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Mammographic Screening: Impact on Survival

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Introduction

Although randomized trials have shown that cancer screening saves lives, they provide little insight into the magnitude of the reduction in death rates that has been achieved, or could be achieved, by screening. The reason is that trials may not reach all individuals in the intervention group, may not have achieved the optimal screening interval, or may contain some patients in the nontreatment arm who have chosen to have screening outside of the trial. Furthermore, the impact of screening during actual practice may be lower than its impact during a trial, where special attention may be paid to compliance. Data on the actual survival of patients who are using screening are also very difficult to collect, and thus may frequently be unavailable. Because at least 15 years are required before one can reach an accurate measure of lethality, our knowledge of the impact of screening on survival during the most recent two decades must invariably be incomplete. To be able to estimate the actual effect of screening on the cancer death rate, we have developed two methods: (1) a Computer Simulation Model of Cancer Growth and Detection, which can estimate the impact of various patterns of screening use, particularly various screening intervals, on the cancer death rate; and (2) the SizeOnly Equation, which can estimate the risk of cancer death from data on tumor size. Here I will review both the application of these methods to breast carcinoma and the general medical implications of these findings; readers interested in the mathematical details and data can find them in the references.

Why Screening Works

Screening is believed to reduce cancer death by bringing cancers to medical attention at smaller, and thus more survivable, sizes. Surprisingly, although this idea has been appreciated for almost a century, there had not been a rigorous explanation for why this results in a lower level of cancer death, nor had there been a mathematical way to capture the relationship between tumor size and risk of cancer death. We found that a starting point could be made from an appreciation that the main cause of death for many cancers, including breast carcinoma, is the spread of cancer cells. If one or more cancer cells has spread to the periphery before the cancer has been removed by surgery and/or radiation therapy, then cancer will remain in the body and may give

rise to distant, lethal, metastatic disease (Michaelson, 1999; Michaelson *et al*., 1999, 2002a, 2005). Consider p as the probability, for every cell in a tumor of N cells, that a cell will leave the mass and give rise to distant metastatic disease. We have been able to develop simple mathematical expressions for estimating the value of this probability of spread from data on the survival rates of patients with tumors of various sizes (Michaelson, 1999; Michaelson *et al*., 1999, 2002a, 2005). Surprisingly, these calculations found that for breast carcinoma, renal cell carcinoma, and melanoma, the value of p changes as tumors increase in size, N, such that the relationship between p and N is well fit to a power function:

$$p = aN^b \quad (1)$$

where $b \sim -2/3$ for all three cancers that we have examined, while the value of a is characteristic of each malignancy. A very likely explanation for why the value of p declines with tumor size in a way that is captured by Eq. (1) is that as tumors get bigger there are more cells to "push aside" before a cancer cell can get out. In fact, we have been able to demonstrate this mathematically (Michaelson *et al*., 2005).

As we might imagine, given that p is the probability that a cell will leave a mass of cancer and give rise to distant metastatic disease, and N is the number of cells in that mass of cancer, the overall chance that the mass has given rise to such a lethal event, L, is roughly p times N. (For more precise methods of calculating the value of L, see Michaelson, 1999 and Michaelson *et al*., 2002a, 2005.) Because Eq. (1) allows us to estimate the value of p, and because breast carcinomas have been found to grow exponentially over the sizes that they are seen clinically, this made it possible to develop a computer simulation that could recapitulate the simultaneous day-to-day increase in tumor cell number, N, and lethality, L (Michaelson *et al*., 1999, 2001). The results of this computer program revealed an essential and unobvious feature of breast cancer biology: the chance of lethal metastatic disease does not increase gradually over time, but changes dramatically over a relatively short period. For example, the simulation results suggest that while 92% of breast carcinomas of 7 mm are curable by local excision, by 1½ years, when the tumors have reached 18 mm, only 75% will still be curable, and in an additional 1½ years, having reached 47 mm, only 33% are curable. This result of the simulation provides a likely explanation for why mammographic screening works: the rate of breast carcinoma growth, the probability of breast cancer spread, and the mammographic detectability of breast cancers, all have such fortuitous values that mammography is capable of finding tumors just before the point in time when there is an explosive increase in the fraction of cancers incurable by local treatment.

Cancers Become More Lethal as They Increase in Size

We could also use Eq. (1) to derive an expression, which we have called the SizeOnly Equation (Michaelson *et al*., 2002a), for relating tumor size, D, to the risk of cancer death, L:

$$L = 1 - e^{-QD^Z} \quad (2)$$

where e is the exponential constant, $Z = 1.33$ and $Q = 0.0062$. The SizeOnly Equation has proven to be remarkably good at predicting the risk of death for a considerable number of populations of breast carcinoma patients, as well as for subpopulations of patients whose tumors were detected at screening or detected on clinical grounds (Michaelson *et al*., 2002a, 2003d). As we shall see, this has proved to be a very useful tool for gauging the impact of screening from data on the sizes of the tumors found in women who used or did not use screening.

Present and Future Life-saving Impact of Screening

Only two studies (the Health Insurance Plan of New York (HIP) and Swedish Two-County Trials) have had the statistical power to detect the survival difference between women who are screened and women who are not screened. No trials have as yet compared different usages of screening, such as different screening intervals. Nor are there likely ever to be such trials, which would be prohibitively expensive to carry out and would not yield results for decades. Thus, we must rely on other methods to estimate the impact of such various usages of screening, such as various screening intervals, on the reduction in breast cancer death. One such approach is computer simulation (Michaelson *et al*., 1999, 2000, 2001; Blanchard *et al*., 2004, 2006). We saw the core of our simulation in the "Why Screening Works" section. However, before this simulation could be used to make useful predictions of the consequences of various usages of screening, the simulation had to be provided with accurate information on cancer growth, detection, and lethality. To do so, we developed new mathematical methods and collected new data (Michaelson *et al*., 2001) for estimating the sizes at which cancers become detectable at screening and on clinical grounds (Michaelson *et al*., 2003b), the growth rate of breast carcinoma (Michaelson *et al*., 2003c), and the probability of the spread of cancer cells (Michaelson *et al*., 2002a, 2005). The computer simulation was also provided with data from the U.S. Census and SEER (Surveillance Epidemiology and End Results) national cancer data repositories on the age-associated incidence of breast carcinoma (Ries *et al*., 2000), U.S. life expectancy by age, and age structure of the U.S. population (Anonymous, 1998). Our simulation also incorporated information on the costs of

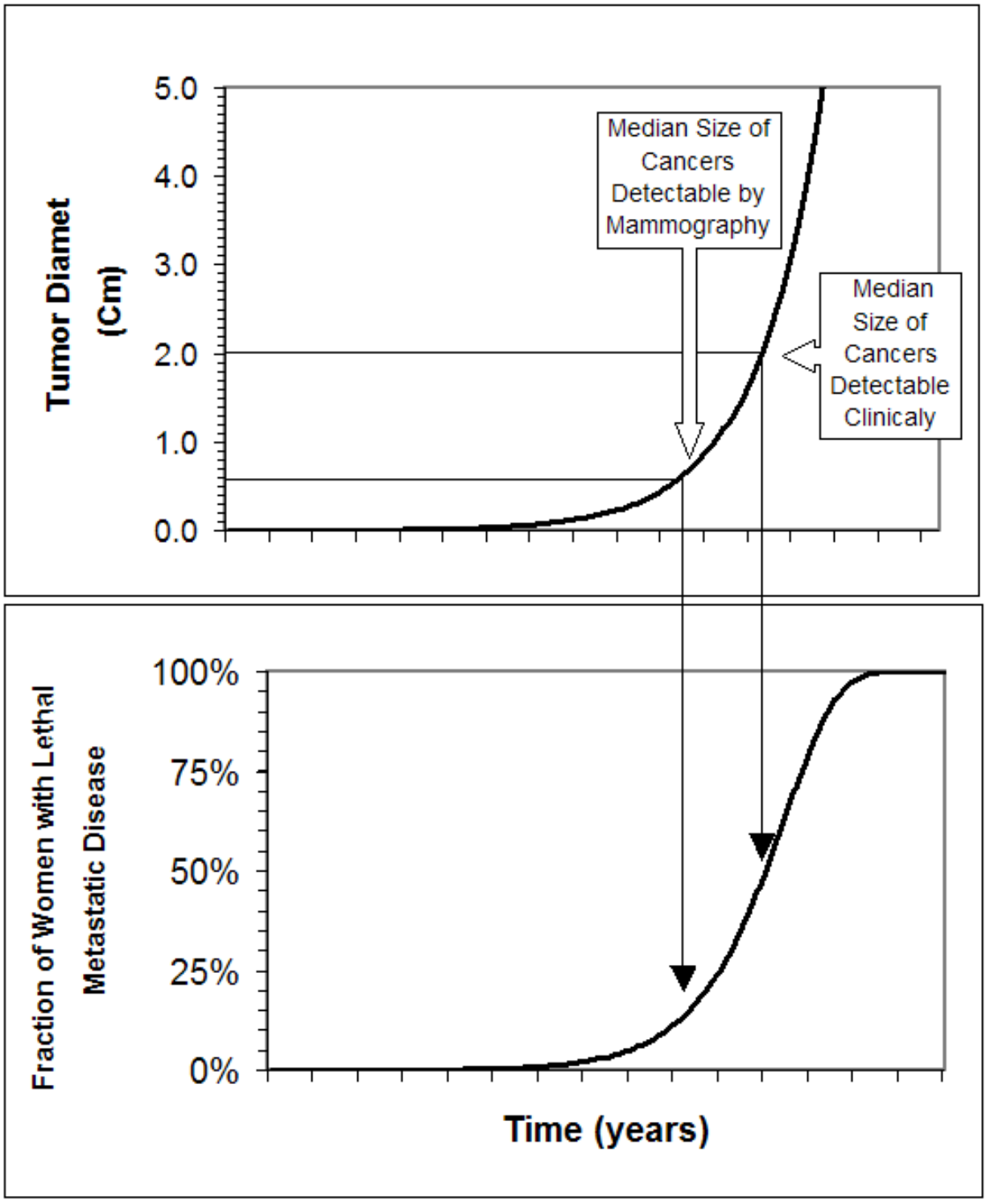

FIGURE 1. **Simultaneous calculation of breast cancer growth, based upon a doubling time of 130-days, and the probability of distant metastasis spread, Shown are the median tumor sizes detectable by screening mammography and detectable in the absence of screening.**

screening: both the direct costs associated with screening itself and the indirect costs, such as those that might arise from such expenses as biopsies used to rule out cancer in women with spurious signs that appear at screening. These cost data were used in the simulation to calculate the cost/benefit values of screening.

These simulation results revealed that high levels of breast cancer survival should be achievable if women are screened with sufficient frequency. For example, the simulation results indicated that for women age 65, breast cancer survival of > 90% should be achievable if the women utilize screening at least once a year, and even higher survival levels with more frequent screening. In contrast, screening every 3 years would appear to achieve a more modest survival of ~ 85%, while screening every 5 years yields a survival rate of ~ 75% (see end).

The simulation method made it possible to estimate the expected survival rates for both individuals and the population as a whole (estimated for all women, including those not using screening). The simulation was also made to provide values for the benefit of screening, in terms of "Cancer Free Years of Life Saved" per mammogram or per woman. For example, the simulation results revealed that the American Cancer Society recommendation of yearly screening from age 40 should be a highly effective strategy, yielding a populationwide 88% chance of breast cancer survival, which corresponds to ~ 66% populationwide reduction in death. Less intensive patterns of screening yielded lower levels of breast cancer survival. In contrast, the simulation revealed that the pattern of screening used in the United Kingdom of one mammogram every 36 months from age 50 to age 70 is capable of achieving only a 12% populationwide reduction in death (end).

Surprisingly, the simulation revealed that there might even be additional benefit from screening as frequently as twice a year from age 30. Such a strategy would appear capable of achieving a populationwide 91% chance of breast cancer survival, which corresponds to a 74% reduction in death, in comparison to women who do not use screening. Using a well-established mathematical technique, the equimarginal method (Samuelson and Nordhaus, 1998; Friedman 1990), it could be seen that this was also an efficient usage of screening, reaching the maximal reduction in death that was practical. Little additional benefit was to be derived by screening more frequently than twice a year, or screening women younger than 30. At the other end of the age spectrum, the simulation found no upper age limit where women no longer receive benefit. The simulation also revealed that a biannual screening strategy for women age 30 and older is cost-effective, with a cost of ~ $10,000 for each cancer-free year of life saved. Most medical procedures are far more expensive for the years of life that they save (Tengs *et al*., 1995). Organ transplant operations may have costs that reach into the millions of dollars per year of life saved. Indeed, these calculations tell us that even at this most intensive usage of screening, mammography remains, after immunization, one of our cheapest ways of saving lives (see end).

Life-saving Potential of Screening

What do these simulation results mean in terms of the number of breast cancer deaths that might be prevented by the optimized use of screening? Reaching the predicted survival level of 88% by prompt annual attendance screening from age 40, as predicted by the simulation, would mean an enormous reduction in breast cancer death because the current level of breast cancer survival is believed to be ~ 55–70%. Because there are more than 40,000 breast cancer deaths in the United States per year, this translates into tens of thousands of lives saved. The simulation also indicates that twice-yearly screening from age 30 might reach populationwide breast cancer survival levels of 91%. Because more than 200,000 women are found to have breast carcinoma in the United States each year, this translates into more than 5000 extra lives saved. The simulation results also indicate that women's widespread failure to follow the current guidelines probably leads to much higher breast cancer death rates, perhaps two or three times higher, than might be expected among the few women now using screening regularly.

Tumor Size and Survival

A second source of information on the benefit of screening could be found in data on the sizes of the cancers seen among women who used, or did not use, screening (Michaelson *et al*., 2001, 2002a, 2002b, 2003d). As we have noted, when such size data are available, the SizeOnly Equation provides a way to estimate the survival of such women. A particularly informative data set included information on 810 breast carcinoma patients treated at Massachusetts General Hospital in the 1990s (Michaelson *et al*., 2001). Of the 810 cancers, 204 were found clinically in women who had never used screening, 427 were found by mammography at screening, and 179 were found as palpable masses in women who had had a previous negative screening mammogram (Michaelson *et al*., 2001). The 179 cancers detected on clinical ground in women who had had at least one previous negative mammogram were especially informative because the time since the previous negative mammogram was known for each patient; 68 of the cancers were found within a year of the previous mammogram, and 111 were found more than a year afterward. By using tumor growth data to backcalculate the likely size of each of these 111 cancers, it could be seen that virtually all would have been too small to have been detected at screening at the time of the previous mammogram. Thus, almost all of these 111

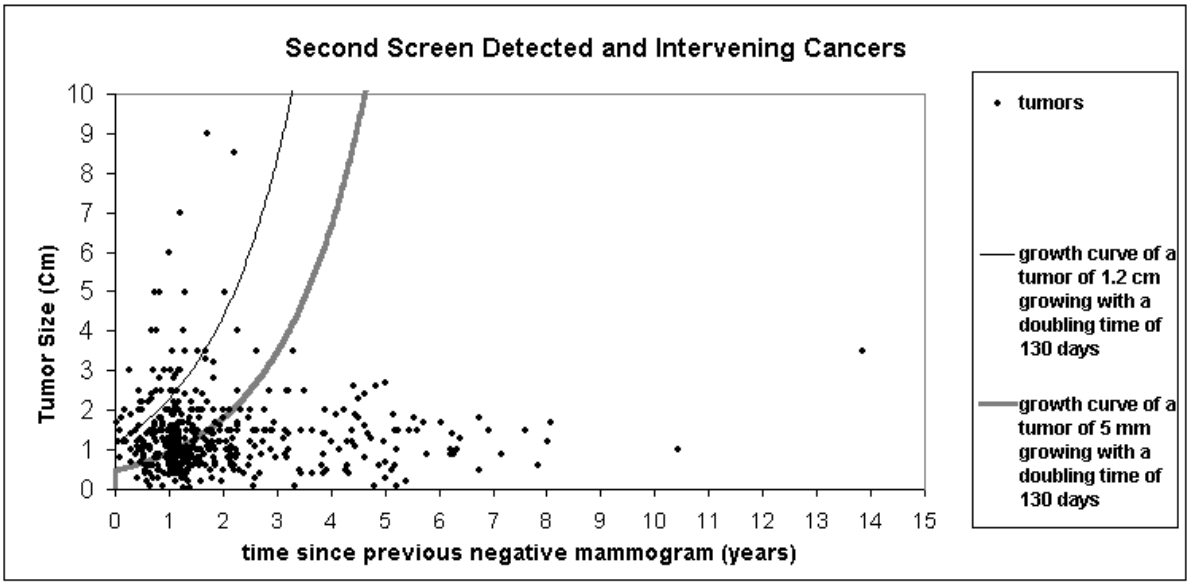

FIGURE 2 Scatter plot showing tumor size versus time since the previous negative mammogram for tumors found in women with a history of screening. Also shown are two expected growth curves, one of which is for a tumor that would have been 5 mm at the time of the negative mammogram, and other of which would have been 12 mm at the time of the negative mammogram, based upon a tumor doubling time of 130 days. Tumors above the light curve would have been 12 mm or larger, based upon a tumor doubling time of 130 days, when they were missed at the time of the previous negative mammogram, while tumors above the wide grey curve would have been 5 mm or larger. (Michaelson et al 2003b)

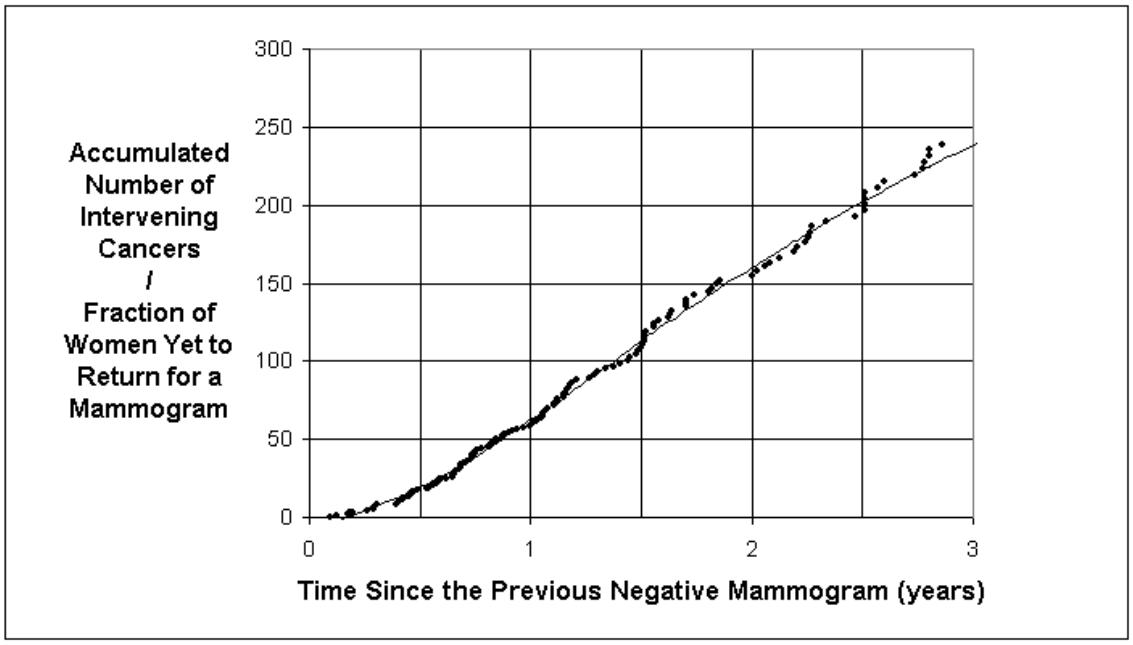

FIGURE 3 Accumulation of the non-mammographically detected cancers found in women with a previous negative mammogram (*Intervening Cancers)*. By dividing the number of these tumors by the fraction of women yet to be screened, the rate of appearance of these tumors could be visualized. Note that for approximately the first six months after the negative mammogram, the rate of accumulation appears to be reduced (Michaelson et al 2003c).

clinically detected cancers appeared at larger, and thus more lethal, size because the women had failed to come back on time for their annual mammograms. Calculations made with the Size Only Equation with data on the size of the cancers seen in the 179 women who had never used screening indicated that these women could expect a 25% breast carcinoma death rate. Similar calculations made with data on the size of the cancers seen in the 492 women with cancers found either at screening (427) or clinically within a year of the mammogram (68) indicated that these women could expect a 16% breast carcinoma death rate (Michaelson *et al*., 2002a, 2003d). In other words, women who attend screening regularly can expect to reduce their risk of breast cancer death by a third, to 16%. Note that the breast carcinoma survival rate estimated from size data for women who attend screening regularly, at 84%, agrees closely to the value of 88% estimated by the simulation model stated earlier.

These size data also gave evidence of how the effectiveness of screening is reduced when women do not return on time for their annual mammograms (Michaelson *et al*., 2001, 2002a, 2003d). This can be seen by considering the mixture of breast carcinomas found at screening together with the palpable cancers found within various periods of time after the negative mammogram. Such data reveal that the greater the delay in return to screening, the greater will be the average size of the cancers in the population. Very few palpable cancers are seen within the first 6 months after a negative mammogram, but they begin to appear in considerable numbers from ~ 6 months onward (Michaelson *et al*., 2003b, d). By ~ 9 months, these palpable cancers appear at a regular rate that continues for many years. We call the period soon after a mammogram, when few palpable cancers are seen, the "protective shadow of mammography." The data on the time course of the appearance of palpable cancers and the impact of these cancers on the average size of the cancers in the screening populations revealed that this protective shadow lasts only ~ 6 to ~ 9 months (Michaelson *et al*., 2003b, c). These size data could also be translated into expectations of survival for women who used screening at various intervals by the Size Only Equation. These data suggest that once one year has passed there is no grace period for return to screening; any amount of delay in return will increase tumor size and thus the level of breast carcinoma death.

These size data also provided a means for estimating the impact of patient age and the density of the breast on the efficiency of detection (Michaelson *et al*., 2003d). This could be accomplished by examining the mixture of cancers found at screening and after screening as palpable masses. These studies revealed that although the cancers tended to be larger for women with denser breasts and younger women than for women with less dense breasts and older women, women of all ages and density groups who used screening had smaller, and thus less lethal, cancers than women who did not use screening. This appeared to be the case even for women as young as 30 years. Thus, these calculations indicate that although screening is likely to be less effective in women in their thirties than in older women, screening should still be expected to lead to a reduction in tumor size and lethality in this age group.

False-positives

Screening is not without its negative consequences, particularly "false-positives" that lead to biopsies and other medical interventions among women who subsequently are not found to have cancer. One widely quoted study, by Elmore *et al*. (1998), "estimate[d] that among women who do not have breast cancer, 18.6% will undergo a biopsy after 10 mammograms." Remarkably, no women in this study had undergone 10 mammograms. It has long been appreciated that if a radiologist does not have access to a patient's previous mammogram, the patient is at much higher risk for a false-positive outcome. Thus, populationwide estimates of the rate of false-positives, such as those provided by Elmore *et al*. (1998), are fraught with the confounding influence of the intermittent use of screening on the overall false-positive rate. Fortunately, the very large number of women who had undergone screening at Massachusetts General Hospital made it possible to examine the false-positive rate among women who had chosen to use screening with various degrees of regularity (Michaelson, in press). These studies revealed that while the overall populationwide rate of false-positives leading to biopsies and false-positive mammography assessments were similar to those found in other studies, such as those reported by Elmore *et al*. (1998), much of the burden of these false-positive events was borne by women who used screening intermittently. For example, 2.9% of the women who had a screening examination in 1996 and received five mammograms over the next 5 years had false-positives leading to biopsies, while 4.6% of women who utilized only three mammograms over the 5-year period had a biopsy not revealing cancer. Among women who used screening regularly, the risk of having a biopsy not revealing cancer declined to 0.25% per year after several years of screening, a value that is lower than the risk of these events among women not using screening. These findings are reassuring, for they indicate that increased use of screening should not be expected to lead to increased rates of false-positives. In fact, the somewhat counterintuitive, but encouraging, lesson from these data is that prompt attendance to mammographic screening actually leads to a reduced occurrence of false-positive mammographic results and unnecessary biopsies (Michaelson, in press).

How is Screening Actually Used?

The database of women who attended screening at Massachusetts General Hospital over the past two decades provided an unusually rich source of information on the

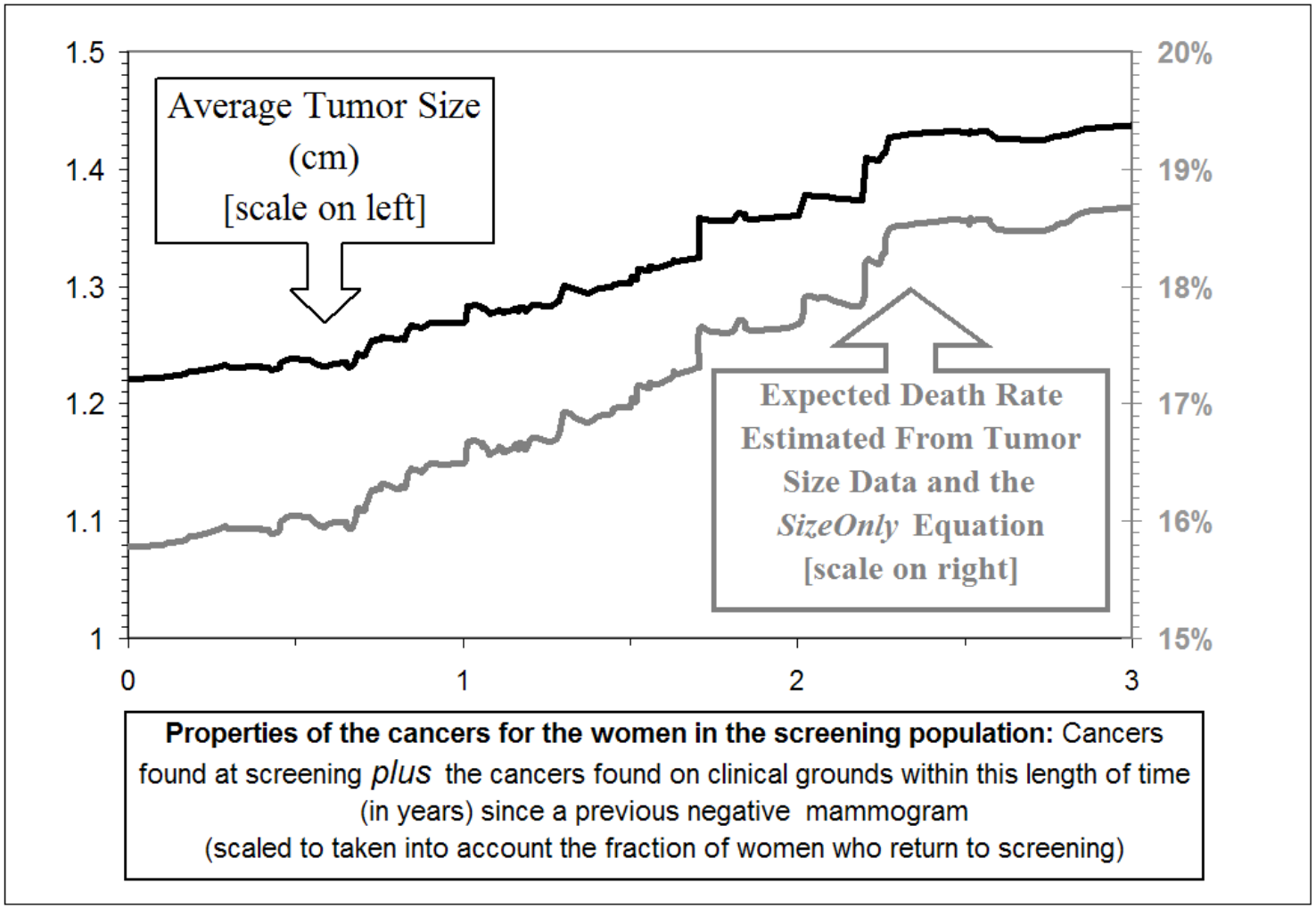

FIGURE 2. Properties of the cancers for the women in the screening population: Cancers found at screening plus the cancers found on clinical grounds within this length of time (in years) since a previous negative mammogram (scaled to taken into account the fraction of women who return to screening). For unscaled image of these data, see reference **8. For the data on the fraction of women who return to screening at various points in time after a previous mammogram use to scale these values, see reference*. Average Tumor Size (cm) [black lines, scale on left]. Expected Death Rate Estimated From Tumor Size Data and the *SizeOnly* Equation [grey line, scale on right]. (Michaelson et al 2002b)

patterns of screening, and indeed, made possible detailed analysis of the patterns of screening use to be carried out to date (Blanchard *et al*., 2004; Colbert *et al*., 2004). These studies revealed that most women begin screening close to their fortieth birthday, as recommended, but that prompt return after that is rare: very few return on time for their subsequent mammograms, and many never return. It is this failure of women to return promptly for their annual mammograms that is the critical failure-point in our ability to use screening to its maximal life-sparing potential.

That most women begin screening near the age recommended could be seen from data on women screened at Massachusetts General Hospital between 2000 and 2002. The median age of the women attending the first mammograms was 40.4; 60% of women began screening by age 40, and almost 90% by age 50 (Colbert *et al*., 2004). These data agree with national results. For example, the Behavioral Risk Factor Surveillance Survey found that by 1997, 85% of women over the age of 40 report having had at least one mammogram.

These favorable findings indicating that most women are beginning screening near their fortieth birthdays were not seen among specific subpopulations of women, particularly women of lower socioeconomic status. Thus, while the median age of first mammogram for women in the population as a whole was 40.4 years, the median age of first mammogram was 41.0 for African-American women, 40.3 for Hispanic women, 41.2 for women without a primary care physician, 46.6 for women without private health insurance, 49.3 for women who did not speak English, and 55.3 for women who both lacked private health insurance and spoke a language other than English (Colbert *et al*., 2004).

As noted, most women begin screening near their fortieth birthday as recommended, but most do not come back on time, or do not come back at all. This failure has very negative health consequencse. For example, of the women who had a negative mammogram at Massachusetts General Hospital in 1992, only 6% had nine more screening mammograms during the next 10 years, whereas 40% of these women had fewer than five mammograms over the decade and 18% never returned. The median number of mammograms used during the decade was five, and computer simulation analysis suggests that this degrades the life-sparing benefit of screening by ~ 50% (Blanchard *et al*., 2004). These findings agree with those made in other populations. For example, Ulcickas-Yood *et al*. (1999) reported that only 16% of the women who had a mammogram between 1983 and 1993 at the largest HMO in Michigan took advantage of all five mammograms during the 5-year period following the index mammogram. Sabogal *et al*. (2001), using 1992–1998 California Medicare data, found that only 30% of non-HMO women age 65 and older who utilized screening did so regularly without missing screening more than 2 years in a row. Phillips *et al*. (1998), using several sources of data, found that while 70% of women age 50–74 have had at least one mammogram, only 16% have utilized annual screening.

Women from traditionally underserved socioeconomic, racial, and ethnic groups; women without insurance; and women who did not speak English were found to be less likely to return on time, although these associations were small in magnitude. Women attending their first mammogram or those who had not previously returned promptly for screening were also less likely to return on time. Women age 55–65 had higher levels of usage than younger or older women. However, none of the subpopulations of women sorted by age, race, ethnicity, zip code, income, previous screening use, or medical history approached either of the extremes of widespread failure to return or prompt annual screening over extended periods of time. Although women who returned on time for the last exam were more likely to return on time for their next exam, even this correlation was not particularly strong. These data indicate that it is not the characteristics of the woman, but the performance of the system, that is the main reason many women do not return on time. Issues such as the shortage of screening facilities, and thus long waiting time for making appointments, no doubt contribute to the problem. Practical difficulties in reminding and tracking women would seem to be the likely reasons many women failed to return on time for their mammograms.

As might be expected, women with a prior breast cancer had a higher degree of screening use than the population as a whole (Blanchard *et al*., 2004). However, even among this group, considerable numbers of women did not return on time, or indeed at all, for screening. Since annual screening in this group serves the double purpose of detecting local recurrence and detecting second breast cancers, for which these women are at higher risk, the fact that utilization is far from ideal in this population is of considerable concern.

Women obtaining their first mammogram were found to be at particularly high risk for not returning. Indeed, one in four of such women will never return for a subsequent mammogram (Blanchard *et al*., 2004).

Present Status of Breast Cancer Screening

Both the computer simulation studies and the studies of the sizes of the breast carcinomas found among women who use screening indicate that very high breast carcinoma survival rates (~ 90%) should be achievable by screening if women follow the American Cancer Society's recommendation of prompt annual screening from age 40. However, studies of the actual utilization of screening suggest that we fail to achieve most of the life-saving benefit of screening principally because most women fail to return on time, or not at all, for their annual mammograms.

The simulation studies indicate that even higher survival rates might be achieved by twice yearly screening from age 30. Such a screening strategy would also appear to be highly cost-effective. Screening more frequently than twice a year, or in women younger than age 30, appears to yield very little additional benefit. The transition from once yearly screening from age 40, to twice yearly screening from age 30, would appear to have the potential to save as many as 5000 lives each year in the United States. It is striking that ~ 5% of the invasive cancers occur in women younger than 40 (Ries *et al*., 2000). Furthermore, since younger women have many more years of productive life, the potential loss in years of life is even greater, with ~ 10% of the potential years of life that could be lost to breast cancer being located in women younger than 40. Analysis of the sizes of the cancer seen in the screening populations of women of various ages (Michaelson *et al*., 2003d) also suggests that screening should be effective in this group, in terms of bringing cancer to medical attention at smaller, and thus less lethal, sizes. As regards the benefit of screening twice a year, it is relevant that the "protective shadow of mammography"—the time period after a negative mammogram when the rate of appearance of larger palpable masses is reduced—only lasts ~ 6 months. This provides empirical support for the computer simulation results that indicated that we could expect benefit by reducing the screening interval to as frequently as twice a year. Finally, the data do not support concerns that increasing the frequency of screening will increase the occurrence of false-positive events; this suggests that women who attend screening regularly actually have a lower level of such negative events (Michaelson, in press).

One in four women will attend their first mammogram and never return again (Blanchard *et al*., 2004). Clearly, the screening experience itself is discouraging many women from receiving the benefit of screening. One year after the single screening experience, the cancers found among these women will be just as large and just as lethal as the cancers found among women who never use screening. The simulation data suggest that this will double the risk of cancer death among these women.

Many women find mammography unpleasant and stressful. One impressive study found that if women are provided with a button that controls the compression of the mammography paddle, they perceive less pain associated with screening (Kornguth *et al*., 1993) Although this study was published 14 years ago, such a device has yet to become available commercially. It seems plausible that greater attention to the human-factors aspect of screening would appear to have a considerable impact on the reduction in breast cancer death by increasing the percentage of women who return.

Among the women who do return, 2, 3, or more years elapse between visits (Blanchard *et al*., 2004). Both the simulation studies, and the studies carried out on the time course of the appearance of larger palpable cancers after a negative mammogram, show that there is no grace period for return to screening. Once a year has passed, women are back in the same group as women who never use screening, in terms of the regular rate of appearance of larger, palpable masses (Michaelson *et al*., 2003b). Our computer simulation studies indicate that this alone probably reduces the life-sparing potential of screening by 50%. A number of studies have shown that as many as 40% of women who make appointments for screening examinations will forget to show up (McCoy *et al*., 1991; Margolis *et al*., 1993). It seems plausible that greater attention to tracking and reminding women, so as to help them make and then attend their annual screening examinations, could lead to considerable reductions in breast cancer death.

Analysis of the actual screening usage pattern among women who use screening at Massachusetts General Hospital (Blanchard *et al*., 2004; Colbert *et al*., 2004) and elsewhere (Ulcickas-Yood *et al*., 1999; Sabogal *et al*., 2001; Phillips *et al*., 1998) indicates that the greatest reduction in breast cancer death should be achievable simply by finding ways to encourage women to return on time for their annual screening mammograms. Most women, perhaps as many as 85%, begin to go to screening close to their fortieth birthdays. Thus, little is to be gained from populationwide efforts to encourage entry into the screening process. Instead, public health efforts should be focused on those subpopulations of women at highest risk for not using screening: women without private insurance, women without a primary care physician, and women who do not speak English. Most of our efforts to reduce breast cancer death should be concentrated on finding ways to encourage women who have already come for a mammogram to return *promptly* and *repeatedly*.

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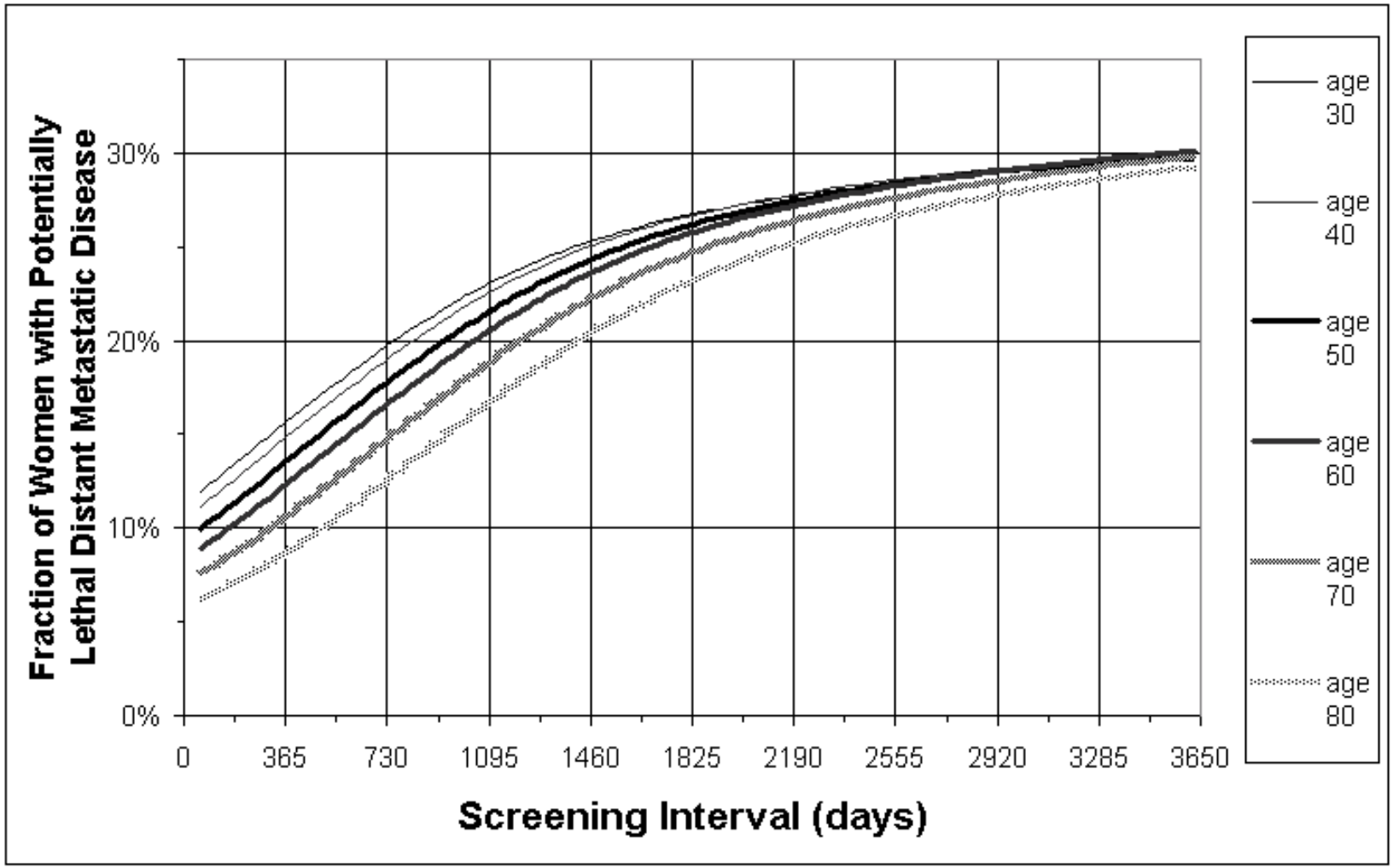
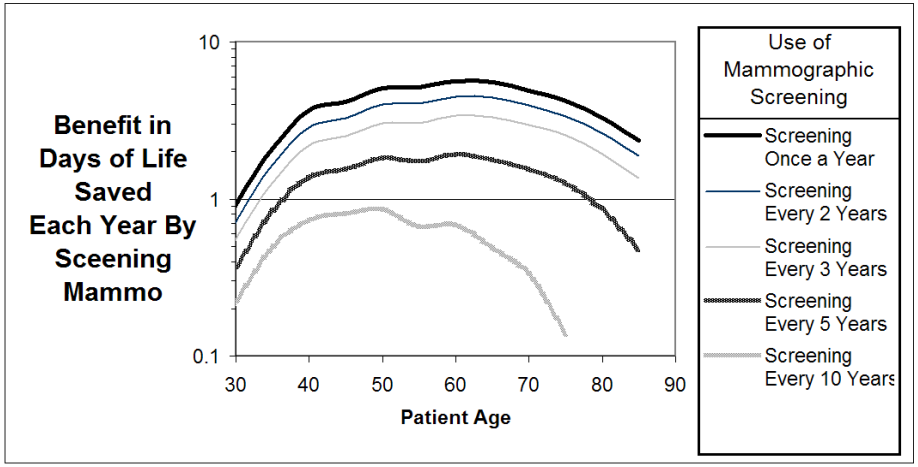
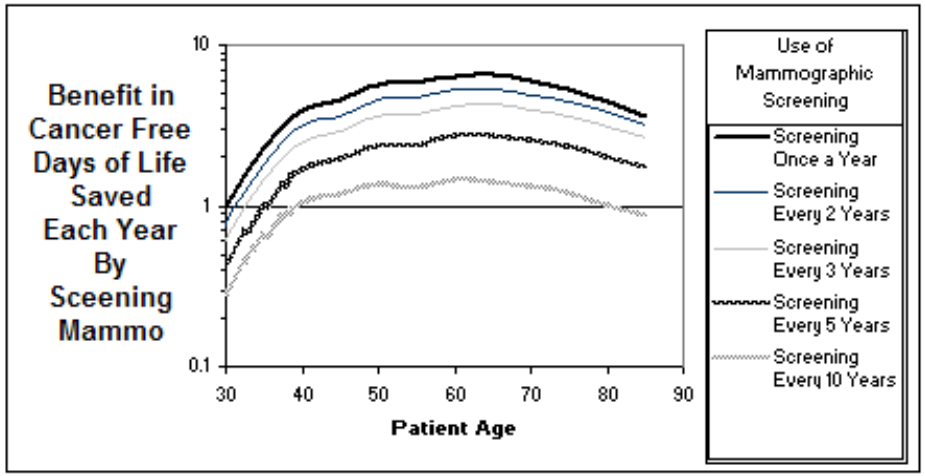

Fraction of Women with Potentially Lethal Distant Metastatic Disease
30%
20%
10%
0%
0
365
730
1095
1460
1825
2190
2555
2920
3285
3650
Screening Interval (days)
age 30
age 40
age 50
age 60
age 70
age 80





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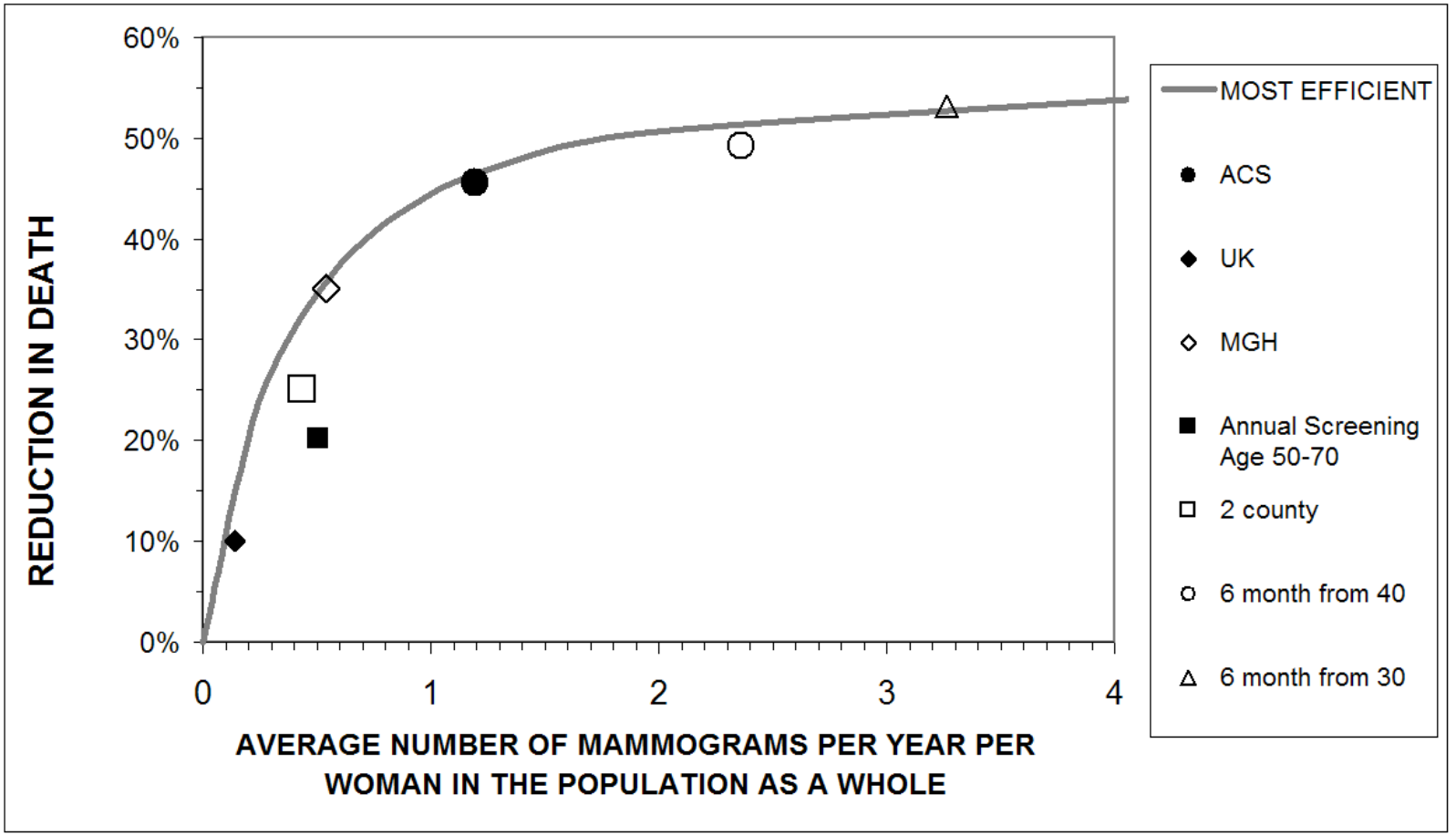

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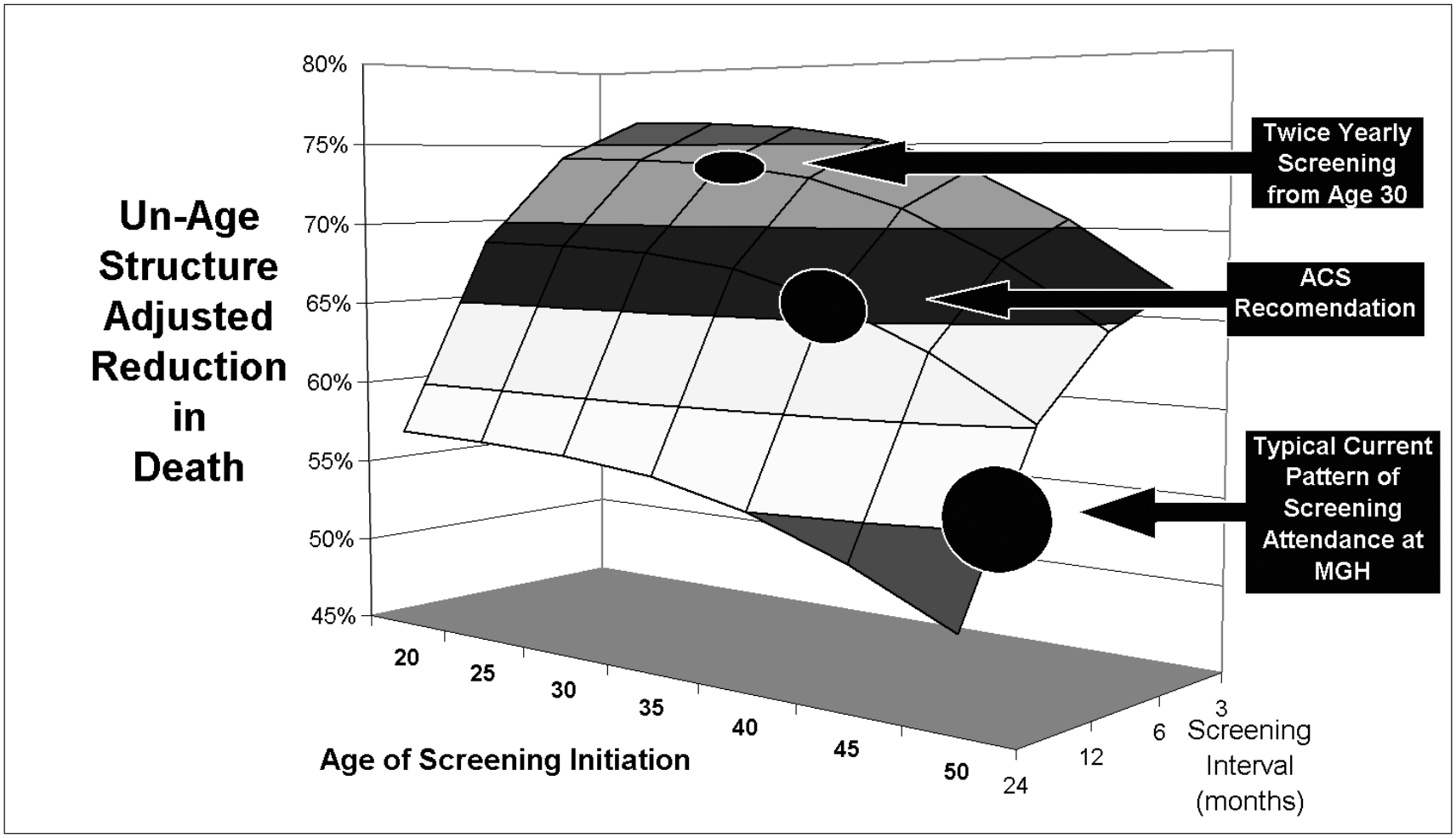
Un-Age Structure Adjusted Reduction in Death
80%
75%
70%
65%
60%
55%
50%
45%
Twice Yearly Screening from Age 30
ACS Recomendation
Typical Current Pattern of Screening Attendance at MGH
20
25
30
35
40
45
50
Age of Screening Initiation
3
6
12
24
Screening Interval (months)

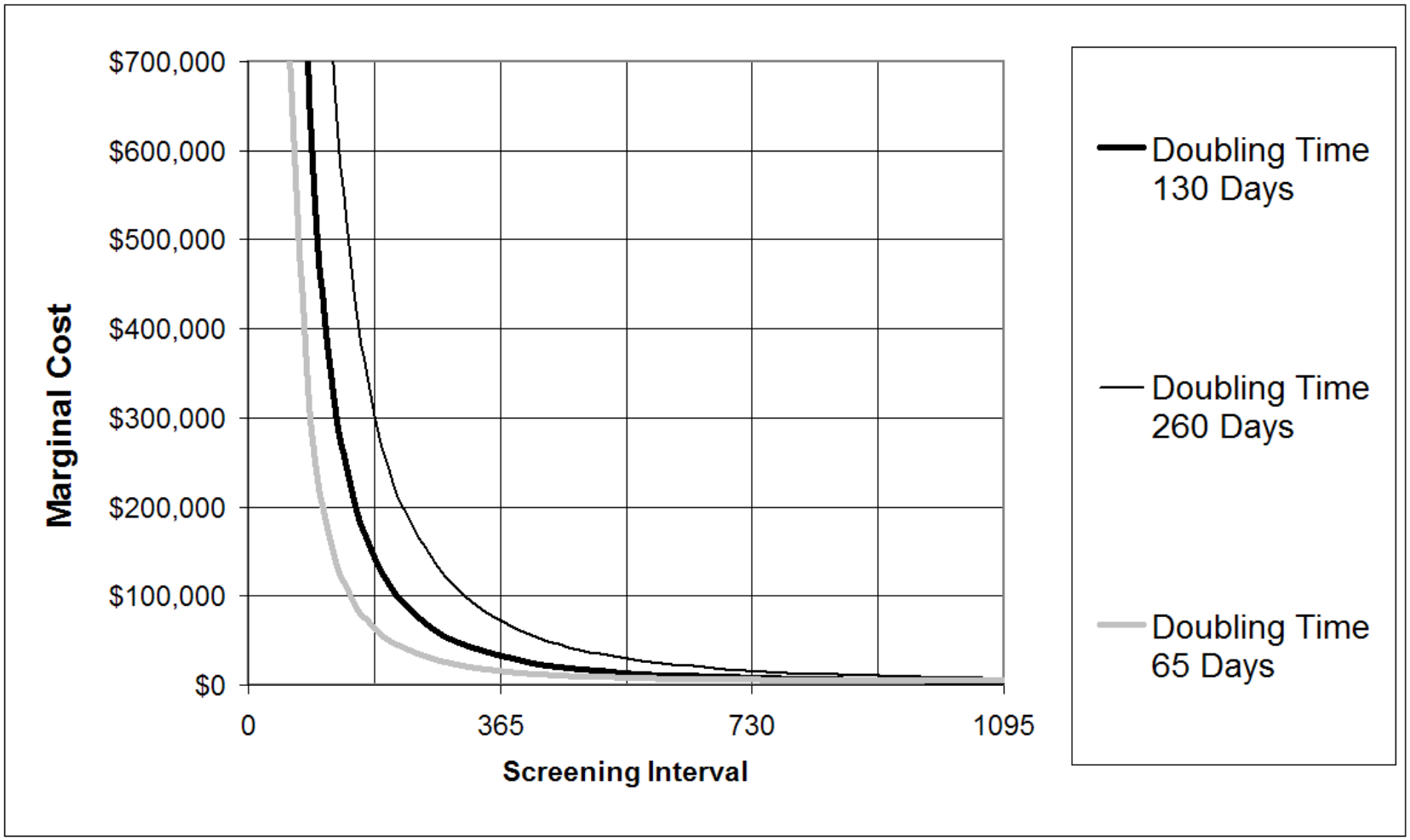
$700,000
$600,000
$500,000
$400,000
$300,000
$200,000
$100,000
$0
Marginal Cost
0
365
730
1095
Screening Interval
Doubling Time 130 Days
Doubling Time 260 Days
Doubling Time 65 Days

TABLE I

The Consequences of Various Life-Long Screening Strategies, as Determined by Computer Simulation Analysis

	Marginal Benefit (hours of life saved for the last mammogram)	SCREENING INTERVAL (MONTHS) age 20	age 30	age 40	age 50	age 60	age 70	age 80	Reduction in Br Ca death (un-age-structure-adjusted)	Reduction in Br Ca death (USA population)	Survivors	Average Benefit (To Each of the Women in the Population as a whole, in cancer free years of life saved)	Average Benefit (To Each of the Women found to have breast cancer, in cancer free years of life saved)	Marginal Benefit (hours of life saved for the last dollar spent on screening)	Marginal Cost (in dollars, for the last cancer free years of life saved (USA population)	Average Screening Costs (in dollars per cancer free years of life saved) (USA population)	Program Screening Costs (screening dollars per woman per year averaged over the whole USA population of women over age 20)
Most Efficient Strategies Estimated by the Equimarginal Method	-	none	none	none	none	none	none	none	0%	0.0%	65.1%	-	-	-	-	-	$0
	283	none	none	none	none	51	54	none	10%	7.9%	68.6%	0.09	0.52	5.66	$1,548	$994	$2
	270	none	none	none	none	46	49	none	15%	10.9%	70.2%	0.12	0.70	5.40	$1,622	$1,010	$3
	254	none	none	none	none	43	45	none	20%	13.9%	72.0%	0.14	0.87	5.08	$1,724	$1,009	$3
	240	none	none	none	none	40	43	60	25%	17.1%	73.7%	0.18	1.09	4.80	$1,825	$1,064	$4
	229	none	none	none	116	39	41	55	30%	20.1%	75.3%	0.21	1.30	4.58	$1,913	$1,109	$5
	212	none	none	none	44	36	38	49	35%	23.3%	77.1%	0.25	1.50	4.24	$2,066	$1,154	$6
	189	none	none	none	38	33	35	44	40%	26.1%	78.8%	0.29	1.73	3.78	$2,317	$1,214	$7
	160	none	none	none	33	30	32	39	45%	30.5%	80.6%	0.36	2.16	3.20	$2,738	$1,448	$10
	125	none	none	36	28	26	28	34	50%	34.6%	82.3%	0.42	2.57	2.50	$3,504	$1,685	$13
	91	none	none	28	23	22	24	29	55%	38.7%	84.1%	0.49	2.96	1.82	$4,813	$2,046	$16
	60	none	none	22	19	18	19	23	60%	42.7%	85.9%	0.55	3.33	1.20	$7,300	$2,596	$22
	34	none	120	16	14	13	15	18	65%	46.6%	87.6%	0.61	3.70	0.68	$12,882	$3,536	$30
	15	none	22	10	9	9	10	12	70%	50.5%	89.4%	0.67	4.07	0.30	$29,200	$5,966	$48
	13	none	20	10	8	8	9	12	70.7%	51.0%	89.6%	0.680	4.12	0.25	$35,000	$6,002	$52
	11	none	18	9	8	8	9	11	71.2%	51.4%	89.8%	0.686	4.16	0.22	$40,000	$6,322	$56
	10	none	17	8	7	7	8	10	71.7%	51.7%	90.0%	0.691	4.19	0.19	$45,000	$6,628	$59
	9	none	16	8	7	7	8	10	72.1%	52.1%	90.2%	0.697	4.23	0.17	$51,250	$7,756	$63
	8	none	15	8	7	7	8	10	72.4%	52.3%	90.2%	0.700	4.25	0.16	$55,000	$8,397	$66
	7	none	14	7	6	6	7	9	72.9%	52.8%	90.4%	0.708	4.29	0.13	$65,000	$10,127	$72
	6	35	13	7	6	6	7	8	73.3%	53.1%	90.6%	0.713	4.32	0.12	$75,000	$11,033	$78
	5	**29**	**12**	**6**	**5**	**5**	**6**	**8**	**73.8%**	**53.5%**	**90.7%**	**0.719**	**4.36**	**0.10**	**$90,000**	**$11,895**	**$85**
	4	25	11	5	5	5	5	7	74.3%	53.8%	90.9%	0.724	4.39	0.08	$110,000	$12,909	$94
	3	21	9	5	4	4	5	6	74.9%	54.3%	91.1%	0.731	4.43	0.06	$146,000	$14,456	$107
	2	17	8	4	3	3	4	5	75.6%	54.9%	91.4%	0.740	4.49	0.04	$220,000	$17,261	$132
	1	12	5	3	2	2	3	4	76.5%	55.6%	91.7%	0.751	4.55	0.02	$440,000	$23,428	$185
UK	-	none	none	none	36	36	none	none	12%	10%	68.9%	0.15	0.89	-	-	$1,353	$4
MGH-actual	-	none	none	none	17	17	17	17	56%	35%	84.6%	0.36	2.18	-	-	$1,707	$14
ACS	-	none	none	12	12	12	12	12	66%	46%	88.1%	0.56	3.38	-	-	$2,978	$30
12 months 40-70	-	none	none	12	12	12	12	none	33%	29%	76.4%	0.46	2.76	-	-	$3,489	$24
NCI	-	none	none	none	12	12	12	12	60%	38%	85.9%	0.39	2.35	-	-	$2,225	$19
12 months 50-70	-	none	none	none	12	12	none	none	25%	20%	73.7%	0.27	1.66	-	-	$2,473	$13
2 COUNTY	-	none	none	24	33	33	33	none	29%	25%	75.0%	0.36	2.20	-	-	$1,916	$11
6 month from 40	-	none	none	6	6	6	6	6	71%	49%	89.8%	0.61	3.67	-	-	$5,415	$59
6 month from 30	-	none	6	6	6	6	6	6	74%	53%	90.7%	0.71	4.28	-	-	$8,948	$82

Estimates based upon a breast cancer doubling time of 130 days; Costs based upon a per mammogram cost of $50. For other values, see TABLE II. Note that survival values are for the population as a whole, that is, including both the women screened and the women who are not screened.

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TABLE II

	Reduction in death (USA population)	Cost, in dollars per cancer free year of life saved (USA population) at $50 Per Mammo	Cost, in dollars per cancer free year of life saved (USA population) at $50 Per Mammo Plus False Positive Costs	Cost, in dollars per cancer free year of life saved (USA population) at $100 Per Mammo	Cost, in dollars per cancer free year of life saved (USA population) at $100 Per Mammo Plus False Positive Costs	Cost, in dollars per cancer free year of life saved (USA population) at $200 Per Mammo	Cost, in dollars per cancer free year of life saved (USA population) at $200 Per Mammo Plus False Positive Costs	Cost, in dollars per year of life saved
Screening Mammography (UK): Every 36 months age 50-70	10%	$2,706	$4,059	$5,412	$6,765	$10,824	$12,177	
Screening Mammography (ACS): Every 12 months from age 40	46%	$5,956	$8,934	$11,913	$14,891	$23,825	$26,803	
Screening Mammography: Every 12 months age 40-70	29%	$6,979	$10,468	$13,958	$17,447	$27,916	$31,405	
Screening Mammography: Every 12 months from age 50	38%	$4,449	$6,674	$8,898	$11,123	$17,797	$20,021	
Screening Mammography: Every 12 months age 50-70	20%	$4,947	$7,420	$9,894	$12,367	$19,788	$22,261	
Screening Mammography: Swedish 2 County Trial	25%	$3,831	$5,747	$7,662	$9,578	$15,325	$17,241	
Screening Mammography: Every 6 months from age 40	49%	$10,830	$16,246	$21,661	$27,076	$43,322	$48,737	
Screening Mammography: Every 6 months from age 30	53%	$17,896	$26,844	$35,792	$44,740	$71,585	$80,533	
FOCBT every year + sigmoidoscopy every 3 years age 65+								$43,000
Adjuvant chemotherapy, stage I node (-) breast cancer								$24,000
Lovastatin treatment for men age 45-54 for hyperlipidemia								$34,000
Heart Transplantation for patients age 50 with terminal disease								$100,000
AZT for people with AIDS								$26,000
Influenza vaccination for all citizens								$140
Home dialysis for chronic end-stage renal disease								$20,000-$46,000
3-Vessell coronary bypass graft surgery								$12,000-$100,000
Kidney transplantation for renal disease								$17,000-$29,000

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For comparison, the cost/year of healthy life gained has been estimated to be US$ 46 249 for renal dialysis and US$ 113 087 for coronary artery bypass surgery in the USA (Schulman et al, 1991).

American society generally accepts treatments as appropriate if they cost less than about $50,000 per quality-adjusted life-year gained. However, the notion of quality-adjusted life-years is complex, explains Dr. Deyo. One would not want to give the same credit to a lifesaving treatment that leaves somebody blind for the next 10 years as one that leaves a person with perfect vision for the next 10 years. It is not simple to measure the cost part of the ratio either, further complicating the issue of cost-effectiveness. For instance, the charge for direct medical care is not the same as the total care costs for an illness. Finally, there is the issue of opportunity costs. This refers to the fact that if we spend our money doing one thing, we cannot spend it for doing something else. For example, if an extra $500 million is spent on bypass surgery, there is $500 million less for prenatal care, cancer screening, or other services.
See "Cost-effectiveness of primary care," by Dr. Deyo, in the January 2000 Journal of the American Board of Family Practice 13(1), pp. 47-54.