Special Article

GAINS IN LIFE EXPECTANCY FROM MEDICAL INTERVENTIONS — STANDARDIZING DATA ON OUTCOMES

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ABSTRACT

Background The gain in life expectancy is an important measure of the effectiveness of medical interventions, but its interpretation requires that it be placed in context. The interpretation of gains in life expectancy is particularly problematic for preventive interventions, for which the gains are often just weeks or even days when averaged across the entire target population.

Methods We tabulated the gains in life expectancy from a variety of medical interventions as reported in 83 published sources and categorized them according to target population and disease. We considered prevention in populations at average risk for particular diseases, prevention in populations at elevated risk, and treatments in populations with established disease.

Results The gains in life expectancy from preventive interventions in populations at average risk ranged from less than one month to slightly more than one year per person receiving the intervention, but the gains were as high as five years or more if the prevention was targeted at persons at especially high risk. The gains in life expectancy from treatments of established disease ranged from several months (for coronary thrombolysis and revascularization to treat heart disease) to as long as nine years (for chemotherapy to treat advanced testicular cancer).

Conclusions A gain in life expectancy from a medical intervention can be categorized as large or small by comparing it with gains from other interventions aimed at the same target population. A gain in life expectancy of a month from a preventive intervention targeted at populations at average risk and a gain of a year from a preventive intervention targeted at populations at elevated risk can both be considered large. The framework we developed for standardizing gains in life expectancy can be used in the interpretation of data on the outcomes of interventions. (N Engl J Med 1998;339:380-6.)

THE gain in life expectancy is an important outcome of many medical interventions. It can help patients and physicians decide whether the benefits of an intervention outweigh its harm or help an insurance company decide whether or not to cover a new medical procedure. It can help a pharmaceutical company decide whether a new drug is sufficiently more effective than the standard drugs to be worth marketing or help an expert panel designing guidelines for clinical practice sharpen its recommendations. Although there are well-developed criteria for assessing the quality of evidence of the effectiveness of a medical intervention (for example, the P value of a statistical test or the adequacy of controls for confounding), there is no criterion for assessing its magnitude.

It is especially difficult to establish a perspective on the gains in life expectancy from preventive interventions, because frequently only a small fraction of the recipients of the intervention actually realize any benefit, driving down the average gain. Thus, strategies aimed at preventing life-threatening diseases may appear ineffective alongside treatments for those who are already ill.

In this article, we propose that a gain in life expectancy from a medical intervention can be categorized as large or small by comparing it with gains from others of its type — that is, with other interventions aimed at the same target population. We present a comprehensive set of data on published gains in life expectancy from medical interventions, stratified according to the target population. This work is a contribution to the developing technology of calibrating and standardizing the effectiveness of medical interventions, and it can help inform a clinician's intuition or a policy maker's judgment about the importance of a life-extending preventive service or treatment.

In the field of public health, the effectiveness of preventive services is usually measured in terms of the number of cases prevented or the number of lives saved. Thus, the effectiveness of aggressive screening for colorectal cancer has been estimated to be approximately 2000 cases prevented per 100,000 persons screened.[1] This type of measurement, however, does not tell us how premature the avoided deaths would have been. For example, preventing a teenager's death from an automobile accident would be regarded differently from preventing a death from

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hospital-acquired pneumonia in a patient with end-stage cardiac disease.

By contrast, the effectiveness of medical treatments is often measured in terms of the increase in the proportion of people alive at fixed points in time — typically, changes in one-, two-, or five-year survival. Such changes can be given in relative or absolute form, which often leads to confusion. For example, a base-line mortality rate of 20 percent is reduced to 19 percent by a 5 percent reduction in relative risk, but it is reduced to 15 percent by a 5 percent reduction in absolute risk. Reporting the effectiveness of a treatment as a relative improvement is misleading, because the base-line death rate is ignored, but reporting improvements in survival rates in absolute terms still leaves some questions unanswered. Are the survivors all destined to live "normal" lives? What is the justification for focusing on a particular interval after the intervention (e.g., 5 years), given that two populations with the same chances of surviving for 5 years may, by virtue of risk factors or coexisting illnesses, have very different probabilities of surviving the first 12 months or the following 20 years? The same questions are unanswered by another common measure, the increase in the median survival time (or half-life) of the cohort, which is often used for reporting the results of clinical trials of treatments for cancer and other progressive diseases.

An argument for a new measurement — the number of people who must be treated in order to prevent one expected death or, more generally, to produce one successful outcome — has been made on the grounds that this would give the clinician an idea of how to apportion effort.[2] This measurement is inversely proportional to the number of lives saved and, again, does not tell us how long the survivors will live.

A much richer understanding of lifesaving effectiveness comes from comparing the full survival curves of treatment and control groups. The great advantage of the gain in life expectancy as a measure of outcome is that it is a direct measure of the shift in the survival curve caused by the intervention. Mathematically, the gain in life expectancy is the area between the two survival curves (Fig. 1). In contrast, each of the two traditional methods of measuring the effectiveness of treatments captures only one dimension of the shift in the survival curve and may even be misleading if the survival curves for the treatment and control groups cross.

There are two challenges associated with using the gain in life expectancy — one for the analyst and one for the user of the analysis. First, survival data are almost always censored, because some members of the cohort are still alive at the end of the clinical trial or observational study. A model must be constructed to extrapolate the survival curves beyond the end of the study, and the estimate of the gain in life expectancy may be very sensitive to the choice of model.

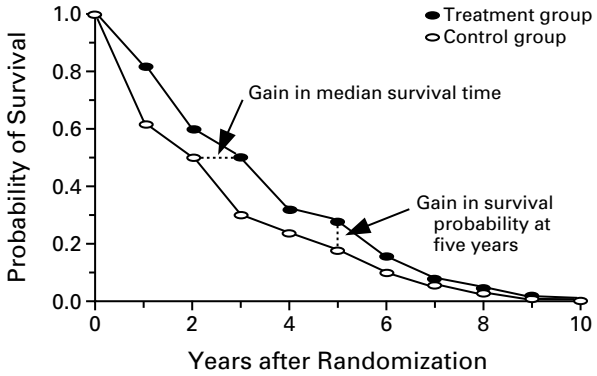

Figure 1. Hypothetical Survival Curves for a Treatment Group and a Control Group.

The life expectancy of an individual person corresponds to the area under the relevant survival czzzurve. Thus, the gain in life expectancy from the intervention is represented by the area between the two curves. Adapted from Naimark et al.[3]

Second, because the gain in life expectancy is a two-dimensional measure of effectiveness, it is cognitively difficult to develop an intuitive feel for what constitutes a large or a small gain. A gain is usually thought of as a certain gain at the end of life rather than as a probabilistic gain throughout the remainder of life.[3] (Often, most of the gain in life expectancy — the upward shift of the survival curve — occurs soon after the intervention.) This cognitive distortion is greater for preventive interventions than for treatments, because the base-line life expectancy is generally greater.

METHODS

Hypotheses

We began with some hypotheses about how the magnitudes of the gains in life expectancy might vary according to the characteristics of the target populations. Of the characteristics currently recorded, age, sex, and race are the primary determinants of life expectancy in the general population. In populations with risk factors for particular diseases and in populations with established diseases, these demographic factors become less important as the relative risk rises or the clinical status worsens.

The prevalence and incidence rates of the disease in the target population set upper bounds on the gain in life expectancy from a preventive intervention. Thus, a screening intervention can never lead to a large gain in life expectancy if the disease has a low prevalence, and a vaccination program can offer only a limited gain if the disease has a low incidence. Conversely, curative or palliative interventions are targeted at populations in which everyone already has the disease, so there is the potential for large gains. However, the same factor that makes the potential gain large — a poor prognosis — will often drive down the actual gain if survivors have other risks that reduce the potential gain in longevity.

Specifically, we might expect to find the following hypotheses to be true. First, the gains for older populations will be smaller than those for younger populations for several reasons: disease-specific mortality and competing risks of death increase with age, fatal complications from treatment are more likely, and there are fewer years that can be gained by averting a death.[4] Second, the gains for women will be a little larger than those for men if the disease is not sex-specific in either occurrence or severity, because women

have lower age-specific mortality rates than men. Third, if only a few people actually benefit from the intervention (e.g., because of a low incidence of disease in the case of primary prevention or a low prevalence of disease in the case of screening), the average predicted gain will necessarily be small, even if the lives of those few people are extended by many years. And fourth, the more advanced the disease in the target population, the poorer the prognosis for the population and the greater the potential gain from treatment, but that gain will be correspondingly harder to realize. These hypotheses cannot be tested formally with our data, since we are limited to a sample of interventions for which the gains in life expectancy have been estimated in published papers. Nevertheless, they explain some of the variation in gains seen in our results.

Collection of Data

For this study, the gains in life expectancy from various medical interventions were taken directly from or were calculated from data in 83 published sources, many of which were found through a Medline search. Sources were selected if they reported gains in life expectancy or the data required for a simple calculation of gains and if they were published in English. The quality of the analysis (other than as indicated by the publication of the report in a peer-reviewed journal) was not a criterion, since our aim was to gather information on gains in life expectancy for as wide a variety of interventions as possible. We made no attempt to select the "best" article when we found more than one on the same intervention, because comparing analyses of the same or similar interventions can be valuable. We rejected some sources because the technology of the intervention has changed substantially or is no longer used.

It is rare for the primary purpose of a study to be the calculation of gains in life expectancy. The majority of the articles that yielded the information we sought were either decision analyses[5] or cost-effectiveness analyses.[6] Many of these analyses were appended to clinical trials or epidemiologic investigations to quantify the magnitude of a clinical benefit. Many analyses of cost effectiveness could not be used as sources, because the authors had adjusted the reported gains in life expectancy for health-related quality of life or had discounted them to present value (or both), without reporting the corresponding unadjusted and undiscounted values, as is currently recommended.[7]

Some important interventions do not appear in our study. Investigators examine interventions that are salient because they are new, because they are controversial, or both. For instance, screening for and treatment of early-stage breast cancer are currently under intense scrutiny because of the controversy over the optimal age at which women should begin periodic mammographic screening. Thus, breast cancer is prominent in our results. We were able to find the gain in life expectancy from a new drug for survivors of stroke — ticlopidine — but not the gain from the standard drug, aspirin. Our results include some interventions that are used commonly and some that are seldom used; those presented here should not be interpreted as reflecting the full range of life-extending interventions.

Some authors modeled the gains in life expectancy for the typical patient, whereas others modeled the gains for many target populations, varying age, sex, risk factors, clinical status, and occasionally, race in their models. We do not present all these subgroup analyses; rather, we report the gains in life expectancy for selected target subpopulations and indicate that the results of other analyses are available in the cited articles.

Some authors reported gains in life expectancy as point estimates, whereas others reported ranges. These ranges are sometimes formal confidence intervals or credible intervals and sometimes reflect the effect of varying a key parameter or modeling assumption in a sensitivity analysis.

We converted all the gains in life expectancy to months. The number of significant figures and decimal places varies somewhat. In cases in which the gains were very small, they are necessarily reported to as many as three decimal places, but this does not imply any judgment of greater precision. For several interventions, we calculated the gains in life expectancy from data provided in the primary sources. Generally, these calculations involved a straightforward conversion of lives saved to life-years saved per person, with life tables used to estimate life expectancy.

Owing to space constraints, the tables we present here show gains in life expectancy from only 31 of the 83 published sources. The complete set of gains, as well as the details of our methods of calculating them from the primary-source data, is available on the following Web site: www.hsph.harvard.edu/organizations/hcra/peemt.html.

TABLE 1. PREVENTION IN POPULATIONS AT AVERAGE RISK.

DISEASE AND INTERVENTION	TARGET POPULATION	GAIN IN LIFE EXPECTANCY (MO)*	
		MALE SUBJECTS	FEMALE SUBJECTS
Cardiovascular disease			
Exercise consuming 2000 kcal/wk for 30 yr[8]	35-year-old men	6.2	NA
Quitting cigarette smoking[9]	35-year-olds	10	8
Hormone-replacement therapy with estrogen only for women who have had hysterectomies[10]	50-year-old women	NA	13
Cancer			
10 yr of biennial mammography[11]	50-year-old women	NA	0.8
Pap smear	20-year-old women	NA	
Every 3 yr for 55 yr[12]			3.1
Every yr for 55 yr[12]			3.2
Annual fecal occult-blood test, plus barium enema or colonoscopy	50-year-olds		
Every 5 yr for 25 yr[1]		2.5	2.2
Every 3 yr for 25 yr[1]		2.8	2.5
Infectious disease			
Measles vaccine[13]	Infants	0.09	
Rubella vaccine[13]	Infants	0.10	
Mumps vaccine[13]	Infants	0.01	
Pertussis vaccine[14]	Infants	0.11	
Hepatitis B virus vaccine[15]	Newborns	0.26	
	Adolescents	0.12	
	Adults	0.03	

*NA denotes not applicable.

RESULTS

Since we propose that a gain in life expectancy from a medical intervention can be categorized as large or small by comparing it with gains from other interventions aimed at the same target population, we present our results in tables organized primarily according to target population.

Tables 1 and 2 show data on preventive strategies, and Table 3 shows data on treatments. It is impossible to draw a clear distinction between prevention and treatment. For instance, prophylaxis against *Pneumocystis carinii* pneumonia in patients infected with the human immunodeficiency virus is, strictly speaking, a preventive strategy, but we chose to categorize it as a treatment.

In cases in which the gains in life expectancy estimated for men and women are different, both are presented. If the gain is not sex-specific, it is centered

TABLE 2. PREVENTION IN POPULATIONS AT ELEVATED RISK.*

DISEASE AND INTERVENTION	TARGET POPULATION	GAIN IN LIFE EXPECTANCY (MO)	
		MALE SUBJECTS	FEMALE SUBJECTS
Cardiovascular disease			
Reduction of diastolic blood pressure to 88 mm Hg[9]	35-year-olds with hypertension		
	Diastolic blood pressure of 90–94 mm Hg	13	11
	Diastolic blood pressure of >105 mm Hg	64	68
Reduction of cholesterol to 200 mg/dl (5.2 mmol/liter)[9]	35-year-olds with hypercholesterolemia		
	Cholesterol level of 200–239 mg/dl (5.2–6.2 mmol/liter)	6	5
	Cholesterol level of >300 mg/dl (7.8 mmol/liter)	50	76
Reduction of weight to ideal level[9]	35-year-olds		
	<30% over their ideal weight	8	6
	≥30% over their ideal weight	20	13
Quitting cigarette smoking[9]	35-year-old smokers	28	34
Hormone-replacement therapy with estrogen and progestin[10]	50-year-old women with a history of coronary artery disease	NA	11 to 26
	50-year-old women at high risk for coronary artery disease	NA	7 to 19
	50-year-old women at high risk for breast cancer	NA	−6 to 10
	50-year-old women at high risk for hip fracture	NA	2 to 13
Cancer			
Initial office biopsy to evaluate postmenopausal bleeding, followed by dilation and curettage or hysterectomy if needed[16]	Women at high risk	NA	
	50-year-old		6.0
	70-year-old		2.2
Prophylactic bilateral mastectomy[17]	Women who carry *BRCA1* or *BRCA2* mutation	NA	
	30-year-old		35 to 64
	50-year-old		12 to 28
Prophylactic bilateral oophorectomy[17]	Women who carry *BRCA1* or *BRCA2* mutation	NA	
	30-year-old		4 to 20
	50-year-old		1 to 10
Infectious disease			
Hepatitis B virus vaccine[15]	12-to-50-year-olds at high risk for hepatitis	0.15 to 0.24	
	Newborn babies whose mothers have been exposed to or have hepatitis B	0.28	
Testing of the blood supply for HIV[18]	Surgical patients		
	30-year-old	0.27	
	50-year-old	0.15	
	70-year-old	0.06	
Preoperative autologous blood donation[19]	Patients undergoing coronary-artery bypass grafting	0.002 to 0.004	

*NA denotes not applicable, and HIV human immunodeficiency virus.

between the columns for male and female subjects in the tables.

The age of the target population is the age from which the gain in life expectancy is estimated. For instance, in Table 1, the three-month gain associated with Pap smears is the gain that can be expected for 20-year-old women who embark on a lifelong screening program; a woman who begins screening for cervical cancer at 50 years of age will increase her life expectancy by less than three months.[12]

Table 1 shows the gains in life expectancy associated with prevention in populations at average risk. In these populations, the incidence and prevalence of disease matter enormously. For example, a program of physical exercise begun at the age of 35 years increases life expectancy by 6.2 months,[8] and complete cessation of smoking at the age of 35 increases life expectancy by 9 months,[9] but a decade of biennial mammography begun at the age of 50 increases life expectancy by only 0.8 month.[11] Even the highly effective childhood vaccines against measles, rubella, and pertussis offer gains in life expectancy of only approximately 0.1 month each.[13,14] For the preventive interventions targeted at people at average risk, it is evident from Table 1 that a gain on the order of only a month can be considered large.

TABLE 3. TREATMENTS OF PERSONS WITH ESTABLISHED DISEASE.*

DISEASE AND INTERVENTION	TARGET POPULATION	GAIN IN LIFE EXPECTANCY (MO)	
		MALE PATIENTS	FEMALE PATIENTS
Cardiovascular disease			
Myocardial revascularization with coronary-artery bypass grafting or percutaneous transluminal coronary angioplasty[20]	Men with coronary artery disease		NA
	1 Vessel	1–7	
	2 Vessels	0–8	
	3 Vessels	4–14	
Routine beta-blocker therapy[21]	55-year-old men who survive acute myocardial infarction		NA
	Low risk of recurrence	1.2	
	Medium risk of recurrence	4.1	
	High risk of recurrence	5.6	
Thrombolytic therapy with recombinant tissue plasminogen activator during suspected acute myocardial infarction[22]	Patients with suspected acute myocardial infarction	15	
Thrombolytic therapy with recombinant tissue plasminogen activator as compared with streptokinase[23]	Patients with suspected acute myocardial infarction		
	Inferior infarction	0.8–3.1	
	Anterior infarction	1.2–3.5	
Implantable cardioverter–defibrillator[24]	Survivors of cardiac arrest with recurrent ventricular arrhythmias that do not respond to conventional therapy	36–46	
Amiodarone therapy[24]	Survivors of cardiac arrest with recurrent ventricular arrhythmias that do not respond to conventional therapy	14–16	
Heart transplantation[25]	Candidates with end-stage cardiac failure	31–99	
Ticlopidine as compared with aspirin[26]	Patients at high risk for stroke	0.6	
Cancer			
Radical prostatectomy or radiation therapy, as compared with watchful waiting, with delayed hormonal therapy if needed[27]	65-year-old men with localized prostate cancer	1–11	NA
Adjuvant chemotherapy[28,29]	Women with breast cancer	NA	
	Node-positive		3.6
	Node-negative		7.7–11
Chemotherapy[30]	Patients with extensive small-cell lung cancer	6.6–8.2	
Chemotherapy[31]	Patients with advanced non–small-cell lung cancer	1.8–2.9	
Chemotherapy[32]	Men with advanced testicular cancer	107	NA
Autologous bone marrow transplantation as compared with standard chemotherapy[33]	Patients with relapsed non-Hodgkin's lymphoma	72	
Other			
Prophylaxis against *Pneumocystis carinii* pneumonia and toxoplasmosis[34]	Patients with advanced HIV disease	5.3	
Prophylaxis against *Mycobacterium avium* complex, fungal infections, or cytomegalovirus[34]	Patients with advanced HIV disease	0.2–0.3	
Elective surgery as compared with expectant management[35]	50-year-olds with symptomatic gallstones	1.7	3.4
Interferon therapy[36]	35-year-olds with chronic hepatitis B who are positive for hepatitis B e antigen and do not have cirrhosis	37	
Appendectomy[37]	Patients with suspected acute appendicitis		
	Probable	9–31	
	Possible	2–5	

*NA denotes not applicable, and HIV human immunodeficiency virus.

Table 2 shows the gains in life expectancy associated with prevention in populations at elevated risk. In some cases, the elevated risk is only slightly greater than the average risk for the disease; in other cases, it is much greater. Many of the interventions shown in this table yield gains on the order of a year. For example, 35-year-old male smokers who quit smoking gain 28 months of life expectancy,[9] and 50-year-old women at elevated risk for coronary artery disease gain 7 to 19 months from hormone-replacement therapy.[10] At the other extreme, the gain from preoperative autologous blood donation is very small — about two hours.[19]

Table 3 shows the gains in life expectancy associated with treatment in target populations with established cardiovascular disease, cancer, or other diseases. The gains from treatment of coronary artery disease increase with the severity of the disease, but few exceed a year. Most of the cancer treatments yield gains that are much smaller than those from the three aggressive preventive interventions shown in Table 2.[16,17] However, there are gains of several years associated with a number of the treatments shown in Table 3, such as implantable defibrillators for survivors of cardiac arrest (36 to 46 months),[24] bone marrow transplantation for relapsed non-Hodgkin's lymphoma (72 months),[33] and chemotherapy for testicular cancer (107 months).[32]

DISCUSSION

Those who provide and pay for medical care make decisions about preventive strategies and treatments in an environment in which quantitative measures of outcome are increasingly common. By collecting and categorizing the gains in life expectancy from a wide variety of medical interventions, we have developed benchmarks for the size of the gain that can be expected in various populations, thus providing a valuable resource for those who set clinical-practice guidelines or make intervention-specific decisions about insurance coverage. Moreover, the organization of gains in life expectancy according to target population, disease, and type of intervention has established a framework that can be used for the presentation of other standardized data on outcomes.

Virtually all life-extending medical care has both positive and negative effects on health-related quality of life, and sometimes reduction in morbidity is the main outcome of the intervention, with the life-saving benefit as a bonus. Information on gains in quality-adjusted life expectancy is available from many medical cost-effectiveness and decision analyses, and could be presented systematically alongside information on gains in life expectancy. Similarly, since many of the data on gains in life expectancy and quality-adjusted life expectancy are available from cost-effectiveness analyses, cost-effectiveness ratios — measured in both dollars per year and dollars per quality-adjusted year — could be added to our tables. Such efforts are fraught with difficulties, however, and until investigators follow reasonably uniform practices when conducting cost-effectiveness analyses, the results will be of limited value.

Although the gain in life expectancy is a richer measure of the effectiveness of "lifesaving" interventions than those used traditionally, it should not be used simplistically in clinical decision making. The reported gain in life expectancy is averaged across the target population receiving the intervention and offers no information about the distribution of the gains in life expectancy actually realized by particular patients. The mean gain may reflect a small gain for most members of a population but a very large gain for a few members who might have died prematurely without the intervention. For example, consider the triennial cervical-cancer screening program[12] shown in Table 1. The mean gain in life expectancy from screening is about 3 months for the target population, but the women whose cancers are detected preclinically actually gain an average of 25 years. Similarly, the average gains from vaccination of infants are all very small, but those whose deaths are averted gain virtually their whole lifetimes. Viewed this way, the gains of months in life expectancy from preventive interventions will often be equivalent to gains of years from medical treatments.

At the other extreme, those making decisions about the allocation of medical resources may be interested in the overall effect of interventions on the life expectancy of the whole population. A highly effective intervention will have a very small effect on the life expectancy of the population if the disease is rare. For example, the gain in life expectancy from chemotherapy for testicular cancer is about nine years for those receiving the intervention (Table 3).[32] However, because this disease is so rare, the gain from making this treatment available to the man at average risk is about one hour. This gain is very small in comparison with the population-wide gains of months from the preventive interventions for coronary heart disease[9] shown in Table 1.

The gains in life expectancy from medical interventions intended to prevent disease seem small because of the effect of averaging across a population, most members of which would never contract the disease. Our analysis establishes that a gain of a month from a preventive strategy aimed at the general population signals an important intervention.

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REFERENCES

1. Eddy DM. Screening for colorectal cancer. Ann Intern Med 1990;113: 373-84.
2. Laupacis A, Sackett DL, Roberts RS. An assessment of clinically useful measures of the consequences of treatment. N Engl J Med 1988;318: 1728-33.
3. Naimark D, Naglie G, Detsky AS. The meaning of life expectancy: what is a clinically significant gain? J Gen Intern Med 1994;9:702-7.
4. Welch HG, Albertsen PC, Nease RF, Bubolz TA, Wasson JH. Estimating treatment benefits for the elderly: the effect of competing risks. Ann Intern Med 1996;124:577-84.
5. Kassirer JP, Moskowitz AJ, Lau J, Pauker SG. Decision analysis: a progress report. Ann Intern Med 1987;106:275-91.
6. Russell LB, Gold MR, Siegel JE, Daniels N, Weinstein MC. The role of cost-effectiveness analysis in health and medicine. JAMA 1996;276:1172-7.
7. Siegel JE, Weinstein MC, Russell LB, Gold MR. Recommendations for reporting cost-effectiveness analyses. JAMA 1996;276:1339-41.
8. Hatziandreu EI, Koplan JP, Weinstein MC, Caspersen CJ, Warner KE. A cost-effectiveness analysis of exercise as a health promotion activity. Am J Public Health 1988;78:1417-21. [Erratum, Am J Public Health 1989;79: 273.]
9. Tsevat J, Weinstein MC, Williams LW, Tosteson ANA, Goldman L. Expected gains in life expectancy from various coronary heart disease risk factor modifications. Circulation 1991;83:1194-201. [Erratum, Circulation 1991;84:2610.]
10. Grady D, Rubin SM, Petitti DB, et al. Hormone therapy to prevent disease and prolong life in postmenopausal women. Ann Intern Med 1992; 117:1016-37.
11. Lindfors KK, Rosenquist J. The cost-effectiveness of mammographic screening strategies. JAMA 1995;274:881-4. [Erratum JAMA 1996;275: 112.]
12. Eddy DM. Screening for cervical cancer. Ann Intern Med 1990;113: 214-26.
13. White CC, Koplan JP, Orenstein WA. Benefits, risks and costs of immunization for measles, mumps and rubella. Am J Public Health 1985;75: 739-44.
14. Hinman AR, Koplan JP. Pertussis and pertussis vaccine: reanalysis of benefits, risks, and costs. JAMA 1984;251:3109-13.
15. Bloom BS, Hillman AL, Fendrick AM, Schwartz JS. A reappraisal of hepatitis B virus vaccination strategies using cost-effectiveness analysis. Ann Intern Med 1993;118:298-306.
16. Feldman S, Berkowitz RS, Tosteson ANA. Cost-effectiveness of strategies to evaluate postmenopausal bleeding. Obstet Gynecol 1993;81:968-75.
17. Schrag D, Kuntz KM, Garber JE, Weeks JC. Decision analysis — effects of prophylactic mastectomy and oophorectomy on life expectancy among women with *BRCA1* or *BRCA2* mutations. N Engl J Med 1997;336:1465-71. [Erratum, N Engl J Med 1997;337:434.]
18. Carson JL, Russell LB, Taragin MI, Sonnenberg FA, Duff AE, Bauer S. The risks of blood transfusion: the relative influence of acquired immunodeficiency syndrome and non-A, non-B hepatitis. Am J Med 1992;92:45-52.
19. Birkmeyer JD, AuBuchon JP, Littenburg B, et al. Cost-effectiveness of preoperative autologous donation in coronary artery bypass grafting. Ann Thorac Surg 1994;57:161-8.
20. Wong JB, Sonnenberg FA, Salem DN, Pauker SG. Myocardial revascularization for chronic stable angina: analysis of the role of percutaneous transluminal coronary angioplasty based on data available in 1989. Ann Intern Med 1990;113:852-71.
21. Goldman L, Sia STB, Cook EF, Rutherford JD, Weinstein MC. Costs and effectiveness of routine therapy with long-term beta-adrenergic antagonists after acute myocardial infarction. N Engl J Med 1988;319:152-7.
22. Levin LA, Jonsson B. Cost-effectiveness of thrombolysis — a randomized study of intravenous rt-PA in suspected myocardial infarction. Eur Heart J 1992;13:2-8.
23. Mark DB, Hlatky MA, Califf RM, et al. Cost effectiveness of thrombolytic therapy with tissue plasminogen activator as compared with streptokinase for acute myocardial infarction. N Engl J Med 1995;332:1418-24. [Erratum, N Engl J Med 1995;333:267.]
24. Larsen GC, Manolis AS, Sonnenberg FA, Beshansky JR, Estes NAM, Pauker SG. Cost-effectiveness of the implantable cardioverter-defibrillator: effect of improved battery life and comparison with amiodarone therapy. J Am Coll Cardiol 1992;19:1323-34.
25. O'Brien BJ, Buxton MJ, Ferguson BA. Measuring the effectiveness of heart transplant programmes: quality of life data and their relationship to survival analysis. J Chronic Dis 1987;40:Suppl 1:137S-158S.
26. Oster G, Huse DM, Lacey MJ, Epstein AM. Cost-effectiveness of ticlopidine in preventing stroke in high-risk patients. Stroke 1994;25:1149-56.
27. Fleming C, Wasson JH, Albertsen PC, Barry MJ, Wennberg JE. A decision analysis of alternative treatment strategies for clinically localized prostate cancer. JAMA 1993;269:2650-8.
28. Hillner BE, Smith TJ. Efficacy and cost effectiveness of adjuvant chemotherapy in women with node-negative breast cancer. N Engl J Med 1991;324:160-8.
29. Messori A, Becagli P, Trippoli S, Tendi E. Cost-effectiveness of adjuvant chemotherapy with cyclophosphamide + methotrexate + fluorouracil in patients with node-positive breast cancer. Eur J Clin Pharmacol 1996; 51:111-6. [Erratum, Eur J Clin Pharmacol 1997;51:427.]
30. Goodwin PJ, Feld R, Evans WK, Pater J. Cost-effectiveness of cancer chemotherapy: an economic evaluation of a randomized trial in small-cell lung cancer. J Clin Oncol 1988;6:1537-47.
31. Jaakkimainen L, Goodwin PJ, Pater J, Warde P, Murray N, Rapp E. Counting the costs of chemotherapy in a National Cancer Institute of Canada randomized trial in nonsmall-cell lung cancer. J Clin Oncol 1990; 8:1301-9.
32. Shibley L, Brown M, Schuttinga J, Rothenberg M, Whalen J. Cisplatin-based combination chemotherapy in the treatment of advanced-stage testicular cancer: cost-benefit analysis. J Natl Cancer Inst 1990;82:186-92.
33. Messori A, Bonistalli L, Costantini M, Alterini R. Cost-effectiveness of autologous bone marrow transplantation in patients with relapsed non-Hodgkin's lymphoma. Bone Marrow Transplant 1997;19:275-81.
34. Freedberg KA, Scharfstein JA, Seage GR III, et al. The cost-effectiveness of preventing AIDS-related opportunistic infections. JAMA 1998; 279:130-6.
35. Ransohoff DF, Gracie WA. Treatment of gallstones. Ann Intern Med 1993;119:606-19.
36. Wong JB, Koff RS, Tine F, Pauker SG. Cost-effectiveness of interferon-alpha 2b treatment for hepatitis B e antigen-positive chronic hepatitis B. Ann Intern Med 1995;122:664-75.
37. Neutra R. Indications for the surgical treatment of suspected acute appendicitis: a cost-effectiveness approach. In: Bunker JP, Barnes BA, Mosteller F, eds. Costs, risks, and benefits of surgery. New York: Oxford University Press, 1977:277-307.