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What Threshold for Adjuvant Therapy in Older Breast Cancer Patients?

By Martine Extermann, Lodovico Balducci, and Gary H. Lyman

Purpose: **To consider the question of when to prescribe adjuvant treatment for elderly breast cancer patients, particularly when comorbidities are present. Knowledge of the threshold relapse risks above which adjuvant treatment is worth prescribing would enhance decision making.**

Patients and Methods: **A Markov analysis of data from the medical literature was conducted. Patients aged 65 to 85 years were considered, along with three levels of comorbidity. The threshold risk of relapse at 10 years (RR10), at which time treatment provides absolute reduction or reduction of an absolute 1% in relapse or mortality, was evaluated.**

Results: **The threshold RR10 for an absolute reduction in mortality risk by adjuvant treatment was low through the age of 85 years. However, for an absolute 1% reduction, the effect of treatment on relapse and the effect of treatment on mortality increasingly diverged. The threshold RR10 for an absolute 1% reduction in relapse risk remained fairly low (5% to 6% for tamoxifen, 12% to 19% for chemotherapy). The threshold RR10 for an absolute 1% reduction in mortality risk, although starting close to the RR10 for an absolute 1% reduction in relapse risk, rose sharply. For tamoxifen, the difference between the two was 4% for an average 65-year-old, 6% at the age of 75 years, and 15% at the age of 85 years. For chemotherapy, the differences were 6%, 12%, and 30%, respectively. Similarly, thresholds increased with increasing comorbidity. In older and sicker patients, the maximum benefit was reached after 5 years rather than 10 years.**

Conclusion: **Older breast cancer patients can expect a reduction in relapse that is fairly similar to that of younger patients. However, the effect on mortality diverges markedly, and attention should be paid to this difference in clinical decision making. Comorbidity should be considered in recommendations for adjuvant treatment, including clinical practice guidelines.**

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CONSIDERABLE improvements in the detection and treatment of early breast cancer have occurred during the past two decades. As a result, several factors compel the clinician to assess the benefits and risk of adjuvant treatment in older patients with breast cancer. First, adjuvant hormonal therapy now reduces the risk of recurrence of estrogen receptor (ER)–positive tumors by an impressive 50%.[1] In addition, adjuvant chemotherapy is increasingly used, even in patients of advanced age, and incremental improvements are credited to its effectiveness.[2,3] Third, the wider use of screening mammograms is causing the tumor stage at diagnosis to shift toward increasingly smaller, low-risk tumors.[4,5] Finally, people older than 65 years represent the fastest growing segment of the population in developed countries.[6,7] Consequently, oncologists are increasingly confronted with older patients with small tumors and must determine whether an adjuvant treatment should be prescribed and, if so, what kind. The problem is further complicated if other health problems are present, even in the absence of life-threatening disease. This latter situation is common, because cancer patients in their seventies and eighties suffer an average of three different comorbidities each.[8,9]

Direct information on the value of adjuvant therapy in older women is limited, especially for cytotoxic chemotherapy. The Early Breast Cancer Trialists' Cooperative Group (EBCTCG) meta-analysis has stratified the effectiveness of adjuvant chemotherapy by decade.[10] However, few patients older than 70 years have been included in randomized studies of chemotherapy (609 in the EBCTCG analysis), and they likely represent a healthy subset. Desch et al[11] have applied a decision analysis model to the effectiveness of chemotherapy in node-negative, ER-negative (ER−) patients aged 60 to 80 years. For an estimated baseline risk of relapse of 5% per year (39% at 10 years), they concluded that chemotherapy produced a small benefit. For a 75-year-old patient, the median survival was increased by 2.4 months, the quality-adjusted survival by 1.8 months, and the risk of relapse at 5 years decreased absolutely by 3%. Although not minimal, the cost-effectiveness was within the range of other accepted interventions until an age of 75 to 80 years. However, this fixed-relapse risk approach in assumed healthy patients is of little help in providing a basis for evaluating the potential benefit of an adjuvant treatment

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Table 1. Data Included in the Model

Data	Baseline (limits)		
	%		Range
Baseline age-related mortality		U.S. population data	
Mortality			
Healthy subgroup		U.S. population data − 0.7%/yr	
Sick subgroup		U.S. population data + 6.79%/yr	
From tamoxifen complications	0.01		0-0.04
From chemotherapy	0.25		0-1
Breast-cancer-specific survival after relapse in control arm, months		32.4	25.2-64.8
Shortening in breast cancer relapse-specific survival after adjuvant treatment, months		6.5	5-9.5
Reduction of relapse rate			
By tamoxifen	50		42-58
By chemotherapy	18		10-26
Complications from tamoxifen requiring stopping			
First one-half year			
Alone	3		1-5
With chemotherapy	5.5		3.5-7.5
Year after	1		0.2-2

for an individual patient who may be affected by comorbid conditions.

This decision analysis has the following goals: (1) to provide clinicians with estimates of the benefit of adjuvant therapy in a user-friendly fashion; (2) to compare the risks of recurrence above which tamoxifen and chemotherapy treatment are beneficial, using the data of the most recent meta-analyses; and (3) to explore the influence of comorbidity on these threshold risks of breast cancer recurrence.

PATIENTS AND METHODS

Model

A Markov model was constructed.[12] For patients with ER-positive (ER+) tumors there were three branches: chemotherapy + tamoxifen for 5 years, tamoxifen alone for 5 years, and no adjuvant treatment. For patients with ER− tumors, the model had two branches: chemotherapy and no adjuvant treatment. Within each branch, three to five Markov states were possible, the number varying depending on what was appropriate for each branch: chemotherapy, tamoxifen, well without treatment, relapse, and death. The length of each Markov cycle was 6 months (1 semester). All patients were assumed to have received standard initial local treatment. Patients aged 65, 70, 75, 80, and 85 years were simulated. A 10-year follow-up period was modeled for all relapse analyses. For mortality, 5-year and 10-year periods were studied and the most favorable threshold was selected (for further details, see Results). The percentage of patients who had died or relapsed at the end of the simulation was recorded, either with the program's tables or with a toll function that recorded information on patients who moved from one Markov state to another between two cycles. One-way and two-way sensitivity analyses were conducted within the ranges listed in Table 1. The software used was Decision Maker 7.05 (SG Pauker, FA Rosenberg, JB Wong, New England Medical Center, Boston, MA).

Data Used in the Model

The data used in the model (Table 1) were obtained from literature published before September 30, 1998, as retrieved from MEDLINE, cross references, and hand review of publications.

Nonbreast cancer mortality rates. The average age-related mortality rate was based on data on life expectancy for women in the United States population, according to the National Center for Health Statistics.[13] This corresponds to a life expectancy of 18.5 years for a 65-year-old patient and 5.9 years for an 85-year-old patient. Age-related mortality was introduced in the model as a table, according to Sonnenberg and Wong.[14] The declining exponential approximation of life expectancy method[15] was used to account for the wide deviation from the average age-related mortality rates found in breast cancer studies and to introduce comorbidity-related mortality rates. The nonbreast cancer mortality rate found in the International Breast Cancer Study Group IV study (median age of the patients, 70 years) was 9% at 8 years overall and as low as 6% in the control group.[16] The nonbreast cancer mortality may be increased above the mean by specific comorbid conditions. In the Framingham study, the disease-specific mortality rate for women after a myocardial infarction was 49.3% at 10 years.[17] This rate, added to the average mortality rate, was used as the upper limit of nonbreast cancer mortality risk. Tamoxifen was assumed to have no impact on noncancer mortality, which conforms to the results of the latest EBCTCG meta-analysis.[1] Thus, three levels of comorbidity were defined: patients with an above average health status, such as the International Breast Cancer Study Group IV participants, patients in average health, and patients with serious comorbidities, such as a myocardial infarction. For the sake of brevity, these groups are referred to as healthy, average, and sick in this article. Their respective life expectancies are detailed in Table 2.

Relapse. The relapse rate from breast cancer was assumed to be constant (declining exponential approximation of life expectancy method) over time, because this agrees well published data, especially for low-risk tumors.[18,19] Median overall survival after relapse ranges from 14 to 30 months.[20-24] This translates into a breast-cancer-specific survival after relapse of 32.4 months (range, 25.2 to 64.8 months). Previous adjuvant treatment has a negative impact on relapse duration,

Table 2. Baseline Life Expectancy for Patients With Various Ages and Comorbidity Levels

Age (years)	Life Expectancy (years)		
	Healthy	Average	Sick
65	20.0	18.5	9.7
70	15.8	14.8	8.6
75	12.1	11.5	7.3
80	8.8	8.4	5.9
85	6.1	5.9	4.5

NOTE. See Methods for definitions of healthy, average, and sick patients used in this study. The average life expectancy is based on the United States population.

Table 3. Baseline RR10 According to Stage

Stage	RR10 (%)
T1N0	14
T2+N0	26
T1N+, one node	22*
T1N+, two to three nodes	20*
T1N+, four to nine nodes	42
T1N+, 10+ nodes	52
T2+N+, one node	36
T2+N+, two to three nodes	47
T2+N+, four to nine nodes	52
T2+N+, 10+ nodes	56

NOTE. Illustrative example compiled from two articles by Quiet et al.[47,48] Values have been extracted from the graphs or, when possible, from the tables.

Abbreviation: T2+, T2 and greater.

* Across the years, these two curves grossly overlap each other.

by 5 to 9.5 months, with no significant difference between adjuvant hormone therapy and chemotherapy.[22,25]

Adjuvant tamoxifen. In the EBCTCG meta-analysis published in 1998, 5 years of adjuvant tamoxifen reduced the risk of relapse by 50% (SD, ± 4%) in patients with ER+ tumors. The meta-analysis shows a risk reduction that lasts for 5 years, with no significant influence from age or menopausal status.[1]

Adjuvant chemotherapy. In the latest EBCTCG meta-analysis, chemotherapy reduced the risk of relapse by 18% ± 4% (mean ± SD) in women aged 60 to 69 years.[10] Few patients 70 years and older were included in the studies analyzed, which results in a wide confidence interval for this group. Because this confidence interval includes the value obtained for patients in their seventh decade, we used that value in our model. In randomized studies that compare them directly, there was a significant difference in effectiveness between anthracycline-containing chemotherapy and cyclophosphamide, methotrexate, and fluorouracil (CMF) chemotherapy.[10] However, the clinical significance of this difference is debated, as a result of the heterogeneity of the regimens used.[26] Also, 70% of the women treated in these studies were younger than 50 years. Because the global effectiveness of chemotherapy decreases after menopause and the pharmacologic behavior of chemotherapeutic agents is altered in older patients,[27] the difference observed in this young population may not be identical to that in older women. Furthermore, many oncologists are reluctant to use anthracyclines in older patients. Taxanes seem to increase the effectiveness of adjuvant chemotherapy.[3] Too few elderly patients have been treated with taxanes, however, for firm conclusions to be drawn for this group. Indeed, the exact amount of benefit from the addition of taxanes is still uncertain. Therefore, in this study, patients were assumed to have received conventional chemotherapy, such as CMF or doxorubicin and cyclophosphamide, and the previously mentioned global risk reduction was used. The effect of chemotherapy seems to be additive to that of tamoxifen and is accounted for as such in this analysis.[10] In accordance with the EBCTCG meta-analysis,[10] the effect of chemotherapy on relapse was assumed to last 5 years.

Complications of tamoxifen and chemotherapy. The reported annual incidence of deep vein thrombosis in patients treated with adjuvant tamoxifen alone ranges from 0.2% to 1.2%.[28-30] No excess risk was found in two studies,[29,30] whereas one reported a 0.15%/yr excess risk.[28] In the baseline analysis presented here, no excess risk was assumed. When tamoxifen is used in combination with chemotherapy, the risk of thrombosis is increased with a total incidence of 3.6%.[31] This is higher than the incidence with chemotherapy alone: 1.2% to 3%.[31,32] In recent studies, the death rate related to proximal deep vein thrombosis is less than 5%.[33,34] The absolute incidence of endometrial cancer in tamoxifen-treated patients is 1.2 to 2.9/1000 patient-years, which represents an overall excess risk of approximately 1/1000 patient-years.[35-37] The reported disease-specific mortality rates from endometrial cancer range from 0% to 26%.[35,37,38] Cessation of tamoxifen as a result of toxicity is reported to be between 2.5% and 7.1%, with no evidence of increased toxicity in elderly patients.[25,28,39,40] In large randomized trials, treatment mortality from adjuvant chemotherapy ranges from 0% to 1%, with a mean of approximately 0.25%[2,31,32,41-45]. Because chemotherapy was given during the first cycle of the Markov process only, nonlethal toxicities with no impact on the continuation of tamoxifen treatment were not accounted for in the model.

End Points

Rather than compile thresholds for multiple breast cancer stages and risk factors, we expressed the study question in the following general way: What is the risk of tumor relapse above which it is worth giving adjuvant treatment? Because the risk of relapse considered is relatively low and breast cancer relapse rates are fairly constant over time,[18,19] we expressed it as the cumulative risk of relapse over 10 years (10-year relapse risk [RR10]). This is the approach used, for example, by the St Gallen consensus panel.[46] For the convenience of the reader, we list in Table 3 examples of RR10 for several stages of disease.[47,48] The reader can adjust these data to the particular risk factors of the specific tumor being treated.

We conducted a threshold analysis for an absolute reduction in mortality. To obtain a better grasp of the clinical impact of the effect of adjuvant treatment, we also defined two alternative types of benefits: an absolute 1% reduction in RR10 and an absolute 1% reduction in mortality risk at 5 and 10 years. A 1% reduction seems to be a minimum value below which few people would accept treatment and cost-effectiveness would be unfavorable.[11,20] In one study, nonetheless, one half of a group of patients with cancer would have accepted chemotherapy for a 1% chance of cure.[49]

RESULTS

ER+ Tumors

When we considered as beneficial any reduction in mortality by the adjuvant treatment, the thresholds (ie, the

RR10s above which treatment produces an absolute mortality risk reduction) were low, even into old age. For tamoxifen, this threshold was a 0.3% to 0.4% RR10. For chemotherapy combined with tamoxifen, this threshold rose from 4% in a healthy 65-year-old to 8% in a sick 85-year-old.

When we considered, though, as a minimum beneficial effect an absolute 1% reduction in relapse or mortality risks, the thresholds were higher and showed a markedly different behavior in relation to age and comorbidity (Fig 1) (For a case example of how Fig 1 is used, see below and Fig 2). The threshold RR10 for an absolute 1% reduction in relapse risk by tamoxifen or chemotherapy was minimally influenced by age and comorbidity. It remained fairly low (5% to 6% for tamoxifen, 12% to 19% for chemotherapy), even into advanced age. The threshold RR10 for an absolute 1% reduction in mortality risk with treatment, on the other hand, although starting close to the threshold RR10 for an absolute 1% reduction in relapse risk, became markedly higher past the age of 75 years. For example, the difference between the two thresholds for hormonotherapy was 4% for an average 65-year-old, 6% for an average 75-year-old, and 15% for an average 85-year-old. For chemotherapy, these differences were 6%, 12%, and 30%, respectively. Similarly, the threshold RR10 for an absolute 1% reduction in mortality risk rose with comorbidity. For example, the difference for tamoxifen was 14% in a healthy 85-year-old and 20% in a sick 85-year-old. Corresponding differences for chemotherapy were 29% and 39% for healthy and sick 85-year-olds, respectively. As a result of increasing competing mortality in older and sicker patients, the maximum benefit in mortality (ie, the lowest threshold RR10 for an absolute 1% reduction in mortality risk) was reached after 5 years instead of 10 years (indicated by asterisks in Fig 1). Indeed, in an 85-year-old patient, chemotherapy could provide an absolute 1% reduction in mortality risk at 5 years but would never provide an absolute 1% reduction in mortality risk at 10 years. Because 1% is a low level of reduction, we explored the threshold RR10s for higher expected reductions (up to 5%) in Table 4 (see case example below).

Sensitivity Analysis

The confidence bands in Fig 1 show the results of the one-way sensitivity analysis of the reduction in relapse rate by tamoxifen and chemotherapy. Although changes in tamoxifen effectiveness had little impact on the thresholds, a change in the effectiveness of chemotherapy led to a significantly higher variation in thresholds. Among the other variables, age and comorbidity were the major factors that influenced the results of the model and have been discussed above. The remaining variables of the model had little influence, with none influencing the threshold RR10s by more than 3%.

Case Examples

Case 1. Consider an 80-year-old woman with a 2.3-cm, node-negative, ER+ carcinoma. She had moderately limiting arthritis, arterial hypertension, and hypothyroidism. According to Table 3, this patient had an RR10 of about 26%. With three comorbid diseases, she was in average health for her age. In Fig 2, we plotted the intersection of her age and her risk of relapse on the graphs that corresponded to her comorbidity level in Fig 1. We see in the graph for the absolute 1% reduction in relapse risk that the intersection falls above the 1% zone for tamoxifen and at the upper limit of the zone for chemotherapy, but above the line in the middle of that zone. This means that this patient would have a greater than 1% absolute reduction in relapse risk over the next 10 years with tamoxifen. She also would have a greater than 1% absolute reduction with chemotherapy, unless a pessimistic assumption is made for the effectiveness of chemotherapy, in which case she would just gain 1% (the upper limit of the zone: a higher risk of relapse is needed to obtain an absolute 1% reduction). If we consider the absolute 1% reduction in mortality risk graph, the intersection falls at the lower limit of the chemotherapy zone, where there is a star. This means that the patient would obtain a greater than 1% absolute reduction in mortality risk at 10 years with tamoxifen. For chemotherapy, that threshold would not be reached unless the most optimistic assumption regarding the effectiveness of chemotherapy is made. In this case, as the star indicates, maximum reduction in mortality would be reached after 5 rather than 10 years.

The model can be adjusted to life expectancy over a short range. According to Table 2, our patient had a baseline life expectancy of 8.4 years. Let us consider a patient from a racial group with a 0.4-year shorter life expectancy (eg, an African-American woman).[13] In this case, the age line would need to be moved 0.4 years to the right to correspond to that of an 80.4-year-old patient in the model. If the patient were to come from a country with a 0.7-year longer life expectancy (eg, a Swiss woman),[50] then the line would be shifted to the left to correspond to a 79.3-year-old patient in the model.

Case 2. Consider a 65-year-old woman with a 3-cm diameter breast cancer, ER+, with three nodes involved. She had hypertension and had had a myocardial infarction. She also had hypercholesterolemia and her gallbladder was removed. What absolute percentage of reduction in mortality could this patient expect from treatment? According to

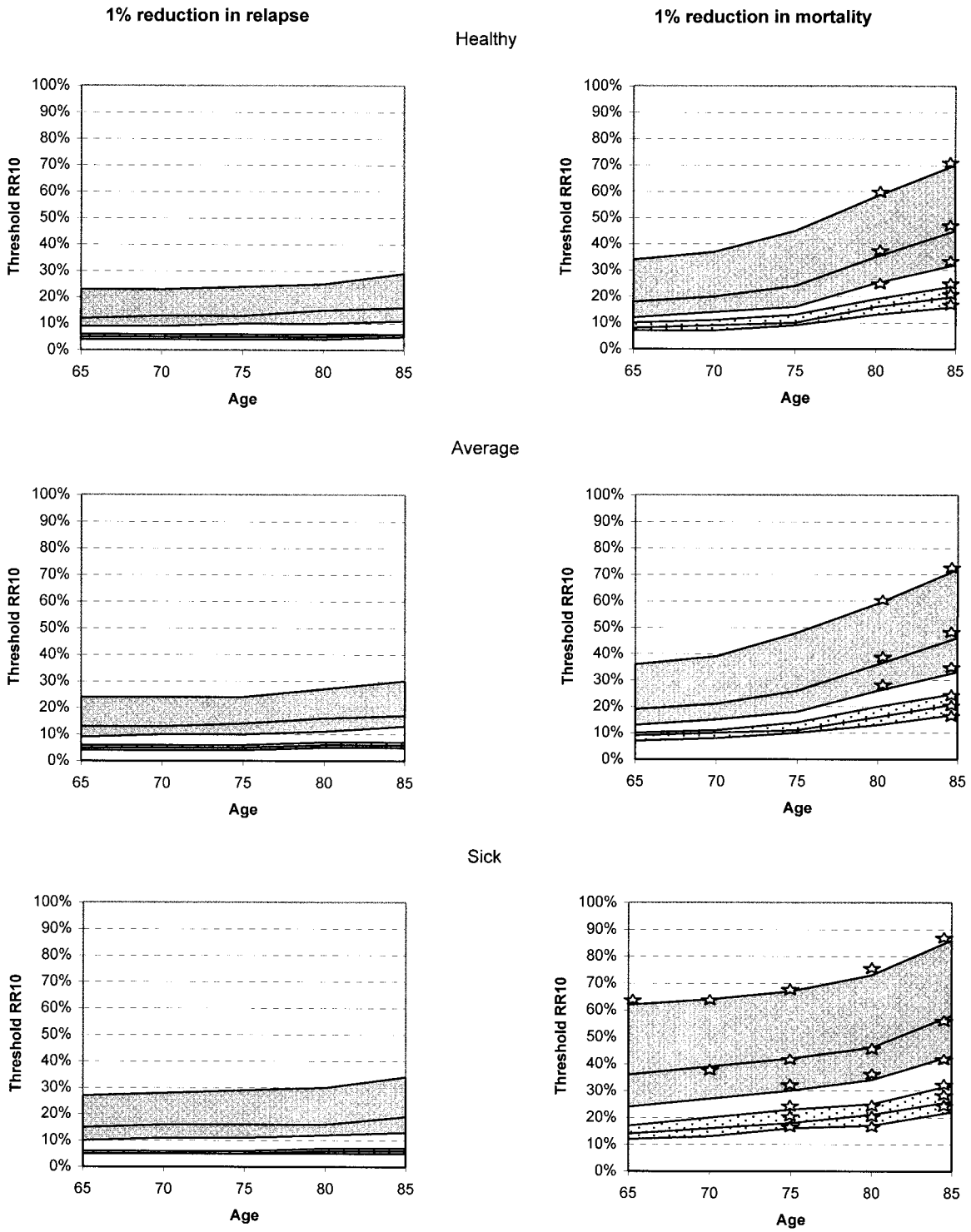

Fig 1. Threshold RR10 for an absolute 1% reduction in relapse and mortality risks (ER+ tumors). On the left are the threshold RR10s for an absolute 1% reduction in relapse risk at 10 years. On the right are the threshold RR10s for an absolute 1% reduction in mortality risk at 10 years or, if ☆, at 5 years. Graphs are organized from top to bottom with increasing level of comorbidity. Chemotherapy, ▨; tamoxifen, □. The line in the middle of each band represents the baseline effectiveness of each treatment (50% for tamoxifen, 18% for chemotherapy). The bands represent the boundaries of the sensitivity analysis on that effectiveness (42% to 58% for tamoxifen, 10% to 26% for chemotherapy). For an example of how to use these graphs for decision making, see Fig 2.

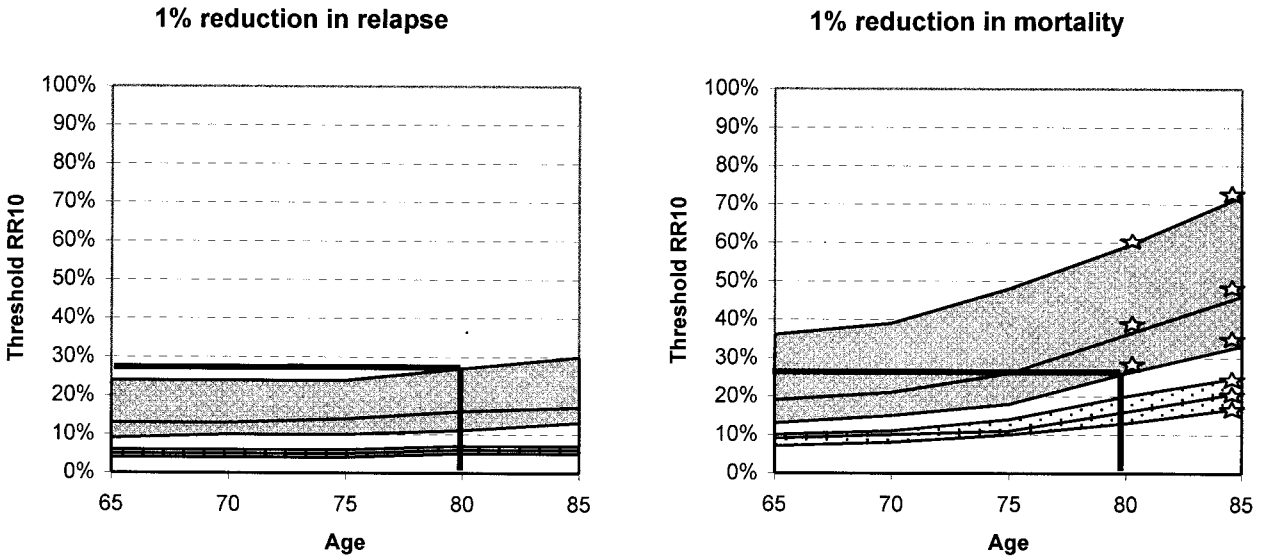

Fig 2. Case example 1. Thresholds for an absolute 1% reduction in relapse and mortality risks for an 80-year-old woman in average health with a tumor that has a 26% risk of relapse at 10 years. The graphs are extracted from Fig 1 with the same legends. See text for details.

Table 3, the risk of relapse of her breast cancer was approximately 47%. She would be classified in the sick category according to her comorbidity level. From Table 4, we can see that she would gain an absolute 3% reduction in mortality risk at 10 years with the use of tamoxifen. She would reduce her mortality risk by an additional 1% to 2% with the addition of chemotherapy, which is far from negligible when compared with other commonly accepted secondary preventive interventions (see Discussion). She would also reduce her risk of relapse by an absolute 9% with tamoxifen and an additional 3% with chemotherapy. This also can be expressed as living, on average, 4.7 more months overall with tamoxifen, plus 2 months with the addition of chemotherapy, whereas life expectancy without adjuvant treatment would be 7.7 years (not listed in Table).

ER− Tumors

The effect of chemotherapy in ER− tumors was also modeled. In contrast with the model for ER+ tumors, these models were highly unstable and assumption-dependent over the range of values tested. In other words, minimal modifications in the hypotheses led to major differences in threshold values. Several factors seemed to play a role. First, few specific published data are available. Most of the

Table 4. Threshold RR10 for Various Expectations of Absolute Benefit in Mortality

		RR10 (%)			
		Healthy		Sick	
	Mortality (% gained)	Tam/None	Chemo/Tam	Tam/None	Chemo/Tam
65 years old					
	1	8	18	14	36
	2	16	34	29	62
	3	23	49	46	79
	4	32	64	58	90
	5	40	81	70	96
85 years old					
	1	20	45	26	58
	2	37	71	49	86
	3	53	88	68	98
	4	68	96	85	
	5	81			

NOTE. The maximum benefit is reached after 10 years in the clear boxes and after 5 years in the shaded boxes. See text for a case example.
Abbreviations: Tam, tamoxifen; Chemo, chemotherapy.

time, ER− tumors represent a small subset in adjuvant studies in the elderly. The distinction between ER-poor and ER− tumors is still a matter of controversy. The latest EBCTCG meta-analysis suggests that chemotherapy may be more effective in postmenopausal ER− patients than in ER+ patients (mean ± SD: 30% ± 5% *v* 18% ± 4%; $P = .03$). However, one third of the patients analyzed were of unknown receptor status.[10] Second, the assumptions concerning the duration of relapse and how it is affected by adjuvant chemotherapy were the major factors of instability. Again, the data can only be extrapolated from studies with mostly ER+ tumors. The precise impact of adjuvant chemotherapy on relapse duration in ER− tumors is unknown. The fact that the relapse rate of ER− tumors is less constant over time than that of ER+ tumors can also complicate the problem.[19] Therefore, although the effectiveness of adjuvant chemotherapy in ER− tumors is well demonstrated,[10] the models did not provide reliable thresholds for practical use.

DISCUSSION

It is clear from this analysis that the benefits of adjuvant therapy on relapse and on mortality diverge widely in older patients, mortality being strongly influenced by comorbidity and age. Therefore, no simple global recommendations can be made. Obviously, patient preferences should play a large role in decision making. It is essential, however, that physicians provide accurate estimates of the risk of relapse and of the effect of tamoxifen and chemotherapy on relapse and mortality to present management options fairly. The results of this study (Fig 1) may serve as a reference for general cases, with representative boundaries to guide clinical discussions. Clinicians should still use the latitude to extrapolate in specific situations (eg, a strongly ER+ tumor would have a 60% chance of response to tamoxifen).[1]

An absolute 1% risk reduction may seem low to some readers, especially when the treatment given is chemotherapy. However, interviews of cancer patients show that a sizable proportion of them (up to one half of them in one study) consider a 1% chance of cure as a valid justification for undertaking chemotherapy.[49,51,52] Patients also would accept a hormone therapy for low expected benefits.[52] Age does not seem to alter the willingness to accept treatment, although older patients may have a somewhat higher threshold in survival benefit to accept the most toxic treatment alternatives.[51,53] In the EBCTCG meta-analysis, the absolute decrease in mortality with chemotherapy for node-positive women aged 50 to 69 years was 2.3% at 10 years.[10] Such a well-accepted intervention as beta-blockers after a myocardial infarction leads to an absolute 1.8% decrease in long-term mortality.[54] Similarly, prolonged antiplatelet therapy for various cardiovascular conditions yields a 2% to 5% long-term decrease in mortality.[55] Therefore, the 1% to 3% absolute reduction in mortality risk that elderly breast cancer patients can expect from chemotherapy according to this model is within the range of effectiveness of common secondary prevention interventions. Given the prevalence of breast cancer in older people, such a degree of benefit translates into a significant impact from a population perspective.

The relative value of the various chemotherapy regimens (for example, doxorubicin and cyclophosphamide *v* CMF) is a hotly debated issue.[10,26] One thing seems certain: if CMF is used, it should be given at the correct dose-intensity.[26,56] Recent results of an intergroup study of node-positive patients point toward an advantage to adding taxanes.[3] Given the shortness of the follow-up (18 months) and the paucity of older patients studied, the size of the benefit in the elderly is difficult to evaluate. The area below the middle line in the chemotherapy thresholds in Fig 1, which correspond to a higher hypothesized effectiveness, can provide an idea of how that added effect might alter treatment. This should allow for some adaptation of the model when the actual effectiveness of adding adjuvant taxanes is known more precisely. Further direct study of various adjuvant chemotherapy regimens in patients older than 70 years is clearly needed. The recent abandonment of upper age limits in cooperative group trials and less stringent study entry criteria should allow the collection of more precise information on this rapidly growing subgroup of the population.

The designation of the three levels of comorbidity in this study was somewhat arbitrary, notably the choice of myocardial infarction as a benchmark of severe morbidity. This choice was based on the fact that myocardial infarction is a common disease and that the associated prognosis is subjectively well recognized by primary physicians and on the availability of specific cohort data. Physicians can use the definition of severe disease used in this study (disease-specific mortality of 50% at 10 years) as a rule of thumb in determining the comorbidity status of their own patients. Physicians can adapt the model to diseases with lower 10-year disease-specific mortalities by plotting their patients' characteristics on both the average and the sick graphs in Fig 2 and by using these data as boundary estimates. Future studies on comorbidity may facilitate the inclusion of specific concomitant diseases in clinical decision making. They may notably assist understanding, in the case of polymorbidity, whether one or two severe diseases are dominant for prognosis or whether the overall burden of disease is the key factor. It is emphasized that comorbidity and functional status are independent predictors of surviv-

al.[8,57] The large majority of older patients with early breast cancer can be expected to have good Eastern Cooperative Oncology Group performance status, although approximately one half of them may have impairment in their instrumental activities of daily living.[8] More work is needed to understand the impact of functional impairment on the prognosis of early breast cancer patients independent from age, comorbidity, and treatment modality.

This study has focused primarily on women with ER+ tumors, in whom the model is stable and reliable. On the basis of the information currently available, models of ER− tumors are unstable. Desch et al[11] assumed no influence of adjuvant treatment on relapse duration in their model. However, assumptions regarding the relapse behavior and the impact of adjuvant treatment on relapse have a strong effect on the thresholds defined for intervention, as detailed in Results. Nevertheless, the model presented here permits a few conclusions pertaining to future research. Although the effect of tamoxifen is well understood and has been described in older patients, experience with chemotherapy is more limited. Even though a clear benefit in relapse can be expected, the benefit in mortality is less evident. Therefore, consideration should be given to using disease-free survival as the primary end point. Also, studies of chemotherapy in patients 75 years and older, as well as in sick patients, can probably be considered mature after a median follow-up of 5 years. Finding reliable and effective ways to include elderly patients with comorbidities in clinical trials is a major challenge that will have to be addressed in the years to come. Whereas one half of breast cancers occur in patients older than 65 years and one quarter in patients older than 75 years, only 17% and 3%, respectively, of patients included in cooperative trials were in these age ranges.[58] Meanwhile, models such as the one presented here can provide assistance to both clinicians and patients who face immediate therapeutic choices.

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