

Incremental Costs of Enrolling Cancer Patients in Clinical Trials: a Population-Based Study

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Background: Payment for care provided as part of clinical research has become less predictable as a result of managed care. Because little is known at present about how entry into cancer trials affects the cost of care for cancer patients, we conducted a matched case-control comparison of the incremental medical costs attributable to participation in cancer treatment trials. **Methods:** Case patients were residents of Olmsted County, MN, who entered phase II or phase III cancer treatment trials at the Mayo Clinic from 1988 through 1994. Control patients were patients who did not enter trials but who were eligible on the basis of tumor registry matching and medical record review. Sixty-one matched pairs were followed for up to 5 years after the date of trial entry for case patients or from an equivalent date for control patients. Hospital, physician, and ancillary service costs were estimated from a population-based cost database developed at the Mayo Clinic. **Results:** Trial enrollees incurred modestly (no more than 10%) higher costs over various follow-up periods. The mean cumulative 5-year cost in 1995 inflation-adjusted U.S. dollars among trial enrollees after adjustment for censoring was \$46 424 compared with \$44 133 for control patients. After 1 year, trial enrollee costs were \$24 645 compared with \$23 964 for control patients. **Conclusions:** This study suggests that cancer chemotherapy trials may not imply budget-breaking costs. Cancer itself is a high-cost illness. Clinical protocols may add relatively little to that cost. [J Natl Cancer Inst 1999;91:847-53]

As health plans have become more adept at reviewing and managing the care received by their covered populations, payment for care provided as part of or incident to clinical research protocols has become less predictable (1). As a matter of federal policy, Medicare does not pay for routine patient care delivered in clinical trials unless that care would be necessary without the trial.

Managed care administrators are understandably concerned that patient enrollment in cancer clinical trials increases medical care cost. Although this concern may be justified in certain well-publicized cases, such as very expensive new treatments for conditions with no currently available therapy, cancer clinical trials span a wide array of interventions and disease stages. Most cancer trials today involve the use of chemotherapy. Little is known at present whether the treatment regimens of cancer trials increase or decrease the costs of care over the remaining lifetimes of cancer patients.

Information on the incremental patient care costs (or cost savings) associated with cancer clinical trials can help put such concerns into proper perspective and, thereby, facilitate arrangements for patients insured by managed care organizations to participate in such studies. To our knowledge, no published study has evaluated the costs associated with participation in

cancer trials. Estimates of differences in patient care costs between trial enrollees and equivalent patients receiving conventional cancer care across a wide spectrum of clinical studies can assist in fiscal planning, negotiations for sharing of patient care costs, and financial risk management.

For these reasons, we conducted a matched case-control comparison of the cumulative incremental patient care costs attributable to participation in phase II and phase III cancer treatment trials from the date of trial entry until either death or 60 months after trial entry.

SUBJECTS AND METHODS

Selection of Case Patients

We identified all residents of Olmsted County, MN, who entered cancer clinical trials at the Mayo Clinic Cancer Center from January 1, 1988, through December 31, 1994. This sampling period permitted relatively complete enumeration of the 5-year history of medical services used by trial participants. The Rochester Epidemiology Project, a cooperative effort of the principal sources of medical care in Olmsted County, provides an umbrella for population-based research, including a comprehensive medical care utilization database (2).¹ The year 1988 was chosen as the earliest date for inclusion in the study for the following two reasons: 1) Health care utilization and cost data are available in electronic form for 1987 and later, and 2) changes in medical technology or in the nature of clinical protocols could invalidate earlier data.

Identification of case patients began with an inventory of all clinical protocols at the Mayo Clinic Cancer Center that were accruing patients during the sampling period. All of the protocols were funded by the National Cancer Institute either through the North Central Cancer Treatment Group or directly to the Mayo Clinic Cancer Center, and all were chemotherapy trials. Selected data on each protocol and on each patient enrolled during the study period were obtained from electronic and paper files maintained at the Mayo Clinic Cancer Center.

All protocols were screened to eliminate nonclinical or ancillary studies, such as those involving only record reviews or secondary analyses of laboratory specimens. The remaining protocols fell into one of the following five trial types: 1) pilot trials, 2) phase I treatment trials, 3) phase II treatment trials, 4) phase III treatment trials, or 5) cancer control trials. We merged the lists of participants in each protocol into a master list of unique patients enrolled in one or more cancer clinical trials, and we further restricted the sample to those who had enrolled in at least one phase II or phase III study.

Many patients participated in more than one cancer trial. Although no patients participated simultaneously in more than one treatment trial, some entered two or more treatment trials sequentially during the study period or participated simultaneously in a treatment and a cancer control study. Approximately 10% of all case patients participated in more than one trial during the study period. We regard multiple trial enrollments partly as consequences of the familiarization of patients with the clinical research environment and the frequent contact between trial participants and clinical research teams. Thus, entering one trial may pre-

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dispose individuals to enter other trials, with their accompanying cascade of cost impacts. Therefore, we did not exclude case patients from the sample if they were enrolled in more than one cancer trial over the study period, provided that the first trial entered was a qualified phase II or phase III treatment trial.

We excluded all trial participants who were not residents of Olmsted County on the date of trial enrollment. Of 2466 individuals enrolled at Mayo Clinic Cancer Center in phase II or phase III cancer treatment trials in the study period, 176 (7%) were Olmsted County residents on the date of trial enrollment.

Selection of Control Patients

The selection of control patients occurred in a two-stage process designed to maximize similarity between case patients and their matched control patients on demographic and clinical characteristics likely to affect both trial eligibility and prognosis independent of the trial. We balanced the goal of achieving demographic and clinical equivalence between case patients and control patients against the constraints on the number of available control patients.

In the first stage, we identified all potential control patients through a review of the Mayo Clinic Tumor Registry. We matched the characteristics of the 176 case patients with those of all cancer patients recorded in the registry. Potential control patients were Olmsted County residents who between 1988 and 1996 were classified as having malignant disease diagnosed before autopsy and as having a date and place of treatment recorded in the Mayo Clinic Tumor Registry. Registry data elements in the first-stage matching criteria included age, sex, site of the primary cancer, stage of cancer, and year of diagnosis. Year of diagnosis pertained either to the initial diagnosis of cancer or to the initial diagnosis of metastatic disease as discussed below. An age range of up to ± 7 years was allowed in matching the control patient with a case patient. Patients were matched for the site of their primary tumor by use of the three-digit code as described in the International Classification of Diseases for Oncology (ICD-O) (3), with additional groupings to minimize the number of case patients for whom no match would be found.

We developed an algorithm to match the date of diagnosis of each potential control patient with that of the case patient. Treatment protocols were divided into those for metastatic and those for nonmetastatic disease. Using this separation, we matched potential control patients with nonmetastatic disease on their initial date of diagnosis of cancer. Potential control patients whose diagnosis date was within ± 3 years of the case patient's diagnosis date were accepted, except for patients with colorectal cancer. Because surgical adjuvant therapy became standard medical practice in 1990 for treatment of colorectal cancer, case patients diagnosed in 1989 and earlier were matched only with potential control patients also diagnosed within 3 years of the case patient in 1989 or earlier. Case patients whose colorectal cancers were diagnosed in 1990 or later were matched only with potential control patients diagnosed in that later period. Case patients entered into protocols for treatment of metastatic disease were matched in the same way, except that the relevant diagnosis date was the date of diagnosis of metastatic disease as recorded in the Mayo Clinic Tumor Registry. Patients with colorectal cancer were again divided into those diagnosed before 1990 and those diagnosed in 1990 or later.

Through the above process, we identified 617 unique potential control patients for 133 case patients undergoing treatment on protocol. Thus, 43 (24%) of the 176 case patients could not be matched in the first stage.

In the second stage, the medical records of potential control patients identified in the first stage were reviewed to further ascertain their appropriateness as matches. Review of the medical records began with the potential control patients for those case patients with the fewest available potential control patients. Potential control patients for each case patient were randomly assigned a rank order for medical record review. If a potential control patient met the eligibility criteria for a case patient's clinical protocol, his or her record was selected and was ineligible for selection as a control patient for any other case patient. In the interests of time, we further elected to restrict the number of potential control patients for any case patient to no more than 10, when a case patient had more than 10 potential control patients.

The matching criteria used in the medical record review were the eligibility criteria specific to the relevant treatment protocol and an assessment of the patient's performance status. We considered performance status to be an important predictor of both longevity and ability to tolerate therapy. Trial eligibility criteria generally included type and stage of cancer, specific laboratory parameters, and performance status as measured by the criteria of the Eastern Cooperative Oncology Group (4). To be considered eligible for the trial, the potential control patient's medical record could have no mention of a condition or finding

violating protocol eligibility at any time from diagnosis date to an assigned trial entry-equivalent date. The trial entry-equivalent date for the control patient was chosen so that the period between the date of diagnosis and the date of entry (or entry-equivalent date) in the trial would be the same for both patients in a matched case and control pair. (For example, if the case patient was diagnosed with cancer of the cervix on January 1, 1990, and entered a phase II or phase III trial for cervical cancer on January 1, 1991, then the matched control patient who was diagnosed with cervical cancer on January 1, 1992, would be assigned a trial entry-equivalent date of January 1, 1993.) The second stage yielded matches for 61 (46%) of the 133 case patients surviving the first-stage matching process.

Cost Measurement

The primary end point of the study was the cumulative 5-year incremental medical care cost. This cost was defined as the total excess cost for case patients compared with that of equivalent control patients incurred from trial entry date or trial entry-equivalent date until the date of death or the end of the 60th 30-day month, whichever came first. The follow-up period was limited to 5 years because too few observations would be available to provide stable cost estimates beyond this period. Secondary end points were the excess cost incurred by participants from the date of enrollment in the trial to the end of the 12th month and the average monthly cost incurred throughout the follow-up period.

The Olmsted County utilization database, an archived source of provider billing data for Olmsted County medical care providers, was the basis for cost estimation. This database is available in electronic format starting with 1987 data and presently containing data through the end of 1995. It captures 90%–95% of all physician and hospital services used by Olmsted County residents (2). The proportion may be even higher for cancer patients.

Although complete capture of all categories of health care costs was the goal, certain categories were excluded, notably outpatient prescription drugs, durable medical equipment, ambulance and other transportation services, outpatient services provided by allied health professionals (such as physical and occupational therapists or clinical psychologists), and nursing home care. The utilization database includes services in these categories provided by the medical facilities participating in the Rochester Epidemiology Project, but it does not include items provided by drugstores, dispensers, distributors, and independent allied health professionals. In the interests of consistency, therefore, we eliminated all such services from the cost estimates. We also did not capture services provided to study subjects outside Olmsted County, such as the Veterans Affairs Medical Center in Minneapolis or the University of Minnesota Hospital, because the utilization database does not include these institutions. Also excluded were the costs of experimental agents provided free of charge by trial sponsors or third parties such as drug companies. These items did not enter the billing systems of the institutions participating in the Rochester Epidemiology Project.

The utilization database contains detailed billing records for every medical encounter and service rendered by the participating providers. We used a costing system developed by researchers at the Mayo Clinic to assign a unit cost to each service. That system assigns a standardized inflation-adjusted unit cost to each service or procedure in 1995 U.S. dollars. Although the services provided represent the practice choices of Olmsted County providers, the value of each unit of service has been adjusted to national cost norms by use of widely accepted valuation techniques (5).²

The use of standardized unit costs is desirable because of the well-known discrepancies between billed charges, which are directly available in the utilization database, and "opportunity" costs in health care (5–8).³ These differences vary by type of service, among providers, and over time, so billed charges can give a distorted picture of cost differences between groups of patients treated with different services over various times. The unit costing system assigns 1995 Medicare fee-schedule rates to all physician and outpatient ancillary services provided from 1987 through 1995. Hospital charges are converted to costs by applying department-level cost-to-charge ratios reported by all hospitals to Medicare. Each unit cost is normalized to a national 1995 value by use of regional hospital market-basket indexes reported annually by the Prospective Payment Assessment Commission (9).

Lifetime (or 5-year) cost is most appropriately measured as the net present value of the stream of costs incurred over time from the trial entry date to the date of death or the end of the 5-year measurement period. The net present value of cumulative cost is the sum of costs incurred at each time point, weighted by a discount factor that reflects the decay in the value of money from trial entry to the time at which the cost is incurred. A commonly used annual discount rate for health care spending is 3% after adjustment for inflation (10). We estimated

cumulative 5-year costs by using discount rates of 0% (i.e., no discounting) and 3%.

Although cost data are available at the level of the individual service and can be reported at any level of aggregation and by any unit of time, the small sample size precluded analysis of specific cost components (e.g., inpatient hospital, physician, and laboratory) or periods shorter than each 30-day interval after the trial entry or trial entry-equivalent date. Preliminary analysis of costs at a more disaggregated level showed no discernible patterns contradicting the findings for total medical costs.

Statistical Analysis

The primary analysis of cost differences was conducted on the total sample of 122 observations, containing 61 matched pairs of case and control patients. Paired comparison formed the primary basis of analysis involving intrapair differences in costs before adjustment for censored observations. Two-sample comparisons were also conducted of the Kaplan–Meier sample average cost, an estimate of mean cumulative (5-year) cost across a population in the presence of censored observations (11,12). The Kaplan–Meier sample average cost estimator has been shown to be an unbiased estimate of cumulative cost under conditions of independent censoring of observations, whereas cost analysis that is not adjusted for censored observations may be biased (12,13).

All comparison-wise type I error rates were set at 5%, and all testing procedures were two-sided. Paired *t* tests based on matched samples of 61 observations provide 80% power to detect differences of 0.37 standard deviation from zero, a moderate effect size according to Cohen's classification (14). The observed standard deviation of the differences in total cost was \$74 354, so the 61 observations provided 80% power to declare an intrapair average difference of \$27 510. Paired *t* tests on log-transformed costs led to no differences in inference and, therefore, are not reported. Power for the nonparametric procedures was of a comparable nature, given the assumptions of nonnormality. All *P* values are two-sided.

RESULTS

Characteristics of Case and Control Patients

Table 1 shows the characteristics of case patients and control patients who survived each step of the matching process. The

133 case patients successfully matched in the first stage were similar to the original sample, except that those case patients for whom matches were found had poorer performance scores on average ($P < .001$).

The first-stage matching process found 617 unique control patients eligible for chart review. Patients with breast cancer and early stage cancers were heavily overrepresented in the pool of potential control patients, whereas patients with gastrointestinal cancers were underrepresented. The disproportionately small number of potential control patients with gastrointestinal cancers may have resulted from the stringent diagnosis date criteria used to match colorectal cancer patients.

Many potential control patients identified in the first stage of matching were rejected in the second stage of matching. Of the 133 case patients surviving the first stage, only 61 were successfully matched in medical record review. These 61 case patients were enrolled in 36 different clinical protocols. The majority (54%) of excluded control patients were not eligible for the trial or were not clinically equivalent to the case patient (Table 2). In 36% of the excluded records, however, discrepancies were found between the medical record and other data sources, particularly the tumor registry.

Comparison of case and control patients showed no statistically significant differences in the proportion of case patients who were censored, in the median number of months of follow-up, or in survival. By the end of the cost measurement period (December 1995), 45 (74%) case patients and 41 (67%) control patients had died. In 34 (56%) of the 61 matched pairs, both case and control patients died; in nine (15%) of the 61 matched pairs, both were still alive at the end of the cost measurement period. Roughly 10 subjects per year had index dates during the period from 1988 through 1991, and roughly five matched pairs per year had index years during the period from 1992 through 1994.

Table 1. Selected characteristics of case patients and control patients*

	Original case patients	First-degree matches			Final matches		
		Case patients	Control patients	Two-sided <i>P</i> †	Case patients	Control patients	Two-sided <i>P</i> †
No.	176	133	617		61	61	
Male, %	44.3	46.6	29.5	.001	50.8	50.8	1.0
Censored, %	NA	18.1	62.6	<.001	24.6	32.8	.32
By site of cancer, % of total patients‡				.001			1.0
Unknown	2.3	3.0	0.8		0.0	0.0	
Gastrointestinal	38.6	39.1	17.7		32.8	32.8	
Genitourinary	13.6	12.0	5.8		14.8	14.8	
Breast	11.9	15.8	44.1		18.0	18.0	
Lung	9.7	12.8	18.0		18.0	18.0	
Central nervous system	8.0	5.3	2.1		3.3	3.3	
Blood	4.0	6.8	9.1		9.8	9.8	
Head/lymphatic	1.8	5.3	2.4		3.3	3.3	
Other	9.1	0	0		0	0	
By stage group, % of total patients‡				.001			1.0
1	11.9	14.3	38.1		9.8	9.8	
2	14.8	12.0	14.6		8.2	8.2	
3	34.1	32.3	23.8		37.7	37.7	
4	34.1	34.6	14.4		34.4	34.4	
Unknown	5.1	6.8	9.1		9.8	9.8	
ECOG score 0–1, % of total patients	90.3	62.6	18.5	<.001	93.4	91.8	.5

*NA = not available; ECOG = Eastern Cooperative Oncology Group.

†Paired *t* test.

‡Not all columns add up to 100 as a result of rounding.

Table 2. Reasons for exclusion of potential control patients through records review

Reason for exclusion	No. of patients excluded	%*
Protocol eligibility violated		
Nonmetastatic disease for metastatic protocol	137	31.2
Site of metastatic disease not appropriate to protocol	8	1.8
Age outside protocol eligibility requirement	1	0.2
Other eligibility criteria not met	30	6.8
Patient otherwise nonequivalent		
Too ill or poor performance status	43	9.8
Metastasis outside trial entry time frame	19	4.3
Data errors		
Misclassified in Mayo Clinic Tumor Registry	109	24.8
Not an Olmsted County resident	4	0.9
Treated at Federal Medical Center	24	5.5
Enrolled on study protocol	22	5.0
Control patient matched to another case patient	22	5.0
Patient eligible for standard treatment	2	0.5
Other miscellaneous	18	4.1

*Numbers in this column do not add up to 100 as a result of rounding.

The index date differed between the case patient and the matched control patient by 38 days (average, mean, and median; paired *t* test *P* = .55; Wilcoxon signed rank *P* = .54). The maximum difference in index dates observed was just over 1000 days. Control patients were followed on average 3.7 months longer than case patients (median = 0; *t* test *P* = .3; Wilcoxon *P* = .53).

Thirty-six subjects (30% of the 122 observations in the study) were censored at termination of cost measurement (December 1995). Of the 36 censored observations, the medical records of 35 subjects were active after the termination date. Thus, one study subject (a case patient) was potentially lost to follow-up before the cost measurement termination date.

About one half of the patients in the 61 matched pairs were drawn from the population of patients with gastrointestinal or genitourinary cancers (Table 1), and 18% of the patients had

breast cancer. All but 17% of the patients had late stage tumors. The sexes were represented about equally. All but four of the case patients as well as five of the control patients had an Eastern Cooperative Oncology Group performance status of either 0 or 1.

Cost Comparisons

Summary statistics for total costs before adjustment for censored observations are given in Table 3. The mean 5-year cost per patient was slightly more than \$40 000 for both case and control patients, but costs for case patients were approximately 5% higher than those for control patients, who did not participate in trials. These results were not statistically significant, however, and variability among the pairs was marked. Some case patients incurred costs that were more than \$200 000 greater than the costs incurred by their matched control patients, whereas some control patients incurred costs that were more than \$200 000 greater than the costs incurred by their matched case patients (Fig. 1).

Discounting health care costs to their present value made little difference to the cost estimates or to the estimated differences between case and control patients, largely because a high proportion of patients lived for less than 1 year and the selected annual discount rate was low. For example, the mean intrapair difference in 5-year discounted costs was \$1998 compared with an undiscounted difference of \$2120. Because cost levels and differences were generally insensitive to discounting, we report only undiscounted costs.

In the first 30 days, patients enrolled in trials cost an average of \$569 more than the control patients. Costs incurred during the first 90 days were almost identical between the two groups. By the end of the first year, however, the mean difference between case and control patients had risen to about \$900, or about 4% of the mean cost for a patient not enrolled in a cancer trial. The difference in median cost at the end of the first year was statistically significant (*P* = .03), but the difference in means was not. Differences beyond the second year became more difficult to interpret because of the small number of patients surviving at that point. Overall, the average cost associated with being enrolled in a clinical trial was consistently 5%–11% higher than

Table 3. Mean (median) costs for various times from index date (1995 U.S. dollars)

Period	Total cost from index date*				Two-sided <i>P</i> ‡
	Case patients (n = 61)	Control patients (n = 61)	Difference† (case – control)	% difference	
First month	\$5718 (\$1842)	\$5149 (\$1941)	\$569 (-\$453)	11.1	.78 (.43)
First 3 months	\$11 955 (\$6172)	\$11 937 (\$5347)	\$18 (\$752)	0.2	1.0 (.69)
First 6 months	\$18 492 (\$9052)	\$17 427 (\$6138)	\$1065 (\$3830)	6.1	.84 (.01)
First year	\$24 660 (\$14 213)	\$23 763 (\$11 881)	\$898 (\$6771)	3.8	.88 (.03)
First 5 years	\$43 495 (\$29 639)	\$41 375 (\$19 185)	\$2120 (\$7284)	5.1	.22 (.13)

*All costs are undiscounted and for censored observations.

†The transitive property of subtraction applies only to the means (e.g., the mean of the differences is the difference of the means). The other statistics are calculated on the basis of intrapair differences.

‡Paired *t* test.

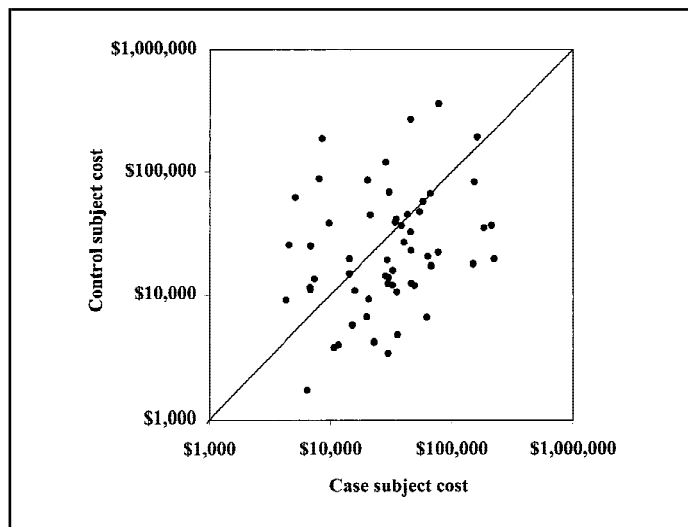


Fig. 1. Five-year cost comparison (log scales) for various case and control pairs presented in U.S. dollars adjusted to 1995 levels.

the average costs associated with not being enrolled in clinical trials.

For every 30-day month that a patient was alive and available to follow-up, the mean difference between case and control patients was \$247, and the median difference was \$366 (Table 4). Although neither of these measures was statistically significant, the median difference did have a *P* value of .06. Thirty-nine (64%) of the pairs involved case patients who incurred more expenses than the matched control patient. Table 4 also presents the maximum monthly cost incurred for each patient. This analysis tests whether patients who enter trials experience bolus amounts of treatment upon initial entry or cause the system to incur greater catastrophic costs as a result of closer monitoring. Case patients had slightly higher costs on average (\$177 and \$1342 difference in the mean and median, respectively). However, in a substantial minority (25 pairs or 41%) of the 61 pairs, the maximum cost for the control patient was higher than that for the case patient.

We analyzed costs in the months preceding death for the 34 matched pairs in which both subjects died during the study period (Table 5). Costs in the last few months of life were higher for case patients than for control patients. In roughly 65% of the 34 pairs, case patients incurred greater costs consistently over the last year of life. Total 5-year costs in this subgroup averaged

\$49 400 per control patient, so costs incurred in the last 3 months of life amounted to about 15% of the total for control patients but were almost 29% for case patients. Patients in trials had monthly costs during the last 3 months that were twice as high as during the previous 9 months, whereas the monthly costs for control patients did not rise appreciably as death approached.

Kaplan–Meier Analyses

Kaplan–Meier survival analysis did not reveal a statistically significant difference in survival (logrank *P* = .06), but control patients in the sample survived longer than did case patients (median survival time = 724 days and 493 days, respectively). After 1 year, the adjusted survival rate in case patients was 63 survivors per 100 subjects, compared with 68 survivors per 100 subjects in control patients.

The cumulative 5-year Kaplan–Meier sample average costs for case and control patients without discounting are shown in Fig. 2. The average cumulative 60-month cost after adjustment for censoring was \$46 424 for the case patients and \$44 133 for the control patients, a difference of 5.2%. This difference was not statistically significant (*P* = .833) based on an estimate of variance obtained by the bootstrap method involving 10 000 simulated samples (15). At the end of the first 12 months, the Kaplan–Meier sample average cumulative cost was \$24 645 for case patients versus \$ 23 964 for control patients, a difference of 2.8%. In 61% of the bootstrapped samples, case patients had higher 5-year Kaplan–Meier sample average costs than control patients. Discounting at a rate of 3% per year had minimal effect on the results. Thus, the estimated costs for each group and cost differences between the two groups were essentially the same when adjustments were made for censored observations as when they were not.

DISCUSSION

This population-based study of the incremental patient care costs associated with participation in cancer trials showed that trial enrollment was associated with a modest (5%–10%) increase in costs over various follow-up periods. These results were robust across a variety of statistical procedures and distributional or logistic assumptions. The bulk of additional costs attributable to trial participation occurred in the first few months after trial enrollment. The observed cost differences decreased as time progressed. However, of those pairs whose members were

Table 4. Monthly cost estimates (1995 U.S. dollars)

	Case patients (n = 61)	Control patients (n = 61)	Intrapair difference* (case – control)	Two-sided <i>P</i> †
Cost per month of follow-up				
Mean (95% CI‡ for mean)	\$2536 (\$1894 to \$3178)	\$2290 (\$1360 to \$3220)	\$247 (–\$728 to \$1222)	.61
Median	\$2052	\$1100	\$366	.06
Minimum	\$89	\$63	–\$17 077	
Maximum	\$15 319	\$22 751	\$12 838	
Maximum monthly cost				
Mean (95% CI‡ for mean)	\$10 709 (\$7510 to \$13 908)	\$10 531 (\$6328 to \$14 734)	\$177 (–\$5094 to \$5548)	.95
Median	\$6379	\$5545	\$1342	.36
Minimum	\$278	\$268	–\$73 560	
Maximum	\$72 178	\$82 095	\$68 003	

*The transitive property of subtraction applies only to the means (e.g., the mean of the differences is the difference of the means). The other statistics are calculated on the basis of intrapair differences.

†Paired *t* test.

‡CI = confidence interval.

Table 5. Mean (median) costs incurred (in U.S. dollars) within various times from death

Period	Case patients (n = 34)	Control patients (n = 34)	Intrapair difference* (case - control)	Two-sided P†
Last months	\$4038 (\$1313)	\$3009 (\$223)	\$1029 (\$307)	.44 (.18)
Last 3 months	\$11 487 (\$8844)	\$7311 (\$5189)	\$4176 (\$3769)	.05 (.04)
Last 6 months	\$18 304 (\$14 600)	\$10 789 (\$10 142)	\$7514 (\$6417)	.01 (.01)
Last year	\$27 068 (\$23 174)	\$27 566 (\$14 284)	-\$498 (\$9235)	.95 (.07)

*The transitive property of subtraction applies only to the means (e.g., the mean of the differences is the difference of the means). The other statistics are calculated on the basis of intrapair differences.

†Paired *t* test.

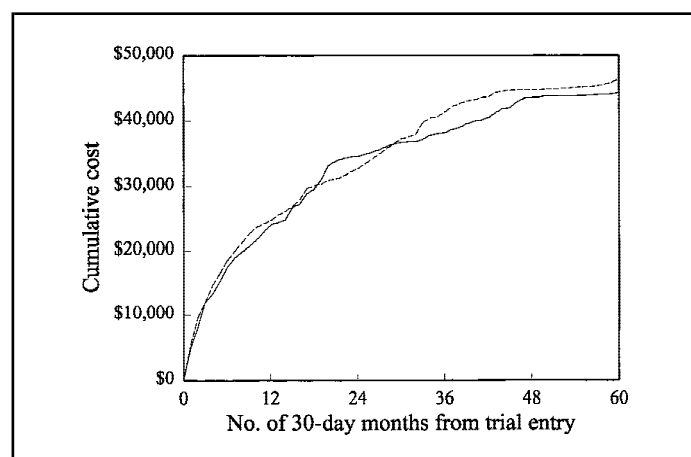


Fig. 2. Mean cumulative cost derived by the Kaplan–Meier sample average estimate. Data for the cost are expressed in U.S. dollars adjusted to 1995 levels. **Dashed line** = case patients. **Solid line** = control patients. The 95% confidence interval (CI) at 12 months after trial entry was \$17 893–\$31 397 for case patients and \$13 244–\$34 664 for control patients. At 60 months after trial entry, the 95% CI was \$33 312–\$59 536 for case patients and \$27 610–\$60 675 for control patients. These 95% CIs were based on estimates of variance obtained by the bootstrap method involving 10 000 simulated samples.

both followed until death, case patients incurred a substantially higher cost in the last 3 months of life than did control patients. Control patients in this sample lived longer than did trial participants, which may explain in part the decline in cumulative cost differences averaged across all subjects over the follow-up period.

Although several important categories of medical care costs went unmeasured, these were largely services that would be unlikely to differ systematically with trial enrollment. The most notable exception is outpatient prescription drugs. Experimental chemotherapeutic drugs are typically donated by the trial sponsor and would, therefore, not be part of the cost burden to patients or to insurers. However, other drugs, such as those for palliation of side effects or cancer symptoms, would add to patient care costs. If these outpatient prescription drug costs are higher under investigational protocols, their exclusion underestimates the incremental cost of clinical trials to patients and insurers. Also, to the extent that treatment trials compare an experimental drug donated by its sponsor with standard chemotherapy administered to hospital inpatients (whose costs were included in this study), the exclusion of experimental treatment

costs underestimates the cost of cancer trials to society but not to insurers.

The longer survival of control patients in this sample affected the estimate of the per-month incremental costs of enrolling in a cancer trial. When total costs are divided by the number of months during which patients were available to follow-up, they were \$247 per month higher for case patients than for control patients. However, over the full 5-year follow-up period, the Kaplan–Meier sample average monthly cost across the entire sample of case patients was only \$38 higher than that for the control patients.

The high variation in 5-year costs within matched pairs underscores a major limitation of the study: its small sample size and the consequent limited statistical power to estimate true differences with much accuracy. High, unexplained variation in medical care expenditures is the rule rather than the exception throughout medical care. For example, in a study of non-elderly health maintenance organization enrollees in Minnesota, demographic and clinical predictors explained only 5%–10% of the variation in annual medical care costs (16). Our data do suggest that health plans may find it difficult to manage the costs of cancer patients in general unless they can spread the risks across a large population.

This study demonstrated the difficulty that can be encountered in trying to match case patients with eligible control patients by the use of multiple criteria. Our two-stage matching process demonstrated that reliance on data elements typically available in institutional tumor registries is inadequate to ensure equivalence between patient groups. Not only are the data items collected in registries insufficient to describe the clinical and prognostic attributes of patients, but also sometimes they may disagree with the medical record on which they are based. Ironically, the pool of eligible control patients also may have been limited by the strong commitment to clinical research on the part of both cancer clinicians and patients in Olmsted County.

Even with intensive efforts to find equivalent patients through detailed medical records review, the case–control methodology cannot fully rule out the possibility of unobserved selection biases in trial enrollment. Those who choose not to enroll may be predisposed to use medical care more or less intensively than those who do enroll in such studies. Clinicians might also encourage patients with more aggressive disease to enroll in clinical trials. Some control patients might have been improperly declared eligible because clinical findings bearing on eligibility were not recorded in the medical record. We know of no studies

to suggest how such selection biases, if they exist, might be expected to affect treatment costs. Neither medical records nor clinical trial data systems routinely contain information on individuals who were judged eligible but refused enrollment. Systematic collection of such information as part of clinical trial designs would greatly facilitate the matching process in future research of this type.

That this study was conducted on cancer patients who were diagnosed at one institution and who resided in a single county with a population of approximately 110 000 raises questions about the generalizability of the findings across a broader spectrum of health care environments. Most importantly, patients who did not enroll in trials typically were served by the same clinicians and health care providers as those who enrolled. Thus, they were not subjected to different practice styles apart from the circumstances of the trial. In other communities, the probability of trial enrollment might be contingent on the practice styles and referral pathways of the primary care and cancer providers. Larger differences (of unpredictable direction) in medical costs might result.

All of the clinical trials investigated in this study evaluated chemotherapeutic agents. None compared a highly expensive new technology, such as bone marrow transplantation for late stage breast cancer, with much less expensive conventional management, yet managed care organizations clearly focus on such "outlier" trials when they express misgivings about funding clinical research (17). This study offers some reassurance that chemotherapeutic trials may not in and of themselves imply budget-breaking costs. Cancer itself is a high-cost illness. This study suggests that chemotherapy protocols may add relatively little to that cost. Replication of these results in other carefully designed studies across different care settings is needed before conclusive statements about relative costs can be made.

REFERENCES

- (1) Mechanic R, Dobson A. The impact of managed care on clinical research: a preliminary investigation. *Health Affairs* 1996;15:72-88.
- (2) Melton LJ 3rd. History of the Rochester Epidemiology Project. *Mayo Clin Proc* 1996;71:266-74.
- (3) World Health Organization (WHO). *International Classification of Diseases for Oncology*. 2nd ed. Geneva (Switzerland): WHO; 1990.
- (4) Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* 1982;5:649-55.
- (5) Lipscomb J, Ancukiewicz M, Parmigiana G, Hasselblad V, Samsa G, Matchar DB. Predicting the cost of illness: a comparison of alternative models applied to stroke. *Med Decis Making* 1998;18(2 Suppl):S39-56.
- (6) Finkler SA. The distinction between cost and charges. *Ann Intern Med* 1982;96:102-9.
- (7) Finkler SA. The distinction between costs and charges. In: Finkler SA, editor. *Issues in cost accounting for health care organizations*. Gaithersburg (MD): Aspen Publishers; 1994. p. 81-93.
- (8) Kahn AE. *The economics of regulation: volume 1, principles and institutions*. New York (NY): John Wiley & Sons; 1970.
- (9) Prospective Payment Assessment Commission. *Medicare and the American health care system: report to Congress*. Washington (DC): Prospective Payment Assessment Commission; 1997.
- (10) Gold MR, Siegel J, Russell LB, Weinstein MC. *Cost-effectiveness in health and medicine*. New York (NY): Oxford University Press; 1996.
- (11) Etzioni R, Urban N, Baker M. Estimating the costs attributable to a disease with application to ovarian cancer. *J Clin Epidemiol* 1996;49:95-103.
- (12) Lin DY, Feuer EJ, Etzioni R, Wax Y. Estimating medical costs from incomplete follow-up data. *Biometrics* 1997;53:419-34.
- (13) Hallstrom AP, Sullivan SD. On estimating costs for economic evaluation in failure time studies. *Med Care* 1998;36:433-6.
- (14) Cohen J. *Statistical power analysis for the behavioral sciences*. Hillsdale (NJ): Lawrence Erlbaum & Associates; 1988.
- (15) Efron B. *The jackknife, the bootstrap, and other resampling plans*. Philadelphia (PA): Society for Industrial and Applied Mathematics; 1982.
- (16) Fowles JB, Weiner JP, Knutson D, Fowler E, Tucker AM, Ireland M. Taking health status into account when setting capitation rates: a comparison of risk-adjustment methods. *JAMA* 1996;276:1316-21.
- (17) Daniels N, Sabin JE. Last chance therapies and managed care. Pluralism, fair procedures, and legitimacy. *Hastings Cent Rep* 1998;28:27-41.

NOTES

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²Detailed documentation of the unit costing methodology is available from the authors upon request.

³The logic behind the concept of opportunity cost is described by Kahn (8) as follows: "The basic economic problem, in short, is the problem of choice. A decision to produce one good or service is a decision to produce less of all other goods and services taken as a bunch. It follows that the cost to society of producing anything consists, really, in the other things that must be sacrificed in order to produce it." (page 66).

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