ther 1948; 94:22-8.
11. Dubach UC. Urinary estimation of p-aminophenol as a routine test for detection of phenacetin intake. Ger Med Mon 1967; 12:380-4.
12. Peto R, Pike MC, Armitage P, et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. II. Analysis and examples. Br J Cancer 1977; 35:1-39.
13. Kleinbaum DG, Kupper LL, Morganstern H. Epidemiologic research: principles and quantitative methods. Belmont, Calif.: Lifetime Learning Publications, 1982.
14. Armitage P. Statistical methods in medical research. New York: John Wiley, 1971.
15. Ciabattoni G, Cinotti GA, Pierucci A, et al. Effects of sulindac and ibuprofen in patients with chronic glomerular disease: evidence for the dependence of renal function on prostacyclin. N Engl J Med 1984; 310:279-83.
16. Clive DM, Stoff JS. Renal syndromes associated with nonsteroidal antiinflammatory drugs. N Engl J Med 1984; 310:563-72.
17. McGiff JC. Interactions of prostaglandins with the kallikrein-kinin and renin-angiotensin systems. Clin Sci 1980; 59:Suppl 6:105S-116S.
18. Fitzgerald GA, Oates JA, Hawiger J, et al. Endogenous biosynthesis of prostacyclin and thromboxane and platelet function during chronic administration of aspirin in man. J Clin Invest 1983; 71:676-88.
19. Moncada S, Flower RS, Vane JR. Prostaglandins, prostacyclin in thromboxane A2. In: Gilman AG, Goodman LS, Gilman A, eds. Goodman and Gilman's the pharmacological basis of therapeutics. 6th ed. New York: Macmillan, 1980:668-81.
20. Vane JR. The mode of action of aspirin-like drugs. Agents Actions 1978; 8:430-1.
21. Gloor F. Die Kapillarosklerose in den ableitenden Harnwegen bei Schmerzmittel-(Phenazetin)-Missbrauch. Pathologe 1982; 3:132-6.
22. Murray TG, Stolley PD, Anthony JC, Schinnar R, Hepler-Smith E, Jeffreys JL. Epidemiologic study of regular analgesic use and end-stage renal disease. Arch Intern Med 1983; 143:1687-93.
23. Bengtsson U, Angervall L, Ekman H, Lehmann L. Transitional cell tumors of the renal pelvis in analgesic abusers. Scand J Urol Nephrol 1968; 2:145-50.
24. Nanra RS, Stuart-Taylor J, de Leon AH, White KH. Analgesic nephropathy: etiology, clinical syndrome and clinicopathologic correlations in Australia. Kidney Int 1978; 13:79-92.
25. Kaladelfos G, Edwards KD. Increased prevalence of coronary heart disease in analgesic nephropathy: relation to hypertension, hypertriglyceridemia and combined hyperlipidemia. Nephron 1976; 16:388-400.
26. Cove-Smith JR, Knapp MS. Sodium handling in analgesic nephropathy. Lancet 1973; 2:70-2.
27. Krishnaswamy S, Wallace D, Nanra RS. Ischaemic heart disease in analgesic nephropathy. Aust N Z J Med 1974; 4:426.

SPECIAL ARTICLE

EFFICACY AND COST EFFECTIVENESS OF ADJUVANT CHEMOTHERAPY IN WOMEN WITH NODE-NEGATIVE BREAST CANCER

A Decision-Analysis Model

BRUCE E. HILLNER, M.D., AND THOMAS J. SMITH, M.D.

Abstract *Background.* In 1988 the National Cancer Institute issued a Clinical Alert that has been widely interpreted as recommending that all women with node-negative breast cancer receive adjuvant chemotherapy. Acceptance of this recommendation is controversial, since many women who would not have a recurrence would be treated.

Methods. Using a decision-analysis model, we studied the cost effectiveness of chemotherapy in cohorts of 45-year-old and 60-year-old women with node-negative breast cancer by calculating life expectancy as adjusted for quality of life. The analysis evaluated different scenarios of the benefit of therapy: improved disease-free survival for five years, with a lesser effect on overall survival (base line); a lifelong benefit from chemotherapy; and a benefit in disease-free survival with no change in overall survival by year 10. The base-line analysis assumed a 30 percent reduction in the relative risk of recurrence for five years after treatment.

Results. For the 45-year-old woman, the base-line analysis found an average lifetime benefit from chemotherapy of 5.1 quality-months at a cost of $15,400 per quality-year. The 60-year-old women gained 4.0 quality-months at a cost of $18,800 per quality-year. Under the more and less optimistic scenarios, the benefit of chemotherapy varied from 1.4 to 14.0 quality-months for both groups.

Conclusions. Chemotherapy substantially increases the quality-adjusted life expectancy of an average woman at a cost comparable to that of other widely accepted therapies. This benefit decreases markedly if the changes in long-term survival are less than in disease-free survival. Given its uncertain duration, the benefit may be too small for many women to choose chemotherapy. Selective use of chemotherapy to maximize the benefit to individual patients may be possible with refinements in risk stratification and explicit assessment of the patients' risk preferences. (N Engl J Med 1991; 324:160-8.)

IN 1990 breast cancer affected more than 150,000 women in the United States; it will eventually be the cause of death of 25 percent of them.[1] The 1985 Consensus Development Conference on Breast Cancer[2] and the 1988 Clinical Alert[3] affected both the approximately 75,000 women with node-negative breast cancer and the health care professionals who care for them. The Clinical Alert stated that "chemotherapy can have a meaningful impact on the natural history of node-negative breast cancer patients," which was widely interpreted as a recommendation for adjuvant therapy in these women,[4] although controversy has continued over the treatment of such patients who are not in clinical trials.[5,6]

The effectiveness of adjuvant chemotherapy in prolonging disease-free survival in women with node-negative breast cancer is measurable but moderate.[7-10] The effectiveness of adjuvant therapy in prolonging overall survival is less clear.[11,12] Chemotherapy causes

From the Division of General Internal Medicine, Department of Medicine (B.E.H.), and the John N. Dalton Oncology Clinics, Massey Cancer Center (T.J.S.), Medical College of Virginia, Virginia Commonwealth University, Richmond. Address reprint requests to Dr. Hillner at the Division of General Internal Medicine, Box 170, MCV Station, Richmond, VA 23298.

a short-term decrease in the quality of life of most patients, and this must be weighed against a possible chance of prolonged life for the few who will benefit. The chance of dying because of adjuvant therapy is low, but most treated patients have side effects, and the estimated cost of chemotherapy is high — $338 million for the entire group.[6]

The purpose of this study was to explore the effectiveness of adjuvant therapy in women with node-negative breast cancer at different levels of risk of recurrence. We created a model that incorporated the variables of the risk of recurrence, efficacy of adjuvant therapy, duration of benefit from adjuvant therapy, and quality of life. We used decision analysis to evaluate the clinical model, perform sensitivity analyses, and define thresholds that would assist clinicians in choosing therapy.[13]

Methods

Basic Model

We stated the study problem as follows: a woman has undergone surgery for Stage I or IIa breast cancer that is node negative and estrogen-receptor negative. Should she receive chemotherapy? The decision to accept therapy is based on the patient's and her physician's perceptions of benefit, which depend on the patient's prognosis according to clinical variables, the risk and benefit of chemotherapy, and the patient's preference about the prospect of treatment toxicity.

We developed a decision-analysis model involving two groups: 45-year-old premenopausal women and 60-year-old postmenopausal women. Decision analysis uses a decision tree to consider all the available options and their possible outcomes systematically in solving a problem. The methodologic background has recently been reviewed.[13-15]

These groups represent two typical kinds of patients: premenopausal women who commonly are advised to receive chemotherapy, and postmenopausal, older women who have the highest incidence of breast cancer. Our model used a Markov process to calculate the cumulative value of outcomes in each cohort with and without adjuvant therapy. A Markov process is a modeling technique used for conditions in which the prognosis is described by a series of chance events (adverse outcomes), and the value of these outcomes depends on whether and when they occur.[16] A Markov process has been useful for modeling diseases in which the same event — the occurrence of osteoporotic fractures[17] or thromboemboli,[16,18] for example — can happen repeatedly over time.

Figure 1 shows an abbreviated version of the Markov model of prognosis that we used. The figure shows only four of the nine health states used in the model. "Health states" are part of the Markov vocabulary and describe defined categories of health or disease that apply to a person for a finite period of time. Time-

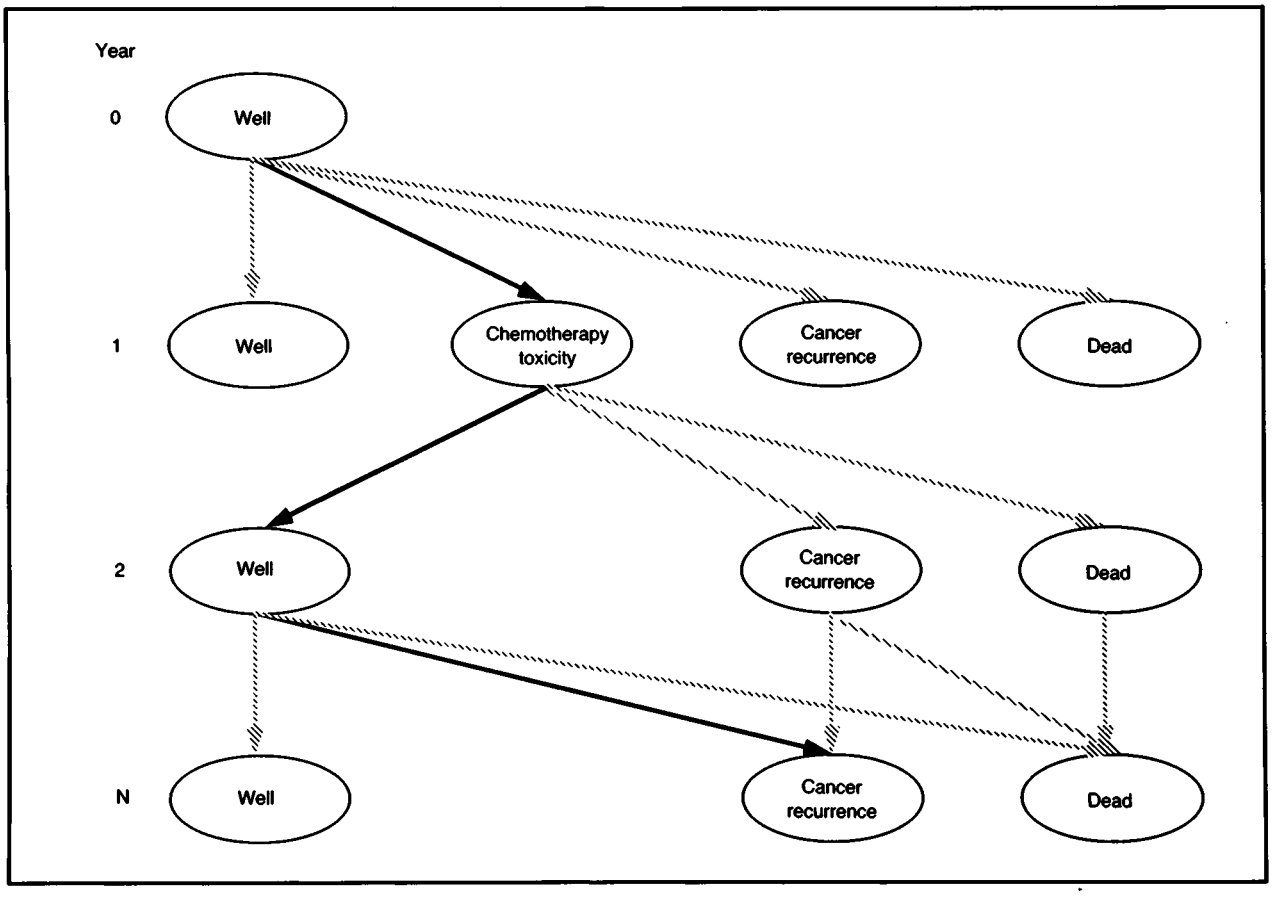

Figure 1. Abbreviated Version of the Markov Model Used in the Study.

As an example, the movements from health state to health state of a woman receiving chemotherapy are indicated by solid arrows. Potential movements are indicated by hatched arrows. The ovals represent states of health at the beginning of each year. In year 0, everyone was in the well oval. From the well oval, movement into any of the other ovals was possible. The chemotherapy-toxicity oval could only be entered during year 1. After entry into the cancer-recurrence oval, return to the well oval was impossible. Cancer could recur during any year. The probability of recurrence was reduced with chemotherapy.

dependent probabilities determined how the patients in our study moved from state to state. All the patients began in the well state. They were tracked through the defined health states at annual intervals. We counted them each year by taking a computer "snapshot" of each woman, and we assigned credits according to the number of women in each health state. We adjusted the credits to reflect the quality of life in each health state (Table 1). For example, a patient who had her first recurrence of breast cancer during the year contributed only 70 percent of a year to the cohort's net credits. The model was run until the entire cohort died or reached the age of 90. We calculated the average number of years of life, as adjusted for quality, for each cohort. A quality-adjusted year of life was a numerical description that combined expected survival and expected quality of life; it was based on the value people place on life in a given state of health. The difference between the groups was thus a measure of the benefit of treatment in terms of quality-adjusted life expectancy.

For each of the two age groups, one cohort received chemotherapy and one did not. Similar Markov processes were used for the four cohorts; only the probability of toxic effects of chemotherapy in the first year and the probability of a first recurrence of breast cancer differed (Table 1). All the patients were assumed to be without metastatic disease at the outset. In each subsequent year a woman could remain free of recurrence (well) or have her first recurrence of breast cancer. If a first recurrence occurred, the patient might respond to salvage therapy (thus entering the post-first-recurrence state) or die. Once a patient had a first recurrence, returning to the well state was impossible. During the year of a first recurrence, the patient could die or survive (first recurrence). If the patient survived, during the next year the patient could continue to respond to salvage therapy given during the first recurrence (thus entering the post-first-recurrence state) or could have a second recurrence. In the year of the second recurrence, the patient could die or survive (second recurrence). We considered a maximum of three recurrences. Almost all patients died within four years. The patients who died in the year of a recurrence contribute nothing to their cohort's net credits.

During the first year, the cohorts that received chemotherapy might have complications associated with treatment — minor toxicity, major toxicity, or death. Minor toxicity was defined as severe nausea and vomiting or weakness sufficient to require a reduction in the activities of daily living but not hospitalization, and major toxicity as complications sufficient to require hospitalization. These health states represented short-term morbidity; with no recurrence of breast cancer, the patient returned to being well in the model's next year.

Modeling the Duration of Benefit from Chemotherapy

A fundamental question is, What is the long-term prognosis for patients treated with chemotherapy? The majority of studies on adjuvant chemotherapy for node-negative cancer have found increases in disease-free survival but no effect on overall survival at the end of the study period. Many oncologists believe that these results are due to insufficient follow-up and that if patients were followed for a sufficient period, a commensurate increase in overall survival would be evident. This belief is based on the assumption that some patients are permanently cured.[19] It is possible, however, that adjuvant therapy delays but does not prevent the eventual recurrence of breast cancer. A tumor might respond to chemotherapy to the extent that it becomes clinically undetectable, but eventually the surviving cells start to grow again, producing a clinical recurrence. Since tumors may be kinetically as well as biochemically heterogeneous, both these outcomes may occur. If so, the initial benefit in disease-free survival would eventually decrease, but a benefit in overall survival would remain.

We repeated our analyses with each of the following assumptions: chemotherapy increases disease-free survival but has less effect on overall long-term survival, chemotherapy has a lifelong benefit in altering both disease-free and overall survival, and chemotherapy increases disease-free survival but does not change overall survival after 10 years. Survival curves for four hypothetical cohorts of patients with breast cancer with an annual probability of recurrence of 10 percent and a relative efficacy of initial treatment of 50 percent are shown in Figure 2. Relative efficacy or reduction in relative risk is the annual decrease in the risk of cancer. The absolute or total reduction in risk would be lower; for the first year it would be 5 percent (10 percent in the untreated group as compared with 5 percent if all patients were treated).[20] With the assumption that the benefit of therapy is limited to the first five years, the risk of recurrence was reduced by 50 percent in the first five years but unchanged in years 6 to 10. The model of maximal benefit assumed that treatment is effective indefinitely. To model an initial benefit in disease-free survival but no change in long-term survival required an increased risk of recurrence in later years. We therefore increased the annual probability by 20 percent for years 6 to 10. With this assumption, the treated groups had a greater average life expectancy due to the benefits of therapy in the first five years, but the number of survivors at year 10 was unchanged. Figure 2 shows that the net benefit of treatment, which is represented by the area between any of the

Table 1. Health States in the Study Model and Their Incremental Values.*

Health State	Incremental Value	
	Base Line	Range
Well	1.00	1.00
Minor toxicity with chemotherapy	0.90	0.70–1.00
Major toxicity with chemotherapy	0.80	0.50–0.95
First recurrence	0.70	0.60–0.80
After first recurrence	0.85	0.70–0.90
Second recurrence	0.50	0.40–0.60
After second recurrence	0.70	0.60–0.80
Third recurrence	0.30	0.20–0.40
Dead	0.00	0.00

*The incremental value or utility of each health state was the factor used to adjust for quality of life. The values applied for one year at a time and were derived from a survey of oncologists and oncology nurses.

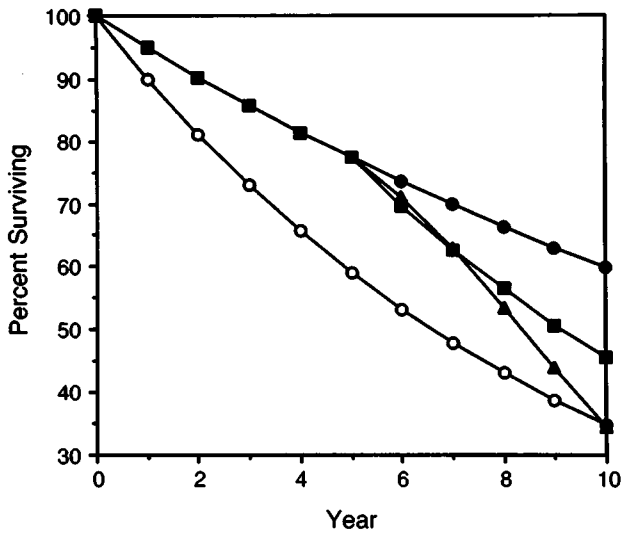

Figure 2. Alternative Models of the Duration of the Survival Benefit of Treatment in Patients with Cancer.

Untreated with adjuvant chemotherapy, the cancer has an annual probability of recurrence of 10 percent (open circles). Solid circles indicate the survival curve if treatment has an indefinite or lifelong benefit in reducing the risk of recurrence by 50 percent. If treatment is beneficial for only five years, the survival curve indicated by the solid squares would be obtained. Triangles indicate the survival curve if treatment delays recurrence but has no benefit in long-term survival. Until year 5 the curves cannot be distinguished from one another. After year 5 the magnitude of the benefit due to treatment varies greatly.

Table 2. Probability and Cost of Recurrence, Complications of Chemotherapy, and Death in Women with Node-Negative Breast Cancer.

VARIABLE	BASE-LINE ESTIMATE	RANGE
Annual probability of recurrence (%)[10,23-25]		
First recurrence	4	1–10
Second recurrence	70	50–90
Third recurrence	90	80–100
Chemotherapy (%)[7-10]		
Efficacy of chemotherapy*	30	0–50
Minor toxicity	60	20–80
Major toxicity	5	0–10
Death within year (%)[26-28]		
Chemotherapy	0.5	0.0–1.0
First recurrence	30	20–50
Second recurrence	50	30–70
Third recurrence	90	80–100
Costs in each Markov state ($)†		
Chemotherapy, if given	6,000	2,500–9,000
Minor toxicity	1,500	500–3,000
Major toxicity	10,000	2,500–12,000
Scheduled visits if well or disease-free	1,000	200–1,000
Nonfatal first recurrence	6,000	2,500–7,000
Nonfatal second recurrence	10,000	8,000–12,000
Death during first recurrence or chemotherapy	25,000	20,500–30,000
Death during second or third recurrence	10,000	8,500–12,000
Discount rate (%)‡	5	0–10

*Relative reduction in the rate of recurrence of breast cancer.

†Charges in 1989 at the Medical College of Virginia and estimates from Medicare data.[29]

‡Both costs and benefits were discounted.

treatment curves and the no-treatment curve, varied markedly between assumptions.

Which approach should be used? Long-term trials in patients with node-positive disease have consistently shown greater benefits of chemotherapy in increasing disease-free survival and smaller benefits in improving long-term overall survival.[21] Since trials[7-10] in patients with node-negative disease have shown benefits only in disease-free survival, we assumed no benefit in long-term overall survival for years beyond the years of follow-up in published reports. We therefore limited the survival benefit of chemotherapy to the first five years after treatment, and we considered the alternative approaches in our sensitivity analyses. A sensitivity analysis is a test of the stability of the results over a range of clinically relevant estimates of probability, structural assumptions, or value judgments. Our other assumptions included the following: that chemotherapy alters only the probability of a first recurrence of breast cancer, making the probability of second and third recurrences the same for both cohorts; that all patients receiving chemotherapy complete the treatment, receive full therapeutic doses, and have no long-term disability (unless there is a fatal complication); that the chemotherapy consists of six cycles of treatment with cyclophosphamide, methotrexate, and fluorouracil[2]; that no patient has a second primary breast cancer; and that this combination of chemotherapy does not increase the risk of secondary tumors.[22]

Summary of the Data

Natural History of Node-Negative Breast Cancer

The risk of recurrence of breast cancer depends on the biologic characteristics of the tumor and is independent of the patient's age (Table 2).[4,11] For the typical patient, the annual probability of a first recurrence is 2 to 7 percent.[23,24,30] Our estimated probability of recurrence of 4 percent per year corresponded to a rate of disease-free survival of 80.4 percent or a rate of recurrence of 19.6 percent after five years. In the sensitivity analysis, we varied the probability of recurrence from 1 to 10 percent per year.[10,23,25]

After the first recurrence of cancer, the rate of response to salvage chemotherapy or hormonal therapy varies with the location of the recurrence but increases long-term survival very little.[26] Most patients receive a palliative benefit, but median survival is about two years.[27-29] Our probability estimates for second and third recurrences were based on a review of the literature and on expert estimates.[27,28,30] The salvage chemotherapy in our model was cyclophosphamide, doxorubicin, and fluorouracil.[27]

Effect and Toxicity of Chemotherapy

We modeled the efficacy of chemotherapy in reducing the risk of a first recurrence of breast cancer by decreasing the probability of recurrence by 30 percent per year for the first five years, on the basis of recently reported trials.[7-10] We limited the duration of benefit because of the experience in patients with node-positive disease, in whom initial disease-free survival exceeded long-term survival.[21] The probability of a first recurrence was therefore 2.8 percent per year in the treated group and 4 percent per year in the untreated group for each of the first five years after therapy.[20] Thereafter, the probability of a first recurrence was the same (4 percent per year). The net effect of chemotherapy after 10 years was thus an absolute gain of about 12 percent in survival. As noted earlier, the toxic effects of chemotherapy could occur only during the year in which it was received. Minor and major toxicity reduced a patient's quality of life and required unscheduled visits to a physician, but only major toxicity required hospitalization. For rates of death from other causes, we used annual age-specific mortality rates for white women in the United States.[31]

Quality of Life

Explicit consideration was given to changes in health or quality of life associated with recurrences of breast cancer and complications of adjuvant therapy. The appropriate way to determine a patient's preferences is controversial, and different methods provide inconsistent results.[32,33] Despite these limitations, there are gross differences in the level of well-being during the stages of treatment and the natural history of breast cancer. We assigned an incremental value for quality of life to each health state. The values shown in Table 1 were determined by a survey of our oncology staff. The adjustments in quality of life with adjuvant therapy apply only to the year in which chemotherapy was given.

Cost of Treatment

The financial cost of therapy varied with the patient's state of health (Table 2). We based costs on 1989 charges at our medical center for physician, laboratory, office, and hospital services and on estimates from Medicare data[29]; our figures were similar to other published estimates.[6] Indirect costs due to loss of earnings and the cost of treatment for other medical conditions were excluded. The cost of chemotherapy was based on six months of outpatient therapy. There were additional costs associated with minor toxicity, among them more office visits, laboratory studies, and drug therapy. The cost of major toxicity was based on a five-day hospitalization plus additional follow-up care. Costs for both cohorts included the annual expenses of scheduled visits and mammograms. Annual costs of treatment assumed outpatient care for nonfatal first recurrences and seven days of hospitalization for nonfatal second or third recurrences. Costs for terminal care varied with the number of recurrences and were greater if death occurred in the year of first recurrence. These aggregate costs were used to determine the cost effectiveness of chemotherapy, defined as the cost per quality-adjusted year of life.[15,34] We used a discount rate of 5 percent[15] to account for the fact that health benefits gained and dollars spent in the future are worth less than health benefits and dollars in the present. We discounted both costs and benefits and varied the rate from 0 to 8 percent in the sensitivity analyses. Using a discount rate of 0 percent and excluding adjustments for quality, we calculated the life expectancy of the average member of each cohort. All calculations were performed with the decision-analysis software program Smltree (Smltree 2.9.1989 [J.P. Hollenberg]).

RESULTS

Base-Line Analysis

Table 3 shows the results in the cohorts of 45- and 60-year-old women receiving chemotherapy for each of the three assumptions of the duration of efficacy of treatment. For example, a 45-year-old woman's aver-

Table 3. Base-Line Analyses in Two Cohorts Receiving Chemotherapy, According to Three Assumptions of Benefit.*

Variable	5 Years of Benefit		Lifelong Benefit		Increase in Disease-Free Survival/No Change in 10-Year Survival	
	45-year-old cohort	60-year-old cohort	45-year-old cohort	60-year-old cohort	45-year-old cohort	60-year-old cohort
Quality-adjusted years of life	11.03	9.49	11.77	9.87	10.72	9.24
Benefit in quality-adjusted months	5.1	4.0	14.0	9.1	1.7	1.4
Cost per quality-adjusted year saved ($)	15,400	18,800	5,100	7,400	48,500	56,800
Life expectancy (yr)†	19.5	14.7	21.4	15.5	—	—
Benefit in life expectancy (mo)†	11.0	7.7	19.3	17.4	—	—

*Results or benefits in the chemotherapy cohorts are compared with those in the cohorts with no therapy. The relative efficacy of chemotherapy was 30 percent.

†Values for life expectancy were neither adjusted for quality nor discounted.

age quality-adjusted life expectancy was 11.03 quality-years if given chemotherapy and 10.60 quality-years if not treated; the benefit was therefore 0.43 quality-years or 5.1 quality-months. The incremental cost per quality-adjusted year was $15,400. The average life expectancy after chemotherapy was 19.5 years, a gain of 11.0 months over life expectancy without treatment. (For comparison, the average life expectancy of a 45-year-old woman without breast cancer is 35.8 years.) For a 60-year-old woman given chemotherapy, the quality-adjusted life expectancy was 9.49 quality-years, a benefit of 4.0 quality-months at an incremental cost of $18,800 per quality-adjusted year. The treated women had an average life expectancy of 14.7 years, an increase of 7.7 months. This compares with an average life expectancy of 22.5 years for 60-year-old women without breast cancer.

Sensitivity Analyses

Sensitivity analyses for plausible ranges of rates of first recurrence of breast cancer and the relative efficacy of chemotherapy in the 45-year-old cohorts are shown in Figure 3. The benefit curve intersects the horizontal axis at the threshold point, the finite point at which two strategies have equal benefits or values for any or all variables.[12] By definition, the cost-effectiveness ratio at a threshold point is infinite. An incremental cost-effectiveness ratio was determined at probabilities of recurrence or efficacies of chemotherapy greater than the threshold levels.

As Figure 3A shows, if the annual probability of recurrence is above 0.4 percent, the use of chemotherapy will be beneficial. The net benefit in quality-years gradually increases in a nonlinear curve as the probability of recurrence increases. Although therapy remains effective at higher risks of recurrence, the increases in the size of the benefit decline. This is due to the limited life expectancy in which to overcome the initial quality-of-life penalty that chemotherapy imposes. Cost effectiveness changes minimally for prob-

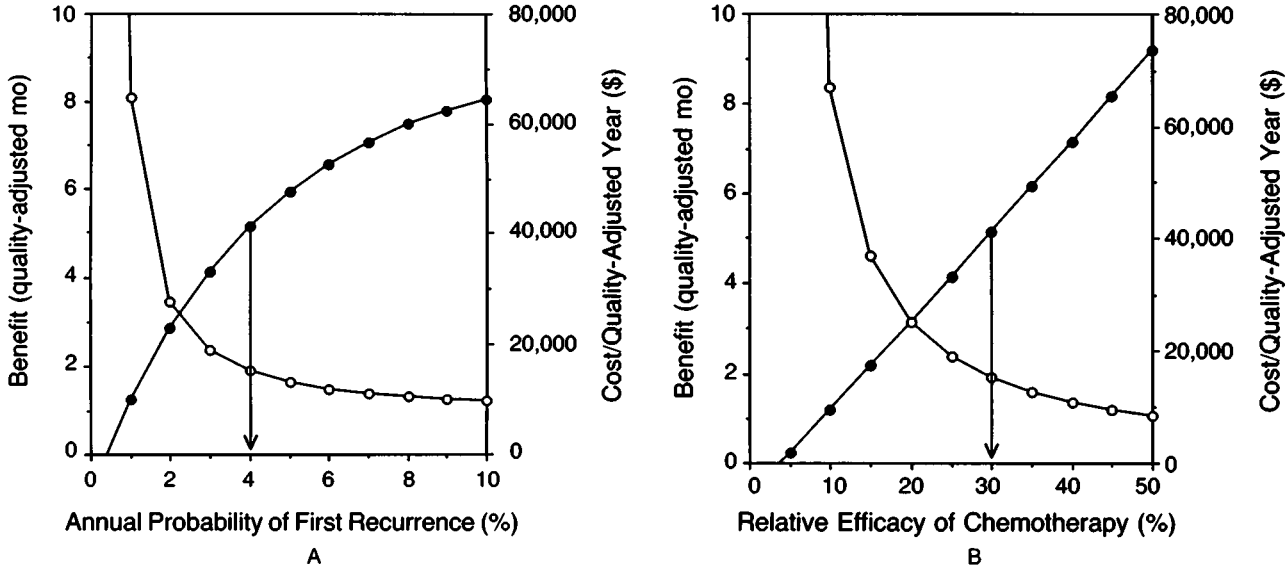

Figure 3. Sensitivity Analyses in the 45-Year-Old Cohorts.

A range of estimates of the annual probability of the recurrence of breast cancer (Panel A) or the relative efficacy of chemotherapy (Panel B) is shown on the horizontal axis. The left vertical axis shows the benefit in quality-adjusted months (solid circles). The right vertical axis shows the incremental cost effectiveness (the cost per additional quality-adjusted year of life) in the chemotherapy cohort as compared with the untreated cohort (open circles). The base-line estimates (a 4 percent probability of recurrence and 30 percent relative efficacy of chemotherapy) are indicated by the arrows. Chemotherapy was assumed to be beneficial for the first five years after treatment.

abilities of recurrence higher than 5 percent per year, and it plateaus at $9,000 per quality-year. For the 60-year-old cohorts the results were similar, but the absolute benefit for any probability of recurrence was lower and the costs were higher.

Figure 3B illustrates the results of changes in the relative efficacy of chemotherapy. The minimal efficacy that will produce a benefit or threshold point is 4.2 percent. The cost-effectiveness curve is very steep at low estimates of efficacy. If a conservative relative efficacy of 15 percent is used, the benefit decreases to about two quality-months at an incremental cost of $36,800 per quality-year.[12] With the best results of recent trials, a 45 percent relative efficacy,[10] the benefit is eight quality-months and the incremental cost drops to $9,900 per quality year.

Figure 4 shows the anticipated benefits of chemotherapy in the 45-year-old cohorts, given different assumptions about the duration of benefit. If chemotherapy is curative in a subset of patients, then that group will have a lifelong benefit in disease-free survival and overall survival. We modeled this optimistic view by allowing the base-line 30 percent reduction in the risk of recurrence to apply for the patient's lifetime. As Figure 4 shows, the threshold for a benefit of therapy is a 2 percent relative reduction in the rate of recurrence; at the base-line relative efficacy of 30 percent the benefit is 14.0 quality-months. An alternative point of view is that chemotherapy is not curative and all women with micrometastatic disease will eventually relapse. We modeled this less optimistic view by increasing the rate of recurrence in years 6 to 10 so that the survival curves for treated and untreated women meet after 10 years and show no further survival benefit. Patients treated with adjuvant therapy still have a slightly increased life expectancy, since the rate of recurrence increases only after year 5. With this less optimistic assumption, chemotherapy is beneficial only if the relative efficacy exceeds 10 percent; at the base-line relative efficacy of 30 percent the benefit is about 1.7 quality-months. The reason for this small benefit is that the penalty in reduced quality of life associated with chemotherapy is immediate, whereas the benefit in improved disease-free survival occurs later and is discounted.

Since there is disagreement about the correct estimates for several of the key variables used in our analyses, we performed sensitivity analyses using best-case and worse-case combinations of recurrence and treatment efficacy (Table 4). In addition, risk preferences may vary greatly among women. We therefore assessed various combinations of discount rates and quality-of-life decrements associated with chemotherapy (Table 4).

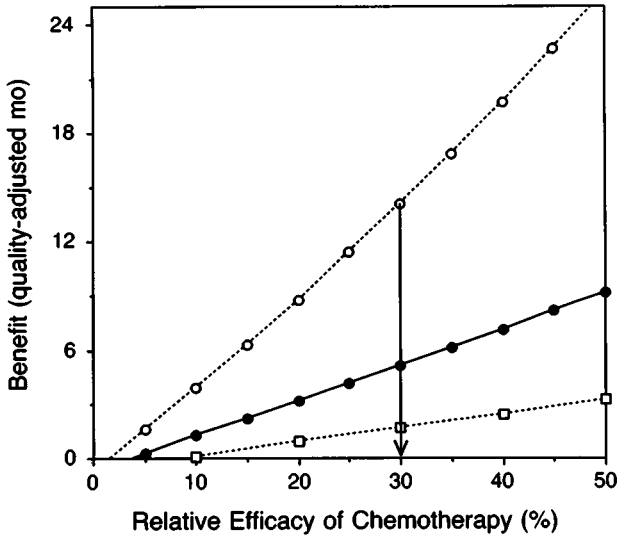

Figure 4. Structural Sensitivity Analyses.

The effects of different assumptions on the duration of benefit from chemotherapy are shown. The base-line assumption (solid circles) is a five-year benefit from chemotherapy. We also considered two alternatives: a lifelong benefit from chemotherapy (open circles) and a benefit in disease-free survival alone, with no survival benefit by year 10 (open squares). The base-line estimate of the relative efficacy of chemotherapy is indicated by the arrow. The magnitude of the benefit of chemotherapy varies greatly between assumptions.

Patients' Questions

Our decision-analysis model allows doctors and patients to explore relevant clinical issues even when

Table 4. Sensitivity Analyses of the Cost and Quality-Adjusted Benefit of Chemotherapy.*

Analysis	45-Year-Old Cohort		60-Year-Old Cohort	
	Quality-Adjusted Benefit	Cost per Quality-Year	Quality-Adjusted Benefit	Cost per Quality-Year
	mo	*dollars*	*mo*	*dollars*
Base line	5.1	15,400	4.0	18,800
Best-case efficacy (lifelong 40% relative efficacy)				
Low risk	7.0	10,700	3.7	19,700
Average risk	19.7	3,400	12.7	5,000
High risk	24.6	2,800	18.8	3,200
Worst-case efficacy (20% relative efficacy/no survival benefit after 10 years)				
Low risk	−0.1	NA	−0.1	NA
Average risk	1.9	40,800	0.8	92,800
High risk	4.7	16,400	2.3	34,600
Worst-case quality of life ("chemotherapy scares me as much as cancer")†				
Low risk	−1.2	NA	−1.6	NA
Average risk	2.7	30,000	1.7	46,500
High risk	8.8	10,200	4.9	15,500
Best-case quality of life ("I will do anything to prolong my life and avoid the return of cancer")‡				
Low risk	3.8	NA	2.4	NA
Average risk	11.2	NA	7,8	NA
High risk	13.9	NA	11.6	NA

*Risk refers to the annual probability of the recurrence of breast cancer. Low, average, and high risks are 1, 4, and 10 percent per year, respectively. NA denotes not applicable.

†Quality of life during chemotherapy is assumed to be the same as during a first recurrence of cancer.

‡No quality-of-life penalty for chemotherapy and no discounting of future years.

data from clinical trials are not complete. We posed these in the form of questions that women might ask their doctors. For the answers to each of the following questions we first assumed our base-line estimates, in which the risk of recurrence was 4 percent per year and chemotherapy reduced the risk by 30 percent for the first five years and improved survival by 12 percent at year 10.

I am willing to accept the initial toxicity if you can add one or two years to my life with chemotherapy. Can you do that? Probably. The question offers another way of quantifying the decrease in quality of life due to chemotherapy. Women who have undergone chemotherapy with cyclophosphamide, methotrexate, and fluorouracil have said that maybe one and certainly two added years would be sufficient benefit to warrant undergoing therapy again.[35] Whether the efficacy of chemotherapy meets these thresholds depends on the duration of the benefit. Given our base-line assumption that the benefit lasts for five years after treatment, chemotherapy must be at least 33 percent effective for 45-year-old women and 47 percent effective for 60-year-old women. With the optimistic assumption that the benefit is lifelong, the minimal efficacy for 45-year-olds drops to 11 percent for one year and 20 percent for two years. Current reports of chemotherapy for women with node-negative breast cancer show relative benefits in disease-free survival of 15 to 45 percent after three to five years[7,9,10]; the long-term survival benefit is unknown but is probably smaller.[11,12,21] If early disease-free survival does not translate into a later survival advantage, chemotherapy may not provide the magnitude of benefit most women require in choosing it.

If quality-of-life issues are important to me, during both chemotherapy and a possible recurrence, and if I accept that the present has greater value than the future (the principle of discounting), can chemotherapy add one year to my life? Probably not. For a 45-year-old woman, chemotherapy must be at least 63 percent effective to gain an additional quality-adjusted year. As discussed above, the reported benefits of adjuvant therapy are substantially below these thresholds. The duration of benefit has a dramatic effect on the thresholds. Given the optimistic view of a lifelong benefit, the thresholds for a gain of one quality-adjusted year drop to 27 percent relative efficacy for 45-year-olds, which is less than our initial estimate, and 38 percent for 60-year-olds, which has been achieved in some studies.

Is chemotherapy effective enough to increase by 10 percent my chance of being disease-free five years from now? Yes, but only for women at high risk. Adjuvant chemotherapy must be more than 55 percent effective to increase life expectancy by 10 percent after five years. Simes et al. found that most women would accept the toxicity of adjuvant chemotherapy if the benefit were a 10 percent greater chance of being alive and disease-free after five years.[35] This absolute gain of 10 percent is an unrealistic goal for a woman at the standard risk of recurrence of 4 percent per year, since the chance of recurrence or death in five years is about 20 percent. For a woman at high risk, however, a 10 percent absolute gain may be achievable. If risk stratification could identify women at high risk of recurrence (10 percent per year, or about 50 percent after five years), adjuvant therapy would still have to be at least 30 percent effective in 45-year-olds and 37 percent effective in 60-year-olds to achieve a 10 percent absolute gain.

If my breast cancer is small (≤1 cm) and has good prognostic factors, will chemotherapy be of any benefit? Yes, but very little. Risk stratification based on tumor size and other prognostic factors has become increasingly feasible and advocated.[36] Tumors no larger than 1 cm have a particularly good prognosis — about 10 percent recurrence after 10 years.[25] We therefore assumed an annual risk of recurrence of 1 percent. Chemotherapy provides a benefit of 38 quality-days for 45-year-old women and 27 quality-days for 60-year-old women, at a cost of $65,000 to $91,000 per quality-year. Chemotherapy is still beneficial because of the very low annual chance of death from other causes. As a group, 45-year-old women have an expected chance of death of only 2 per 1000 in the next year. Even a low-risk tumor, if untreated, thus increases the chance of dying three- to fivefold.

If chemotherapy does not cure me, but just delays recurrence, should I still undergo it? Probably, especially if the risk of recurrence is average or high. This worst-case scenario explores the ramifications if early disease-free survival does not translate into a long-term survival benefit. There may be an overall benefit if the disease-free years outweigh the early toxicity. However, each woman's risk preferences have a great effect on this balance. To make informed choices, women who are willing to risk the early toxicity must know how effective chemotherapy is likely to be in their case. Given base-line adjustments in quality at standard risks of recurrence for both 45- and 60-year-old white women, chemotherapy must be at least 10 percent effective in delaying the recurrence of disease to offer any benefit at all. As Table 4 shows, different risk preferences and rates of discounting markedly affect the decision.

Discussion

Our analysis shows that there is a definite benefit of chemotherapy in women with node-negative, estrogen-receptor–negative disease, if we assume that all women are treated and that the average risk of recurrence is 4 percent per year. For a premenopausal woman of 45, life expectancy would be increased by 11 months; adjusted for quality of life and discounted, the benefit would be about 5 quality-months. For a postmenopausal woman of 60, the benefit would be only about 8 months; adjusted, the benefit would be only 4 quality-months. The financial cost of gaining an additional quality-year of life would be approximately $15,400 in the premenopausal group and $18,800 in the postmenopausal group.

What are the implications of these additional

days and dollars to women with breast cancer, their physicians, insurance companies, and policy makers? Women with breast cancer generally choose adjuvant therapy over the uncertainty of observation. One preliminary report found that nearly 90 percent of the women who had already undergone adjuvant chemotherapy with cyclophosphamide, methotrexate, and fluorouracil indicated that either of two conditions would be sufficient enticement to choose adjuvant therapy again[35]: an additional two years of life expectancy or a 10 percent increase in the chance of being alive after five years. Women who were married or had dependent children were more likely to choose chemotherapy. Unfortunately, women faced with the decision about adjuvant therapy may not receive full information about risks and benefits. In one carefully constructed study of the decision about adjuvant therapy in node-positive breast cancer (in which the benefit in survival is established), patients markedly overestimated their chance of cure: 60 percent of the patients overestimated their chance of cure by 20 percent or more, and nearly 50 percent overestimated their chance of cure even when given numerical values.[37] This suggests that women will overestimate their chance of benefit and choose chemotherapy even when the benefit is known to be small. What will be the choice when the benefit, in terms of long-term survival, is unknown? We suspect (although data are not available to answer the question) that most women, and particularly younger women with dependents, will overestimate their benefit and underestimate toxicity[38]; most will choose chemotherapy if the toxicity is acceptable.[39] Our analysis suggests that for women at a 4 percent risk of annual recurrence, the efficacy of chemotherapy necessary to gain one quality-adjusted year is 62 percent, far greater than the currently attainable level.

What is the proper role of the physician in counseling women with node-negative breast cancer about adjuvant therapy? Physicians usually supply the patient with a clear recommendation, and the patient usually follows it.[37] Our perception is that oncologists are recommending chemotherapy for women with node-negative breast cancer even without a demonstrated survival benefit. Oncologists are prone to accept new forms of treatment as standard before their value has been well documented.[39] The National Cancer Institute's Clinical Alert and the fear of litigation if chemotherapy is withheld appear to allow oncologists only two choices: give chemotherapy even if the benefit is small, or enroll the patient in a clinical trial. Since only a small fraction of eligible patients enter clinical trials and since physicians are reluctant to discuss frankly adverse outcomes (such as lack of benefit or risk of morbidity and mortality), we suspect that most patients will be offered chemotherapy — and most will accept.

Can physicians define a subgroup of women with breast cancer for whom chemotherapy is clearly of sizable benefit, so that only those women will bear the toxicity and cost? The issue is complex, since there is no perfect marker for a low risk of recurrence and no evidence that women at high risk have a better chance of responding to chemotherapy. Patients with a low risk of recurrence may be identifiable by tumor size, morphologic features, or DNA techniques. Tumors with the best prognosis (those less than 2 cm in diameter) may have only a 5 percent chance of causing death in the first five years.[23] Expert morphologic and histologic analysis can identify a subgroup with an excellent prognosis, but this has not yet become standard practice.[40] DNA analysis, carried out by flow cytometry and reported as ploidy and S-phase analysis, may allow the identification of a low-risk subset.[41] Unfortunately, such analysis can be technically difficult, lacks a defined standard, and is not available at many institutions.

Is it possible for physicians to define a subset of women with breast cancer in whom chemotherapy will be most effective? Ideally, this would be the subset at highest risk of recurrence and death, probably those with large (>3 cm), estrogen-receptor–negative, aneuploid, or high-S-phase tumors. The minimal data that are available to answer this critical question suggest that patients whose tumors indicate a poor prognosis are no more intrinsically curable by chemotherapy than those whose tumors indicate a good prognosis. The single study that showed a correlation between the thymidine-labeling index and the response to chemotherapy showed no correlation between the thymidine-labeling index and survival.[42]

If chemotherapy is relatively ineffective in the group at highest risk of recurrence and death, then the benefit to that group is likely to be less than predicted. If we assume in our model that adjuvant therapy is equally effective in cancers with a high risk of recurrence, then therapy is most cost effective in patients at high risk. If chemotherapy is not curative and merely postpones recurrence with no change in long-term survival, then the benefit of therapy decreases markedly. Observation will produce more benefit than treatment unless the relative efficacy of therapy exceeds 10 percent.

When compared with the choices of women who have undergone adjuvant therapy with cyclophosphamide, methotrexate, and fluorouracil, our results suggest that the level of benefit is very close to the typical woman's threshold for choosing chemotherapy. If the optimistic perspective is supported by the results of long-term follow-up of subjects in reported trials, then most women should receive treatment. If these studies show no change in long-term survival, then the benefit appears to be insufficient. However, most women and their oncologists will choose treatment when faced with uncertainty and the overestimation of personal benefit as opposed to risk.[37]

What are the policy implications of our analysis of cost effectiveness for those who pay for cancer care? For the individual patient, the decision has been clear-cut: treat to prolong life despite the cost. In an era of limited health care resources, this approach is increasingly untenable, however. Those who pay for the care

of patients with breast cancer might point to the high cost of gaining an additional quality-adjusted year of life in an attempt to discourage the standard use of chemotherapy in women with node-negative disease. The conundrum for cost-conscious physicians is that the expense of this therapy is within the range of current medical interventions. For both age groups of women, an incremental cost of less than $20,000 per quality-year would be generally acceptable. The true cost effectiveness may actually be lower, since we based the costs of chemotherapy on charge estimates. Other widely accepted medical interventions with costs per quality-adjusted year ranging between $10,000 and $25,000 include hemodialysis for end-stage renal disease, treatment of three-vessel coronary disease, bone marrow transplantation for acute nonlymphocytic leukemia, and treatment of hypertension.[43-46] But if chemotherapy only delays recurrence, then the incremental cost increases markedly. Is it acceptable to spend more than $50,000 for one quality-year? Alternatively, is it acceptable to spend $6,000 for chemotherapy to gain less than two months of life? How much is society willing to spend for a small potential gain, since the effect of adjuvant therapy on survival is unknown? Should the potential benefit be limited to younger women, for whom it is more cost effective, even though a woman alive at the age of 60 may be expected to live another 22 years?

It is important to keep in mind that these decisions affect women who are faced with a frightening, disfiguring, and often fatal disease. It is also an expensive disease with increasingly costly options for treatment. Decisions about treatment that look at cost have always been a part — even if unspoken — of medical practice. Costs and risk preferences should be part of the discussion of the efficacy and toxicity of treatment in these and all other decisions made at the bedside.[47]

References

1. Silverberg E, Boring CC, Squires TS. Cancer statistics, 1990. CA 1990; 40:9-26.
2. Adjuvant chemotherapy for breast cancer. JAMA 1985; 254:3461-3.
3. National Cancer Institute. Clinical alert. Bethesda, Md.: National Cancer Institute, May 16–18, 1988.
4. Ingle JN. Assessing the risk of recurrence in breast cancer. N Engl J Med 1990; 322:329-31.
5. DeVita VT Jr. Breast cancer therapy: exercising all our options. N Engl J Med 1989; 320:527-9.
6. McGuire WL. Adjuvant therapy of node-negative breast cancer. N Engl J Med 1989; 320:525-7.
7. Fisher B, Redmond C, Dimitrov NV, et al. A randomized clinical trial evaluating sequential methotrexate and fluorouracil in the treatment of patients with node-negative breast cancer who have estrogen-receptor–negative tumors. N Engl J Med 1989; 320:473-8.
8. Early Breast Cancer Trialists' Collaborative Group. Effects of adjuvant tamoxifen and of cytotoxic therapy on mortality in early breast cancer: an overview of 61 randomized trials among 28,896 women. N Engl J Med 1988; 319:1681-92.
9. The Ludwig Breast Cancer Study Group. Prolonged disease-free survival after one course of perioperative adjuvant chemotherapy for node-negative breast cancer. N Engl J Med 1989; 320:491-6.
10. Mansour EG, Gray R, Shatila AH, et al. Efficacy of adjuvant chemotherapy in high-risk node-negative breast cancer: an intergroup study. N Engl J Med 1989; 320:485-90.
11. Henderson IC. Adjuvant therapy for breast cancer. N Engl J Med 1988; 318:443-4.
12. Ginsburg AD, Perrault DJ, Pritchard KI, Browman GP, McCulloch PB, Skillings J. Systemic adjuvant therapy for node-negative breast cancer. Can Med Assoc J 1989; 141:381-7.
13. Pauker SG, Kassirer JP. Decision analysis. N Engl J Med 1987; 316:250-8.
14. Sox HC Jr, Blatt MA, Higgins MC, Marton KI. Medical decision making. Boston: Butterworths, 1988.
15. Weinstein MC, Feinberg HV, Elstein AS, McNeil B. Clinical decision analysis. Philadelphia: W.B. Saunders, 1980.
16. Beck JR, Pauker SG. The Markov process in medical prognosis. Med Decis Making 1983; 3:419-58.
17. Hillner BE, Hollenberg JP, Pauker SG. Postmenopausal estrogens in prevention of osteoporosis: benefit virtually without risk if cardiovascular effects are considered. Am J Med 1986; 80:1115-27.
18. Tsevat J, Eckman MH, McNutt RA, Pauker SG. Warfarin for dilated cardiomyopathy: a bloody tough pill to swallow? Med Decis Making 1989; 9:162-9.
19. Norton L. Implications of kinetic heterogeneity in clinical oncology. Semin Oncol 1985; 12:231-49.
20. Fletcher RH, Fletcher SW, Wagner EH. Clinical epidemiology: the essentials. 2nd ed. Baltimore: Williams & Wilkins, 1988.
21. Tannock IF. Adjuvant therapy for node-negative breast cancer. N Engl J Med 1989; 321:471-2.
22. Henderson IC, Gelman R. Second malignancies from adjuvant chemotherapy? Too soon to tell. J Clin Oncol 1987; 5:1135-7.
23. Carter CL, Allen C, Henson DE. Relation of tumor size, lymph node status, and survival in 24,740 breast cancer cases. Cancer 1989; 63:181-7.
24. Fisher B, Slack N, Katrych D, Wolmark N. Ten year follow-up results of patients with carcinoma of the breast in a co-operative clinical trial evaluating surgical adjuvant chemotherapy. Surg Gynecol Obstet 1975; 140:528-34.
25. Rosen PR, Groshen S, Saigo PE, Kinne DW, Hellman S. A long-term follow-up study of survival in stage I (T1N0M0) and stage II (T1N1M0) breast carcinoma. J Clin Oncol 1989; 7:355-66.
26. Henderson IC, Harris JR, Kinne DW, Hellman S. Cancer of the breast. In: DeVita VT Jr, Hellman S, Rosenberg SA, eds. Cancer: principles and practice of oncology. 3rd ed. Philadelphia: J.B. Lippincott, 1989.
27. Bonadonna G. Conceptual and practical advances in the management of breast cancer. J Clin Oncol 1989; 7:1380-97.
28. Henderson IC, Hayes DF, Come S, Harris JR, Canellos G. New agents and new medical treatments for advanced breast cancer. Semin Oncol 1987; 14:34-64.
29. Baker MS, Kessler LG, Smucker RC. Site-specific treatment costs for cancer: an analysis of the Medicare continuous history sample file. In: Scheffler RM, Andrew NC, eds. Cancer care and costs: DRGs and beyond. Ann Arbor, Mich.: Health Administration Press Perspectives, 1989:127-38.
30. Bonadonna G, Valagussa P. Current status of adjuvant chemotherapy for breast cancer. Semin Oncol 1987; 14:8-22.
31. Bureau of the Census. Statistical abstract of the United States, 1989. Washington, D.C.: Government Printing Office, 1989:73.
32. Nelson EC, Berwick DM. The measurement of health status in clinical practice. Med Care 1989; 27:Suppl 3:S77-S90.
33. Mulley AG Jr. Assessing patients' utilities: can the ends justify the means? Med Care 1989; 27:Suppl 3:S269-S281.
34. Detsky AS. Are clinical trials a cost-effective investment? JAMA 1989; 262:1795-800.
35. Simes RJ, Cocker K, Glasziou P, Coates AS, Tattersall MHN. Costs and benefits of adjuvant (adj) chemotherapy for breast cancer: an assessment of patient preferences. Proc Am Soc Clin Oncol 1989; 8:52. abstract.
36. McGuire WL, Tandon AK, Allred DC, Chamness GC, Clark GM. How to use prognostic factors in axillary node-negative breast cancer patients. J Natl Cancer Inst 1990; 82:1006-15.
37. Siminoff LA, Fetting JH, Abeloff MD. Doctor-patient communication about breast cancer adjuvant therapy. J Clin Oncol 1989; 7:1192-200.
38. Weinstein ND. Optimistic biases about personal risks. Science 1989; 246:1232-3.
39. Goldsmith M. Patterns of care; how oncologists are treating stage II breast cancer. Oncology 1987; 1:54-6.
40. Fisher ER. Prognostic and therapeutic significance of pathological features of breast cancer. In: NCI Monographs. No. 1. Washington, D.C.: Government Printing Office, 1986:29-34. (NIH publication no. 86-2860.)
41. Clark GM, Dressler MA, Owens MA, Pounds G, Oldaker T, McGuire WL. Prediction of relapse or survival in patients with node-negative breast cancer by DNA flow cytometry. N Engl J Med 1989; 320:627-33.
42. Sulkes A, Livingston RB, Murphy WK. Tritiated thymidine labeling index and response in human breast cancer. J Natl Cancer Inst 1979; 62:513-5.
43. Stange PV, Sumner AT. Predicting treatment costs and life expectancy for end-stage renal disease. N Engl J Med 1978; 298:372-8.
44. Weinstein MC, Stason WB. Cost-effectiveness of coronary artery bypass surgery. Circulation 1982; 66:Suppl III:III-56–III-66.
45. Welch HG, Larson EB. Cost effectiveness of bone marrow transplantation in acute nonlymphocytic leukemia. N Engl J Med 1989; 321:807-12.
46. Edelson JT, Weinstein MC, Tosteson ANA, Williams L, Lee TH, Goldman L. Long-term cost-effectiveness of various initial monotherapies for mild to moderate hypertension. JAMA 1990; 263:407-13.
47. Durbin M. Bone marrow transplantation: economic, ethical, and social issues. Pediatrics 1988; 82:774-83.