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Does the Breast Cancer Dollar Make Sense?

Richard J. Epstein

The past decade has witnessed a transformation of breast cancer management. Innovative developments such as widespread mammographic screening, breast-conserving approaches to primary disease and adjuvant systemic therapy have improved the quality of breast cancer care in the community. These and other therapeutic developments have been accompanied by substantial increases in consumption of health care resources. With the exception of adjuvant systemic therapy for node-positive disease, the evidence that such increases have been associated with commensurate improvements in disease outcome is weak. Indefinite continuation of this trend may prove incompatible with socioeconomic realities.
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INTRODUCTION

FOR THE past 3 years the economic recession has forced American public opinion to focus critically on the cost-effectiveness of medical care [1]. As a result, combined estimates of survival/quality-of-life gains—often expressed as QALYs, or quality-adjusted life years—have become a popular (if imperfect [2]) yardstick for comparing the dollar value of different medical interventions. Costs per QALY may range from as little as $1500 for pneumococcal vaccination of elderly populations to as much as $500 000 for coronary artery bypass grafting of single vessel disease [3], and it has been suggested that $30 000 per QALY (the annual cost of haemodialysis, or almost double the per capita gross national product) is the current cost-acceptability cutoff point in the USA [4]. With this figure in mind, it is timely to review the cost-effectiveness of four increasingly common scenarios in American breast cancer management: screening mammography in women aged less than 50, breast-conserving therapy, adjuvant chemotherapy for node-negative premenopausal women, and management of metastatic disease.

MAMMOGRAPHIC SCREENING IN WOMEN YOUNGER THAN 50

Mammography works. That is the overall verdict from the nine large studies which have so far analysed the benefits of mammographic screening [5], and it is a verdict supported by the incontestable observation that breast cancer prognosis is related to disease stage at diagnosis [6]. For women older than 50, regular mammography appears to reduce disease-specific mortality from breast cancer by 25–30% [5].

In women younger than 50, however, the verdict is less clear. Most studies have not demonstrated a significant survival advantage associated with screening in this age group, while three studies have unexpectedly suggested a detrimental effect [7–9]. Despite this, regular mammograms every 1–2 years between the ages of 40 and 50 are currently recommended by the National Cancer Institute, the American Cancer Society, and the American College of Radiologists [5]: at an average cost of $125 per two-view mammogram and $50–80 for a follow-up physician visit, these recommendations translate into a judgement that $2.5 billion per year should be expended on screening this cohort. Since as many as 7.5% of routine screening mammograms yield results necessitating further radiographic, surgical and/or pathological assessment [10], the true recommended annual expenditure may exceed $3 billion. This figure may be expected to rise as national mammography capacity increases [11]. The cost of breast screening for women younger than 50 has been calculated to exceed the savings attributable to reduced treatment by about a 100-fold, and the discounted cost per additional year of non-quality-adjusted life expectancy estimated at around $95 000 (1992 dollars) [12].

Although the evidence that screening improves the natural history of breast cancer in women aged less than 50 is weak, increasing numbers of lawsuits are being waged and won on the premise that insufficiently vigilant attempts at early detection have prejudiced the outcome of subsequent clinical disease. The Physicians' Insurers Association of America recently reported that alleged delay in breast cancer diagnosis (DBCD) is the single most expensive and second most common cause of medical litigation in the United States, accounting for 27% of all cancer-related claims at a mean cost of $211 000 per claim [13]—more than twice as frequent and costly as the sum of all complaints relating to any other malignancy, and a powerful stimulus to the 20% of national health care dollars now being devoted to defensive medicine [14]. Since more than two-thirds of DBCD claims relate to women aged less than 50 [13]—and since the sensitivity of mammography for detecting tumours in the denser breasts of this age group has been reported to be as low as 50% [15]—it is not surprising that a similar proportion of DBCD claims involve false-negative, equivocal and/or misinterpreted mammograms [13] (Table 1). This is consistent with the view that mammography plays a strictly supplementary role in the assessment of symptomatic breast disease in younger patients [16], but also implies that the procedure's reliability for detecting early-stage disease (and hence improving disease outcome) in screened patients of this age group is technically limited. Hence, unwittingly or not, the American legal system may be transforming mammography of younger women into a *de facto* form of life insurance subsidised by health care payers.

Mammography works. But does it work well enough to justify current American screening recommendations?

BREAST-CONSERVING THERAPY

Another popular innovation in breast cancer care over the last decade has been that of breast-conserving therapy. In many centres, lumpectomy has substantially reduced the frequency of

Correspondence to R.J. Epstein, Breast Evaluation Clinic, Dana-Farber Cancer Institute and Department of Medicine, Harvard Medical School, 44 Binney St, Boston, Massachusetts 02115, U.S.A.
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Table 1. Proportion of lawsuits implicating mammogram-related problems in contributing to delayed breast cancer diagnosis

Mammogram-related factors contributing to alleged diagnostic delay	Cases (%)
Negative mammogram report	35.7
Failure to perform mammogram	16.4
Equivocal mammogram	14.0
Mammogram misinterpreted	8.9
Failure to pursue mammographic abnormality in presence of palpable mass	5.9
Failure to pursue mammographic abnormality in absence of palpable mass	4.1
Abnormal mammogram filed without physician's knowledge	2.6
Technically inadequate mammogram	1.5

n = 269.
Adapted from the Physician Insurers Association of America study [13].

mastectomy for patients with small (< 4 cm diameter) primary tumours. A 6-week course of adjuvant breast irradiation costing around $10 000 may reduce the absolute risk of local recurrence in this context by 10–25%, but will not affect survival [17]. Hence, if a 25% absolute reduction in local recurrence rates is assumed, the cost per prevented recurrence is $40 000; since about 50% of true local recurrences can be satisfactorily controlled with salvage irradiation [18, 19], the net cost per prevented persistent recurrence in this context (putting aside for a moment the use of salvage mastectomy) is approximately $60 000. A rough calculation as to how this translates into dollars per post-lumpectomy QALY is given in Table 2.

The results of breast conserving therapy have in general been acknowledged to be cosmetically impressive. Surprisingly, comparative studies of psychosocial outcome in patients undergoing either breast conservation or mastectomy have yielded equivocal results [20–22]. The most consistent conclusion has been that the conservative approach improves body image but does not prevent psychological maladjustment or enhance overall quality of life [20, 23–27]. Initial breast-conserving surgery has been associated with paradoxically higher operation charges than mastectomy in many centres in the USA, and these charges are often increased further by the need for re-operation to clear pathologically involved surgical margins; when combined with adjuvant irradiation, the overall cost of breast conservation is about 3-fold that of mastectomy.

Although the perception of routine mastectomy as a sexist anachronism makes it an unfashionable procedure to defend in the setting of early-stage disease, available evidence suggests that in terms of cost-effectiveness it remains the standard against which other local therapies will continue to be measured.

CHEMOTHERAPY FOR NODE-NEGATIVE DISEASE

Perhaps the decade's most remarkable advance in cancer therapy has been the finding that treatment of node-positive premenopausal breast cancer patients with adjuvant chemotherapy confers a 40% mortality reduction in patients followed

Table 2. Estimated cost per QALY of various medical interventions

Intervention	$/QALY
Pneumococcal vaccination*	1500
Haemodialysis†	30 000
Annual mammography (age 50–69)‡	50 000
Annual mammography (age 40–49)§	100 000
Post-lumpectomy radiotherapy‖	75 000
Post-mastectomy radiotherapy¶	200 000
Adjuvant chemotherapy for node-positive premenopausal patients**	1000
Adjuvant chemotherapy for node-negative premenopausal patients††	50 000

* [3]; † [4]; ‡, assuming a cancer detection rate of 2% per decade per screened individual [5], a life expectancy of 30 years for an asymptomatic 50-year-old woman commencing screening, a cost per mammogram of $125, a median age of breast cancer development in this cohort of 67 years, an average life expectancy following diagnosis of 8 QALYs, and a 25% relative reduction of disease-specific mortality from screening; § [12], corrected for quality of life (NB: effectiveness disputed); ‖ assuming cost per radiotherapy course of $10,000, 12% absolute reduction of disease recurrence uncontrollable by mastectomy or salvage irradiation, 2.5 years average survival from time of diagnosis of refractory recurrence (approximately 1.25 QALYs in presence of persistent local disease), and no measurable improvement in quality of life accruing from improved breast cosmesis [20]; ¶ assuming 4% reduction of disease recurrence uncontrollable by salvage irradiation, and life expectancy of 1.25 QALYs in these cases; ** assuming 6 year median prolongation of overall survival [35] (5 QALYs), and $5000 cost of 6 months' CMF chemotherapy; †† assuming significant prolongation of disease-free but not overall survival [36].

for 10 years [28]. At an all-inclusive cost of less than $5000 for an average 6-month course, such treatment now constitutes one of the most cost-effective interventions in contemporary medical practice (Table 2).

Management of patients with node-negative disease, on the other hand, has proven to be a more controversial issue. The natural history of this cohort is that 70% will achieve long-term survival without therapy while 30% wil recurr and succumb [29, 30]; since at least 50% of primary breast cancer patients do not have axillary nodal involvement, much effort is being directed at detecting this 'false-negative' patient subset in the hope that more aggressive adjuvant management will prove beneficial. In the absence of a proven method for delineating this subset, enthusiasm in some quarters has been mounting in favour of treating all node-negative patients—enthusiasm which culminated in a Clinical Alert from the National Cancer Institute implying that this approach become standard [31]. Although still preliminary, published data from randomised studies suggest that chemotherapy of premenopausal patients with node-negative disease is associated with a modest improvement in disease-free survival (DFS) [32, 33]. Major improvements in overall survival have not yet been reported [33, 34], with the exception of one small study in which the control group fared unusually poorly [35]. Should such improvements in DFS constitute a valid endpoint for toxic and expensive therapy? Patients may perceive this to be the case and opt for such therapy despite the expectation that overall survival will be unaffected [36]. What patients perceive, however, is not necessarily what

they get [37, 38]. For example, the benefit from tamoxifen therapy in node-negative patients may be expressed either as a 75% greater chance of remaining disease-free, a 26% reduction in treatment failure, or a 6% reduction in absolute risk of disease-related death [39], and it has been pointed out that such semantic variations may be used either to support active therapy or to encourage conservative management [40]. If it is assumed on the basis of current evidence that chemotherapy does not substantially prolong overall survival in node-negative patients, then the theoretical cost of enhanced DFS in this context has been estimated by one group to be around $50 000 per QALY [36].

The new approach to early-stage breast cancer commits markedly more per-patient health care resources than do older approaches. Whereas a patient presenting in 1982 with a node-negative 2 cm breast primary may have been treated with mastectomy in 5 days for $7000, a similar patient presenting in 1992 may be treated with lumpectomy, re-excision, adjuvant irradiation and adjuvant chemotherapy over 9–12 months for $30 000. Adjuvant therapy of selected node-negative patients may yet mature into a highly cost-effective management modality. But does the available cost-benefit evidence justify 80% of American oncologists prescribing such therapy as part of routine management? [41] And does this evidence justify consigning an entire generation of young women with 'good-prognosis' disease to long-term sequelae such as those due to premature menopause—especially considering that a large proportion of this cohort may be denied subsequent hormone replacement therapy due to medicolegal concerns?

MANAGEMENT OF METASTATIC BREAST CANCER

As in the adjuvant setting, the cost-effectiveness of chemotherapy in metastatic disease can be enhanced either by improving cytotoxic efficacy or by reducing associated expenditure and morbidity. With respect to the former, chemotherapy-induced survival prolongation in metastatic breast cancer has proven difficult to confirm [42–45]. Chemotherapy administered with palliative intent, on the other hand, often proves more toxic and/or ineffective than anticipated by the prescribing physician [45, 46]. Treatment of metastatic disease therefore raises an awkward issue: is active management *per se* associated with a significant placebo effect [47]; and if so, is it ethical to treat patients without expectation of objective benefit even though such treatment is associated with predictable toxicity and expense [48]?

The two most popular breast cancer chemotherapy regimens in the USA are CAF (cyclophosphamide, doxorubicin, 5-fluorouracil) and CMF (CF plus methotrexate). Early studies of doxorubicin-containing drug regimens suggested an increased tumour response rate compared with CMF-style therapies [49], but doubts have since emerged as to whether disease 'responsiveness' necessarily correlates with outcome or palliative benefit [50]. Subsequent studies have indicated that inclusion of doxorubicin increases short-term toxicity [51–53], long-term toxicity [54,55] and expense (Fig. 1) while failing to confer superior outcome to CMF in either the adjuvant [56], neoadjuvant [51] or metastatic [53, 57–59] settings (Fig. 1). Since randomised data indicate that the sequencing of systemic therapies does not affect the course of advanced breast cancer [50, 60], it is difficult to justify up-front deployment of doxorubicin-containing regimens on cost-effectiveness grounds.

A widely-held view regarding systemic anticancer therapies is that 'more is better' [61]. As reasonable as such a view may

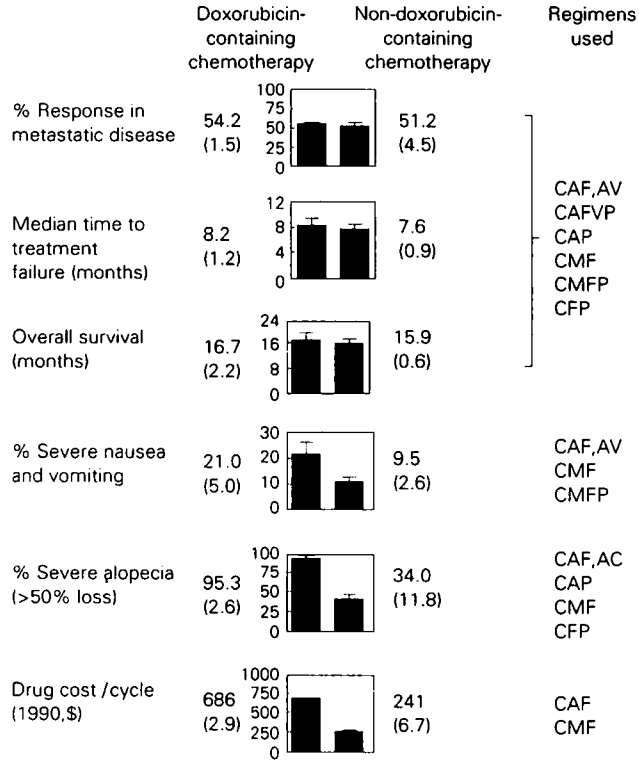

Fig. 1. Comparison of published doxorubicin-containing and non-doxorubicin-containing chemotherapy regimens with respect to efficacy, toxicity and cost. Standard errors for cost were based on three commonly used variations of the standard CMF and CAF protocols [51, 91] with drug prices based on charges to patients attending author's institute. Response/survival data are based on four studies [57–59, 91], nausea data on three studies [51, 58, 59] and alopecia data on three studies [51, 57, 92]. Study selection for each variable was based on data availability and absence of confounding drug combinations.

seem, there are few studies to support it: the addition of hormonal therapy to chemotherapy [60, 62], for example, or the use of combination [63] or high-dose endocrine therapies [64, 65] do not appear to improve clinical outcome in established disease and may even be detrimental [66, 67]. Similarly, prolonged cytotoxic therapy has not been associated with improved outcome relative to either standard-duration [68] or short-course chemotherapy [69]. The most fashionable 'non-standard' chemotherapeutic strategy in the USA at present is high-dose cytotoxic scheduling, an approach which has been convincingly associated with higher tumour response rates [70]. Just as convincing, however, has been the finding from randomised studies and overviews that this approach is associated with greater toxicity [71, 72] and mortality [72, 73] but not survival benefit [74] when compared with standard-dose therapy in either the adjuvant [75, 76] or metastatic settings [77, 78]. This conclusion does not exclude the possibility that a defined benefit for high-dose (or other non-standard-scheduled) chemotherapy may yet emerge in some therapeutic settings [79], but the increased cost of drugs and hospitalisation associated with high-dose protocols does not appear routinely justified by published data. Despite this, a recent survey has suggested that up to 80% of physicians would recommend participation in a nonrandomised study of high-dose chemotherapy with autologous marrow rescue to a young patient with poor-prognosis disease, even though a majority of medical oncologists would decline such treatment

for themselves on the grounds of excess toxicity and unproven benefit [41].

Many physicians who manage breast cancer patients gain reassurance from investigations analysing the nature or extent of disease. An example is that of tumour markers for aggressive disease in premenopausal node-negative patients: parameters such as tumour ploidy, S-phase fraction and c-*erb*B-2 expression are commonly used to define high-risk patients who may derive particular benefit from adjuvant chemotherapy. Since there are abundant data supporting the association of these factors with adverse disease outcome, this trend at first glance seems reasonable; it will be many years, however, before the cost-effectiveness (or even effectiveness) of these predictive tests can be prospectively confirmed. As an illustration of the interpretational chaos within the literature, c-*erb*B-2 is reported to be overexpressed 3–4 times more commonly in comedo-type ductal carcinoma *in situ* than in invasive breast adenocarcinoma [80], and to be associated with an improved prognosis when expressed in either gastric cancer [81] or node-negative breast cancer [82].

Far more information is available regarding the utility of investigations which monitor the integrity of potential metastatic sites. From the patient's viewpoint, such investigations have been shown to produce anxiety rather than reassurance [83] and have not been associated with objective benefit [84]. In one trial mandating regular follow-up bone scans, 0.06% of 7984 studies detected asymptomatic disease at a total cost of over $1.5 million and at a cost per positive scan of $30 000 [85]; the contribution of routine bone scans in the initial evaluation of stage I breast cancer is similarly unrewarding [86], as is that of liver scanning in uncomplicated primary disease [87]. The practice of ordering 'baseline' investigations (e.g. baseline mammograms for otherwise healthy 35-year-old women—as recommended by national organisations—or baseline computed tomography body scans for patients presenting with clinically localised tumours) is equally unsupported by evidence of clinical benefit. Chest X-rays and serum alkaline phosphatase measurements have also been shown to lack clinical utility in the follow-up of asymptomatic breast cancer patients [88, 89]. Since these investigations do not appear effective, their cost-effectiveness is undefined.

CONCLUSIONS

Breast cancer is now a multi-billion dollar industry in the USA, an evolution driven at least in part by the seemingly irresistible trend towards consumer-driven medical decision-making. There is little argument that significant progress has taken place since the days when therapy was monopolised by radical mastectomy; published data suggest, however, that the substantial increases in health resource consumption associated with this progress have not yet yielded commensurate improvements in disease outcome. Pessimism concerning the fate of the national health care system is rife, yet public pressure for constructive change remains unfocused [90]. Despite these gloomy indicators, there is widespread agreement that enhanced medical cost-effectiveness is achievable by using financial incentives to stimulate more intensive physician audit on the one hand and more extensive consumer risk-sharing on the other. This transition will require the creation and maintenance of a constructive dialogue between physicians, patients, health care payers and lawmakers.

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Second Malignancies in Thyroid Cancer Patients: a Population-based Survey of 3658 Cases from Norway

Lars A. Akslen and Eystein Glattre

In a population-based survey of 3658 thyroid cancer patients diagnosed in Norway during 1955–85, a total of 200 cases of second malignancies were observed (30 414 person-years, mean follow-up 8.4 years). Male patients had a significantly increased incidence of urogenital cancer [standardised incidence ratio (SIR) = 1.96, 95% confidence interval (CI) 1.4–2.7], including cancer of the testis (SIR = 11.8, 95% CI 3.2–30.1) and urinary bladder (SIR = 3.0, 95% CI 1.5–5.2). The occurrence of malignant melanoma was also increased among males (SIR = 4.2, 95% CI 1.4–9.7). This apparent association with urogenital cancers among males at the present time cannot be explained, although increased surveillance as well as specific aetiological factors should be considered.
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INTRODUCTION

THE AETIOLOGY of thyroid cancer is not completely understood. However, some factors are thought to be of pathogenetic significance in humans, such as radiation exposure [1–3], dietary habits [4–6] and genetic determinants [7–8]. Hormonal influences may also be involved [5, 9, 10]. In the present study, primary malignant tumours developing subsequent to thyroid cancer were examined among 3658 patients reported to the Cancer Registry of Norway during 1955–1985, with special reference to the possibility of common aetiological factors.

Correspondence to L.A. Akslen.
L.A. Akslen is at the Department of Pathology, The Gade Institute, Haukeland Hospital, N-5021 Bergen; and E. Glattre is at The Cancer Registry of Norway, Oslo, Norway.
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PATIENTS AND METHODS

Since 1953 the Cancer Registry of Norway has received information on almost all cancer patients in the entire population, based on clinical reports, histology and cytology reports, and autopsy records. A total of 3944 thyroid cancer patients were reported to the Registry during 1955–1985. Of these, cases not histologically verified and those diagnosed at autopsy or by death certificate alone were excluded (n = 286), giving a total of 3658 cases for further analyses. Sex, age at thyroid cancer diagnosis and time of diagnosis (month and year) were recorded, and the time between thyroid cancer and subsequent malignancies was calculated. Histological type of thyroid cancer according to the WHO classification [11] was included for patients reported during 1970–1985. Detailed information on treatment with radioactive iodine and external radiation as well as radiation treatment during childhood has not been available.

Second cancers diagnosed within 2 months after the thyroid