Building a model to determine the cost-effectiveness of breast cancer screening in France

P. ARVEUX, MD, *Registre des Tumeurs du Doubs, C.H.U. Saint Jacques, 25030 Besançon Cedex, France,* S. WAIT, PHD, *Laboratoire d 'épidémiologie et de santé publique, Université Louis Pasteur Strasbourg, 67085 Strasbourg Cedex, France &* P. SCHAFFER, MD, *Laboratoire d 'épidémiologie et de santé publique, Université Louis Pasteur Strasbourg, 67085 Strasbourg Cedex, France.*

ARVEUX P., WAIT S. & SCHAFFER P. (2003) *European Journal of Cancer Care* **12,** 143–153

This paper describes the methods and initial validation of a cost-effectiveness model developed to simulate the breast cancer screening situation in France. The first screening pilot programmes were set up in France in 1989 to test the feasibility of a decentralized screening model based in a large number of existing non-dedicated radiology centres. The present cost-effectiveness model was built as a tool to help guide current policy discussions on the future of screening in France. This Markov model compares the costs and effects expected when a screening programme is offered to a given cohort of women to those expected in the absence of screening. The model was initially validated using current results from the Bas-Rhin screening programme and local cancer registry epidemiological data. Over a 20-year period, 315 274 women would attend for screening, of whom 12 491 would be recalled for further assessment. 4423 cancers would be detected, resulting in 637 deaths. Screening allows the detection of 106 additional cancer cases, thereby preventing 92 deaths, and saves 1522 life-years compared with a situation without screening. Breast cancer mortality is reduced by 12.6%, yielding a cost-effectiveness ratio of 137 000 FF per life-year saved. The results of initial analyses suggest that the model is capable of suitably assessing the impact of breast cancer screening in terms of costs and effects. Further scenario analyses are needed to understand the impact of screening policy changes on the costs and effectiveness of future screening programmes.

Keywords: screening, model, breast, cancer, cost-effectiveness.

INTRODUCTION

The impact of screening on breast cancer mortality is contingent on a host of factors, namely the natural history of breast cancer, prognosis and survival, screening quality and efficacy, and population demographics (van Oortmarssen *et al*. 1995). For the purposes of economic or epidemiological analysis, only a model can depict adequately, in a single conceptual framework, the full impact of breast cancer screening in all its inherent complexity (Royston 1999). Cost-effectiveness models have been developed to guide breast cancer screening policy in several countries, including Australia, the United States, the Netherlands, Spain, Sweden, Finland and Norway (Forrest 1987; US Congress Office of Technology Assessment 1987; van der Maas *et al*. 1989;Australian Health Minister's Advisory Council 1990; de Koning *et al*. 1991; Beemsterboer *et al*. 1994; Hristova & Hakama 1996; Plans *et al*. 1996; Norum 1999; Leivo *et al*. 1999). Typically, these models derive screening quality and efficacy data from existing screening programmes and population demographics, epidemiology and treatment patterns for breast cancer from local cancer registries and healthcare datasets. Effectiveness data are most often extrapolated from the randomized clinical trial literature.

The purpose of this paper is to present a cost-effectiveness model developed to simulate the French breast cancer screening situation. The first breast cancer

Correspondence address: Dr Suzanne Wait, Laboratoire d 'épidémiologie et de santé publique, Université Louis Pasteur Strasbourg, 67085 Strasbourg Cedex, France (e-mail suzannewait@aol.com)

screening pilot programmes were set up in France in 1989 to test the feasibility of a decentralized screening model based in a large number of existing non-dedicated radiology centres. The objective was to curtail individual recourse to mammography ('spontaneous' screening) by encouraging women to undergo screening within an organized programme framework (Wait & Allemand 1996; Wait *et al*. 1997). The French health authorities favoured a decentralized model at the time as they thought it inappropriate to invest in new, dedicated screening centres in view of the large overcapacity of existing radiology facilities (Wait & Allemand 1996). Today, there exist over 20 district programmes, the efficacy and costs of which have been reported elsewhere (Wait & Allemand 1996; Séradour *et al* 1997; Wait *et al*. 2000a). Overall, the programmes have been successful in meeting target reference values for quality and efficacy (de Wolf & Perry 1996), with the notable exception of attendance rates, which average 45%. One important obstacle to optimizing the impact of screening remains the high prevalence of individual or 'spontaneous' screening, which, instead of being curtailed, has increased in parallel with the establishment of screening programmes (Wait *et al*. 1997). The direct cost of the French programmes is high (Wait *et al*. 2000a), as is to be expected as compared to a centralized programme based on a limited number of dedicated screening units (de Wolf & Perry 1996). Within this context, French policy makers are currently discussing the future of breast cancer screening policy. The present cost-effectiveness model was built as a tool to help guide these policy decisions.

There exist a number of well-documented, widely validated economic models reported in the literature (Forrest 1987; US Congress Office of Technology Assessment (1987); van der Maas *et al*. 1989;Australian Health Minister's Advisory Council 1990; de Koning *et al*. 1991; Beemsterboer *et al*. 1994; Hristova & Hakama 1996; Plans *et al*. 1996; Leivo *et al*. 1999; Norum 1999). However, all of these models are based on a centralized model of screening and their adaptation to the French screening situation may prove difficult. We felt that this situation warranted the construction of a specific French cost-effectiveness model, which could allow for a representative depiction of the impact of screening within the current context for screening. The model was initially validated based on the results from the Bas-Rhin screening programme. Further scenario analyses, reflecting other screening programmes and policy alternatives, will be reported elsewhere.

Building a complex economic model necessarily implies a number of key assumptions regarding the natural history of breast cancer and its impact by screening. It is important to be aware of these assumptions when interpreting the results of modelling simulations for the purposes of programme evaluation and policy analysis. The purpose of this paper is to describe the underlying assumptions and methods used to build this specific cost-effectiveness model. We then discuss gaps and uncertainties in our knowledge of breast cancer screening and the implication of these for modelling. Results of the initial validation of the model based on the Bas-Rhin screening programme are also presented briefly.

METHODS

Overall description of the model

The model was built based on an existing cost-effectiveness model originally designed to study the impact of colorectal cancer screening in France (Arveux *et al*. 1998; Lejeune *et al.* 2003). The model uses decision-tree analysis with Markov techniques (Sonnenberg & Beck 1993) that allow to analyse cumulated costs and effects over a given time period. The original colorectal cancer model was significantly modified to reflect the natural history and epidemiology of breast cancer and its impact by screening, however, the underlying structure of the model remains valid as it was designed for the simulation of different screening scenarios. Specifically, the model allows for different levels of spontaneous screening in the target population, an important factor in the assessment of any breast cancer screening programme in France (Wait *et al*. 1997).

The purpose of the cost-effectiveness model is to assess the costs and effects of a screening programme within a given cohort of women and to compare these costs and effects to those expected in the absence of screening. The model follows a cohort of women aged 50–65 years who are invited to attend for screening for a period of 20 years, allowing the youngest women entering the programme in year 1 to reach the age of 85. Women are offered screening up to their 65th birthday. From the age of 50–65 and at each successive round of screening, women may attend for screening, not attend, undergo spontaneous screening, or have cancer detected clinically. For these women, the model estimates at each year the prevalence of cancer cases detectable by screening, the number of patients in different combinations of health states according to their age, their underlying risk of breast cancer and attendance at previous screening rounds. This 'screening situation' is compared to a historical 'baseline' situation which follows the same cohort for 20 years, however, it does not allow for any screening to occur. In other words, the final model is the summed distribution of women, cancer cases and costs incurred over a 20-year period for the screening

cohort, compared to what these would have been expected in the absence of screening. The difference of total costs is divided by the difference in total effects measured in terms of life-years saved, yielding a cost-effectiveness ratio expressed as a cost-per life year saved (cost/LYS).

At each screening round, a woman attending for screening may have either a positive result (suspicious lesion), which will lead to further assessment with or without biopsy, or have a negative result (no suspicious lesion). The model accounts for cancer cases detected by screening, cases occurring after a negative screen result (interval cancers or false negatives) and those detected outside the screening programme, either by spontaneous screening or clinical diagnosis. The target population eligible for screening is recalculated every year, as the model subtracts from each year's population eligible for screening the number of women who have had a malignant tumour in the previous year.

Model inputs

In order to be most useful for the purposes of policy-making, the inputs into the model were derived from actual screening programmes as opposed to from the randomised clinical trials literature. The Bas-Rhin breast cancer screening programme was established in 1989 as a pilot project funded by the national French Sickness Fund as well as within the Europe Against Cancer network of cancer screening programmes (Wait & Allemand 1996). Results of this programme have been widely published (Schaffer *et al*. 2000). The protocol allows for women aged 50–65 years to receive a single-view mammogram every 2 years, free of charge, at any of the 56 participating radiology clinics in the district. Screening data is then centralized in a coordinating centre, which also runs a central screening database tracking attendance, screening quality and efficacy at each screening round, as well as a histology registry which gathers histological data on all breast tumours detected in women aged 50–65 residing in the district. Systematic quality assurance of all participating radiology clinics equipment and centralized double or triple reading of all radiological films are other inherent features of the screening programme. Attendance to the programme is voluntary, in that women do not receive a fixed invitation but are encouraged by media campaigns and their treating physician to attend for screening.

All screening parameters (screening attendance, detection rates, positive recall rate, rate of assessment, biopsy rate, screening sensitivity) were obtained from actual programme results from 1989 to 1997 for three complete rounds of screening. All parameters were determined per 5-year age band for prevalent and incident screening rounds.

The target population for screening was calculated based on yearly census data projected from 1990 to 2010 for the Bas-Rhin district based on all-cause mortality, migration and demographic trends (INSEE 2000). Breast cancer incidence data from 1990 to 1997 were obtained from the Bas-Rhin cancer registry (Schaffer *et al*. 1996) and classified by 5-year age band. Incidence rates after 1997 were not available and were assumed to remain constant until 2010 for the purposes of the model. Staging information on all cancer cases detected between 1989 and 1995 was obtained by linking incidence data from the cancer registry with histological data contained in the histology registry. By further linking these data with attendance data from the screening database, we determined stage distributions for screen-detected cancers, interval cancers and cancers detected outside the screening programme by year of screening.

Lead-time

One of the key assumptions of screening, and hence of this model, is that mammography allows to capture a sizable amount of cancer cases that would otherwise have gone undetected until the appearance of clinical symptoms. However, earlier detection may not actually translate into a true impact on prognosis or mortality as it may merely artificially extend survival. The model thereby needs to be able to incorporate an estimate of lead time, that is the time by which detection of cancers is advanced compared to a situation without screening. Lead time is a function of the sojourn time of detected cancers and the sensitivity of the screening programme and is described in (Day *et al*. 1989). The model needs to be able to distinguish between cancers that would have appeared anyway, in the absence of screening, and those that were detected as a true benefit from screening. Our model uses lead time to make this distinction and assumes a value of 2 years. This figure was calculated previously from programme results and allowed for a reasonable fit with screening sensitivity and attendance of the target population (P. Schaffer, pers. comm.).

Staging information

We chose to use histological tumour stage (pTNM) as the prognostic factor for survival, treatment and associated costs. For the purposes of the model, stage was classified into 5 categories: stage 0 (carcinoma *in situ*), stage 1, stage 2 A, stage 2B, and stages 3 A, 3B or 4. These categories

were used to describe cancer cases occurring in each of the subgroups (screening attenders, interval cancers and non-attenders), treatment costs and expected survival. Stage was assigned based on the initial stage of cancer at diagnosis, regardless of whether a recurrence occurred (Hayes & Kaplan 1990). To project the evolution of tumours from one stage to another, the model used actual age-specific stage distributions observed year after year in the Bas-Rhin, thereby bypassing the need to estimate passage times from one stage to another from published, and potentially inaccurate, stage-specific sojourn time. The stage distribution expected in the absence of screening was defined as the stage distribution of cancer cases in women aged 50–65 years in 1985, four years before the onset of screening programmes.

Impact on breast cancer mortality

Most existing models extrapolate effectiveness data from the clinical trials literature to estimate the expected impact of screening on breast cancer mortality. This approach is problematic because it assumes that screening when performed within a non-experimental setting has the same impact as that observed in the highly controlled environment of a randomized clinical trial (Moss & Blanks 1998). Additionally, the major randomized clinical trials for breast cancer screening date back several years and were conducted in Nordic countries, the Netherlands and the US, which have a very different epidemiology of breast cancer from that in France.

For the purposes of our model, we calculated actual stage-specific survival rates from the Bas-Rhin cancer registry data in order to estimate the number of life-years saved by screening and the resulting impact on breast cancer mortality. Detailed staging information was only available for cases detected as of 1989, therefore survival rates were available for a maximum of 10 years after diagnosis. Given this limitation, the model needed to assume that survival at 10 years implied cure. Although this is an optimistic assumption, this method allowed us to use data specific to the screening programmes under study. It also eliminated the risk of relying on less precise survival data from other countries or on obsolete historical data that do not reflect the prognosis associated with currently available treatment.

Resource implications

Costs included in the model are: (i) the cost of the screening programme itself (ii) diagnosis and assessment for positive screen cases (iii) the cost of mammograms carried out on a spontaneous basis (iii) initial treatment and surveillance of breast cancer cases, and (iv) treatment of advanced disease (palliative care). Indirect costs, such as impact on productivity, patient time lost, as well as measures of patient preferences or quality of life were not included in the model.

Screening programme costs were estimated in a detailed microcosting study of the Bas-Rhin screening programme (Wait *et al.* 2000a). Diagnosis and assessment costs (including biopsy) were derived by applying unit costs to average assessment practices reported in a survey of women attending for screening in the Bouches du Rhône district (B. Séradour, pers. comm.). Charges were substituted for unit costs using national tariff tables (Nomenclature Générale des Actes Professionnels). The health care utilization of 228 women diagnosed with cancer in 1995 was quantified by means of a detailed claims analysis of the local Sickness Fund claims database files (Système Informatique de l'Assurance Maladie) as well as individual retrospective hospital chart review from all Bas-Rhin hospitals (Wait *et al.* 2000b). These data were ascertained for 12 months following cancer diagnosis and were inputed as initial treatment costs in the model. Palliative care costs were based on a retrospective review of the hospital charts of 15 women who had died of breast cancer in the Bas-Rhin in 1995. Unit costs, based on hospital per diem rates, were multiplied by ward- and institution-specific lengths of stay to approximate hospital costs for the last 12 months of life. Based on these individual treatment data, average assessment, initial and palliative treatment costs were estimated per tumour stage, age and screening group attendance and fit into the model. All costs were discounted at a rate of 5% in accordance with the French guidelines for economic evaluation (Auray *et al.* 1998).

Model validation and sensitivity analysis

The model was validated using as a base case scenario the Bas-Rhin screening situation, as described above. Sensitivity analyses were conducted around given parameters to verify the robustness of the model and its underlying assumptions.

RESULTS

Results of the simulation of the Bas-Rhin screening situation are presented in Tables 1–3. Based on current screening programme results, the model predicted that 315 274 women would attend for screening, of whom 12 491 would be recalled for further assessment. Within

the entire cohort targeted by screening, 4423 cancers would be detected, resulting in 637 deaths over a 20-year period. Screening allows the detection of 106 additional cancer cases, thereby preventing 92 deaths and saving 1522 life-years compared with a situation without screening. An average of 16.5 life-years are gained per breast cancer death prevented. Breast cancer mortality is reduced by 12.6%.

Screening alters the overall stage distribution of cancers. There is nearly a threefold increase in the number of *in situ* lesions, and a 25% increase in stage I lesions with reference to the expected stage distribution in the absence of screening. Stage 2A and Stage 2B lesions are reduced by a factor of 0.76 and 0.66 respectively. Surprisingly, the screening cohort has a higher share of advanced cancers when compared to the historical control screening (observed-to-expected ratio: 1.25), however, this is explained by the fact that the share of cancers detected by screening only represents approximately 30% of all cancers detected in the population. As a result, the high proportion of advanced stage cancers among non-attenders for screening and appearing as interval cancers translates into a higher overall prevalence of these cancers in the screening cohort than expected in the absence of screening. When one applies to the baseline (reference) population the stage distribution observed among non-attenders, the observed rate of advanced cancers is lower than that expected in the absence of screening.

Table 1. Cumulated effects of breast cancer screening

	Cumulative effects	Observed/ expected ratio*
Attenders for screening	315 274	
Assessed	12 491	
Cancers detected (*n*)*	4423	1.02
In situ	602	2.79
Stage 1	1 728	1.25
Stage 2 A	1 145	0.76
Stage 2B	623	0.66
Stage 3 & 4	325	1.25
Effects		
Breast cancer deaths prevented	92	
Cumulative mortality reduction (%)	12.60%	
Life-years saved	1 522	

*Cancers detected in the entire cohort invited to attend for screening, therefore encompassing screen-detected cancers and cancers detected in non-attenders for screening.

The impact of screening on costs is presented in Table 2. Total costs incurred in the screening cohort amount to 841 million Francs over 20 years, or 540 million if discounted at a rate of 5%. The 'net' cost of screening, as compared to the baseline scenario, is in the order of 200 million French Francs. The screening programme itself accounts for 16% of total costs, the largest cost components being assessment of positive mammograms (34%) and initial treatment of breast cancer (40%). When the difference in cumulated costs is divided by the difference in total effects, one obtains a discounted cost-effectiveness ratio of 131 023 FF per life-year saved (approximately UK £13 000). This amounts to a cost of 2167 000 FF (UK £216 000) per breast cancer death prevented.

Sensitivity analyses

Results of sensitivity analyses are presented in Tables 3 and 4.

Table 3 presents the impact of changing input costs. Twofold increases in the fixed or variable costs of screening programmes change total costs and cost-effectiveness ratios by a maximum of 15%. Changes in costs of initial have the least impact on total costs. The one factor that has a significant impact on total costs and cost-effectiveness is assessment costs: a twofold increase raises the cost-effectiveness ratio by 89%, amounting to a net increase of total costs of the order of 177 million Francs discounted over 20 years.

Table 2. Cumulated costs of breast cancer screening

Costs (French Francs):	No discounting	5% Discounting	% Total costs
Screening, fixed	43 661 760	28 566 407	5.30
Screening, variable	89 853 224	58 855 191	10.90
Screening, total	133 514 984	87 421 598	16.20
Assessment	276 180 435	180 902 270	33.40
Biopsy	6790 398	4731 727	0.90
Initial treatment	343 895 532	220 605 444	40.80
Palliative care	81 488 247	47 305 399	8.70
Total costs	841 869 595	540 966 438	100.00
Total costs in the absence ofscreening	543 126 753	341 582 179	
Net cost of screening	298 742 842	199 384 259	
Cost (FF) per life-year saved	196 315	131 023	

Table 3. Impact of cost variations on total costs

	Base case	Screening fixed cost ×0.5	Screening fixed cost ×0.2	Screening variable cost ×1.5	Assessment cost ×0.5	Assessment cost ×2.0	Initial treatment cost ×0.5	Initial treatment cost ×2.0
Costs (×1000 FF)								
Total cost of screening	540 966	526 683	569 533	570 394	450 515	721 869	430 664	761 572
Net cost of screening*	199 384	185 101	227 951	228 812	110 665	376 823	206 177	185 798
Incremental cost†		– 14 283	28 566	29 428	– 88 719	177 439	6 793	– 13 586
Cost-effectiveness (costs(FF)/LYS)								
Cost-effectiveness ratio	131 023	121 637	149 795	150 361	72 722	247 624	135 487	122 095
Incremental cost-effectiveness†		– 9 386	18 772	19 338	– 58 301	116 602	4 464	– 8 928
Difference (%)		– 7.20	14.30	14.80	– 44.50	89.00	3.40	– 6.80

*Costs of screening – costs expected in the absence of screening.
†Compared with base case scenario (actual screening programme parameters).

Table 4. Sensitivity analysis for increases in screening attendance

	Current compliance (54%)	Current compliance ×0.75 (41%)	Current compliance ×1.25 (68%)	Current compliance ×1.6 (87%)
Attenders for screening (*n*)	315 274	236 456	394 093	504 439
Women recalled for further assessment (*n*)	12 491	9 368	15 614	19 985
Cancers detected (*n*)	4 423	4 392	4 454	4 498
Breast cancer deaths avoided (*n*)	92	65	120	159
Cumulated mortality reduction (%)	12.6	8.7	16.4	21.8
Life-years saved (*n*)	1 522	1 040	2 004	2 679
Costs (discounted at 5%)				
Total costs of screening	540 966 438	484 245 002	597 687 873	677 097 883
Total costs in the absence of screening	341 582 179	341 317 537	341 846 820	342 217 319
Net cost of screening	199 384 259	142 927 465	255 841 053	334 880 564
Cost per life-year saved	131 023	137 484	127 671	125 005
I*ncremental analysis**				
Costs (%)		– 28.3	28.3	68.0
Life-years gained (%)		– 31.7	31.7	76.0
Reduction in breast cancer mortality (%)		– 30.5	30.4	73.0
Cost-effectiveness (%)		4.9	– 2.6	– 4.6

*Percentage difference with reference to the base case scenario of current compliance (actual screening programme parameters).

Compliance to the French screening programmes is low, therefore it was important to estimate the impact of changes in compliance on total costs, mortality and cost-effectiveness. These results are presented in Table 4 for four levels of screening attendance: current attendance (54%), 41% attendance (which corresponds to the average attendance of many of existing screening programmes in France), 68% attendance and 87% attendance. The latter two figures imply an increase of 25 and 60%, respectively, over current compliance rates. Both total costs and life-years gained increase with increasing compliance. Increases in effects outweigh increases in costs, resulting in more favourable cost-effectiveness at higher attendance rates. Most importantly, the potential reduction in mortality is increased by 30% and 70% for increases in attendance to 68% and 87%, with parallel decreases of 2.6% and 4.6% to costs per life-year saved, as compared to the current compliance scenario.

DISCUSSION

Cost-effectiveness results

Assessing the impact of screening on breast cancer epidemiology requires a flexible model capable of reflecting the dynamic nature of the screened cohort and accounting for the full complexity of interrelated factors. The model presented in this paper successfully simulated the screening situation in the Bas-Rhin district in France and will be used for further simulations of screening results and policies. Initial results suggest that the existing decentralized model of screening may allow for a 12.6% reduction in breast cancer mortality in the target population. The cost-effectiveness ratio obtained (137 000 FF or approximately $25 000 per life year gained) falls within the acceptable range of cost-effectiveness for health care interventions, however, it is at the high end of other ratios for breast cancer screening (see Table 4). This result is expected from the French screening programme, as low

attendance in the target population and the high direct cost of screening will have a negative impact on the overall feasibility of screening.

The mortality reduction is somewhat lower than that predicted by other cost-effectiveness models (van der Maas *et al*. 1989; de Koning *et al*. 1991; Leivo *et al*. 1999), however, this is to be expected given low attendance. Indeed, much higher reductions in mortality may be expected if one increases attendance to screening (Table 3). The reduction in mortality drops to 4.9% for a 50% decrease in attendance from present values and reaches 21.8% for an increase in attendance of 60% (total attendance reaching 87%). Increases in attendance have a significant impact on total costs, however, the resulting cost-effectiveness ratios are more favourable and vary only slightly. These results mirror those found in the application of the Dutch MISCAN model to the German situation, which is also characterized by low attendance and a decentralized model of screening (Beemsterboer *et al*. 1994). In this study mortality reduction was 17% for 70% overall attendance, 11% for 47% attendance and 7% for 26% overall attendance. These results underscore the need to focus efforts and resources on optimizing the compliance of women to screening in order to derive the maximal benefit from existing screening programmes.

As previous studies have shown, cost-effectiveness results may vary significantly based on the inputs into the underlying model (Leivo *et al*. 1999). Results of the sensitivity analysis confirm this fact. The focus of this paper is on the methods used to build the model and more sophisticated sensitivity analyses will need to be undertaken to fully understand the impact of model inputs on obtained results.

Implications for modelling of breast cancer screening

Several baseline assumptions and methods used to build the model deserve to be addressed in more detail, as they have important implications for the final outcome of the model.

The comparison

The objective of any cost-effectiveness model is to compare two or more situations in terms of costs and effects. The model described in this paper was intended to assess the impact of a screening programme on resource use and breast cancer mortality, therefore the chosen comparator is a situation in which no screening programme is implemented. For the purposes of our model, we applied the stage distribution and incidence of breast cancer expected based on a historical situation in the Bas-Rhin district 4 years preceding the introduction of screening. Another possibility would have been to use epidemiological data from a neighbouring district in which no screening programme had been implemented. However, this approach was not feasible in practice, as precise staging information is not widely available in France, and rates of spontaneous screening vary significantly from one district to another Wait *et al*. (1997) and would affect the stage distribution and incidence observed. In order to verify the validity of our comparison, we applied the stage distribution observed among non-attenders for screening to the baseline scenario. This comparison, while allowing to determine the 'net' yield of organized screening, has definite limitations, as behaviours of women not attending for screening are impacted upon by the presence of a screening programme, and the impact of screening is thus underestimated. Many authors have chosen to use stage distributions from randomised clinical trials to depict the situation expected in the absence of screening, however, this approach may be flawed (Goetszche & Olsen 2000) as these data are likely to draw an overly pessimistic view of the baseline situation without screening and thereby overestimate the net impact of screening. In light of these constraints, the historical control was thought to be the most suitable and representative depiction of a baseline situation without screening in the Bas-Rhin district.

Lead time and length bias

Length-bias and lead time remain two important considerations in depicting the impact of screening on mortality from breast cancer. Schwartz (1980) developed a model to estimate the percentage of the reduction in breast cancer mortality that was attributable to lead time and length-time biasing, as opposed to a true advance in diagnosis. According to his model, 50% of the difference in 5-year survival between screening attenders and non-attenders is due to lead time and length-time biases. This proportion varied from 20 to 73% according to different hypotheses for breast cancer prognosis in the prevalent round, and averaged about 40% in the incident round of screening. More recently, Moss *et al*. (1994) found that the more favourable stage distribution amongst screening attenders as compared to non-attenders only explained one-third of the difference in survival between these populations, the remaining two-thirds being due to lead time, length-time biasing and other factors). One potential bias that was not accounted for in our model was the healthy volunteer bias, which assumes that screen-attenders have a lower inherent risk for breast cancer than non-attenders, by bias-

ing survival data in favour of screen attenders (Duffy *et al.* 1991). The authors found that prognostic factors were valid predictors of survival in screening attenders, however, they were inadequate in predicting survival patterns among non-attenders in multivariate analyses. We assumed that this effect was not relevant to the French screened population based on ad hoc surveys of screening non-attenders (B. Séradour, pers. comm.).

Length-bias sampling

One of the risks of breast cancer screening is overdiagnosis of indolent or latent breast cancer cases, a bias referred to as length-bias sampling. This overdiagnosis may have important repercussions for the simulation of screening effects. In a Norwegian study, Norum conducted a sensitivity analysis to account for the impact of over-diagnosis on cost-effectiveness results (Norum 1999). Assuming a rate of overdiagnosis of 10% resulted in a 10% increase in the cost-effectiveness ratio. Our model accounted for overdiagnosis indirectly through assumptions of lead time and expected stage distributions.

Preinvasive states

The model assumes that there exist no preinvasive states for breast cancer. One possible exception may be carcinoma *in situ*, however, publications on the natural course of carcinoma *in situ* shed little light on the natural history of carcinoma *in situ* or on its impact by screening (Wright & Mueller 1995; Ernster *et al.* 1996). One study reported that 28% of *in situ* cases, if left untreated, evolved into invasive cancers after 16 years of follow-up (Page *et al.* 1984). A more recent French study, based on over 1004 cases treated between 1972 and 1993 in 16 French hospitals, observed eight deaths from carcinoma *in situ* after an average follow-up of 42 months (Bonnier *et al.* 1999). Our model considered *in situ* cancers as a prognostic category of their own (stage 0), and applied observed incidence, detection and survival rates to these cases. However, it did not necessarily consider these lesions as preinvasive and made no assumptions about the proportion that naturally progressed to invasive stages. Our review of existing cost-effectiveness studies found little information on how this was handled by other authors.

Staging information

Our model hinges on tumour stage, whereas other cost-effectiveness models reported in the literature typically are based on tumour size alone (Van der Maas 1989). The advantage of stage is that it accounts for both the histological size and the growth potential of the tumour as well as the presence of metastases. Another possible prognostic factor would have been the Nottingham Prognostic Index, which combines information on grade, tumour size and nodal involvement to classify tumours according to prognosis. Studies have shown that tumour size only accounts for 20% of the predictive value of the Nottingham index for survival, the remaining 80% are attributable to the impact of grade and nodal status (Haybitte *et al.* 1982). Although historical data on size-specific (Carter *et al.* 1989), NPI-specific (Galea *et al.* 1991; Crisp *et al.* 1993) survival or the presence of metastases (Dickman *et al.* 1999) do exist, we felt that these data did not offer the same sensitivity as stage-specific data, moreover we could not be sure that they accurately reflected prognosis trends in our target population.

The use of stage may have repercussions for our model as we are obliged to compare recent stage distributions in the screening cohort with those found in 1985. This comparison of recent with older staging data may be biased by stage migration in which cancers that were previously described as localized using older and less sophisticated diagnostic techniques may now appear as metastatic. This bias may partly explain the unexpected increase in advanced stage cancers found in the screening cohort compared with the baseline situation. Alternate methods for comparing stage distributions across histological series are discussed elsewhere (McCann *et al.* 1998).

Impact on breast cancer mortality

One of the most difficult aspects of breast cancer screening research is to ascertain from recent screening results the expected reduction in breast cancer mortality (Moss & Blanks 1998; Goetszche 2000). In the present model, the impact on breast cancer mortality was assessed based on stage-specific survival rates derived from the Bas-Rhin registry for cancer cases detected between 1989 and 1995. These estimates yielded a figure of 16.5 years of life saved per death avoided, which is comparable to results from other studies. Most other economic analyses used data from randomized clinical trials to estimate mortality reduction. For example, de Koning *et al.* (van der Maas *et al.* 1989; de Koning *et al.* 1991) combined effectiveness data from the east-west Swedish trials with results from HIP trials and tested a range of 14–46% mortality reduction in their sensitivity analysis. Leivo *et al.* (1999) favoured the use of local mortality data, however, these data were limited to 4 years after the onset of screening and tested results based on changes in the gradualness of

mortality reductions by means of sensitivity analysis. For example, if the full impact on mortality equivalent for the entire 20-year period of study was assumed to be equivalent to that observed after 5 years of screening, the cost-effectiveness ratio was increased by 123%. This result is of interest for the interpretation of our model results, as the impact of stage on survival was only estimated for 10 years after diagnosis. If it can be assumed that survival after 10 years differs from that observed at 10 years, and moreover that stage-specific differences grow further during this time, it may be assumed that the model underestimates the impact of screening on breast cancer mortality.

Resource use

Cost estimates used into economic models are highly dependent on the structure of the health care system, purchasing power parities, health care utilization rates and methods used to estimate resource use and unit costs (van Ineveld *et al*. 1993). For the purposes of our model, we tried to approximate real costs for most of the input data. One exception is the variable cost of screening, for which the national reimbursed tariff was taken as a proxy. Multiplying this variable cost by a factor of 1.5 increased the cost-effectiveness ratio by 14.5%, whereas halving or doubling the fixed cost of screening changed cost-effectiveness ratios by –7.6% and +13.7%. This is an important consideration for policy makers eager to lure radiologists away from spontaneous screening and towards organized screening by increasing reimbursement rates for screening mammograms. These results also suggest that further efficiencies in running the programmes may have significant impact on cost-effectiveness results.

The model demonstrated high sensitivity to changes in assessment costs. This finding may be diminished in a screening situation with lower recall rates than those observed in the Bas-Rhin (9%, 3.8% and 2.4% in the first three rounds of screening). Changes in initial treatment costs had little impact on cost-effectiveness results, however, increases in these costs resulted in a more favourable cost-effectiveness ratio for screening, as initial treatment costs increase with tumour stage and the screening situation has a more favourable stage distribution. Overall, treatment costs are probably underestimated in the model as only initial and terminal costs were included and the costs of recurrences and surveillance after adjuvant treatment were not covered. This approach was also followed by de Koning *et al*. (1991) in the Dutch cost-effectiveness studies.

CONCLUSION

Cost-effectiveness models may be useful tools to guide policy analysis, as they allow to represent in a single con-

Table 5. Published cost-effectiveness analyses of breast cancer screening

Authors (year of publication)	Country	Cost per life year gained (US$)
van Ineveld et al. (1993)	Great-Britain	2 844
van Ineveld et al. (1993)	Netherlands	3 350
Tabar et al. (1989)	Sweden	3 400
de Koning et al. (1991)	Netherlands	3 825
van der Maas et al. (1989)	Netherlands	4 850
Forrest (1987)	England and Wales	4 810
Hall et al. (1992)	Australia	5 321
Plans et al. (1996)	Cataluna, Spain	7 020
Australian Health Minister's Advisory Council. 1990)	Australia	7 897
van Ineveld et al. (1993)	France	9 164
Norum (1999)	Norway	14 000
Beemsterboer et al. 1994)	Germany	15 000
van Ineveld et al. (1993)	Spain	15 326
Hristova & Hakama 1996)	Finland	15 414
Leivo et al. (1999)	Finland	18 955
Eddy (1989)	USA	21 717
Brown (1992)	USA	30 000
US Office of Technology (1987)	USA	34 600
Clarke & Fraser (1991)	Scotland	69 817
Obuko et al. (1991)	Japan	114 300

Adapted from Leivo et al. (1999).

ceptual framework the costs and effects of different screening scenarios over an extended time period. Nonetheless, it is essential to fully understand the unavoidable limitations of these models when interpreting simulated results for policy-making. These limitations do not undermine the value of cost-effectiveness models, however, they underline the need to assess these results within the full cultural, sociological, political and economic context for decision-making.

The model presented in this paper was designed to assess the cost-effectiveness of different screening policies for France and used the data and assumptions of the Bas-Rhin screening programme to validate its basic structure. The results of initial analyses suggest that the model is capable of suitably assessing the impact of breast cancer screening in terms of costs and effects. Further scenario analyses are needed to better understand the impact of shifts in policy on the feasibility of breast cancer screening in France and to help identify optimal screening strategies.

REFERENCES

Arveux P., Lejeune C. & Pitard A. (1998) What are the costs of an efficient screening strategy for colonic cancer? *Gastroenterology and Clinical Biology* **22**, S49–S55.

Auray J.P., Bail J.N., Béraud C., Beresniak A., Balchier C. & Corchaud S. (1998) Recommandations de bonnes pratiques des méthodes d'évaluation économique des stratégies thérapeutiques. *Journal of Econ Médicale* **16**, 329–351.

Australian Health Minister's Advisory Council (1990). Breast cancer screening evaluation committee. Australian institute of health prevention program evaluation series no. 1. Australian Government Publishing Service, Canberra.

Beemsterboer P.M.M., de Koning H.J., Warmerdam P.G. *et al.* (1994) Prediction of the effects and costs of breast cancer screening in Germany. *International Journal of Cancer* **58**, 623–628.

Bonnier P., Body G., Bessenay F. *et al.* (1999) Prognostic factors in ductal carcinoma in situ of the breast: results of a retrospective study of 575 cases. The Association for Research in Oncologic Gynecology. *European Journal of Obstetric Gynecological Reproduction Biology* **84**, 27–35.

Brown M.L. (1992) Economic considerations in breast cancer screening of older women. *Journal of Gerontology* **47**, 51–58.

Carter C.L., Allen C. & Henson D.E. (1989) Relation of tumor size, lymph node status, and survival in 24,740 breast cancer cases. *Cancer* **63**, 181–187.

Clarke P.R. & Fraser N.M. (1991) Economic analysis of screening for breast cancer. Report for the Scottish Home and Health Department 1991.

Crisp W.J., Higgs M.J., Cowan W.K. *et al.* (1993) Screening for breast cancer detects tumours at an earlier biological stage. *British Journal of Surgery* **80**, 863–865.

Day N.E., Williams D.R.R. & Khaw K.T. (1989) Breast cancer screening programmes: the development of a monitoring and evaluation system. *British Journal of Cancer* **59**, 954–958.

Dickman P., Hakulinen T., Luostarinen T. *et al.* (1999) Survival of cancer patients in Finland 1955–94. *Acta Oncologica* **38**, 1–103.

Duffy S.W., Tabar L., Faberberg G.et al. (1991) Breast screening, prognostic factors and survival results from the Swedish two-county study. *British Journal of Cancer* **6**, 1133–1138.

Eddy D.M. (1989) Screening for breast cancer. *Annals of Internal Medicine* **111**, 389–399.

Ernster V.L., Barclay J., Kerlikowske K., Grady D. & Henderson C. (1996) Incidence of and treatment for ductal carcinoma in situ of the breast. *Journal of the American Medical Association* **275**, 913–918.

Forrest P. (1987) *Breast Cancer Screening Report to the Health Ministers of England, Wales, Scotland and Northern Ireland.* Department of Health Social Security, HMSO, London.

Galea M.H., Todd J.H., Elston C.W., Ellis I.O. & Blamey R.W. (1991) Confirmation of a prognostic index for primary breast cancer. *European Journal of Surgery – Oncology* **17**, 414.

Goetszche P.C. & Olsen O. (2000) Is screening for breast cancer with mammography justifiable? *Lancet* **355**, 129–134.

Hall J., Gerard K., Salkeld G. & Richardson J. (1992) A cost-utility analysis of mammographic screening in Australia. *Society of Science Medicine* **34**, 993–1004.

Haybitte J.L., Blamey R.W., Elston C.W.et al. (1982) A prognostic index in primary breast cancer. *British Journal of Cancer* **45**, 361–366.

Hayes D.F. & Kaplan W. (1990) *Evaluation of Patients Following Primary Therapy*. pp. 505–525. Lippencott, Philadelphia.

Hristova L. & Hakama M. (1996) Effect of screening for cancer in the nordic countries on deaths, costs and quality of life up to the year 2017. *Acta Oncology (Suppl 9)*. Scandinavian University Press, Stockholm.

van Ineveld B.M., van Oortmarssen G.J., de Koning H.J., Boer R. & van der Maas P.J. (1993) How cost-effective is breast cancer screening in different EC countries? *European Journal of Cancer* **29A**, 1663–1668.

Institut National Statistique et des Etudes Sociales (INSEE) (2000) *Recensement de la Population, Projections Omphale*. INSEE, Paris.

de Koning H.J., van Ineveld B.M., van Oortmarssen G.J. *et al.* (1991) Breast cancer screening and cost-effectiveness: policy alternatives, quality of life considerations and the possible impact of uncertain factors. *International Journal of Cancer* **49**, 531–537.

Leivo T., Sintonen H. & Tuominen R. & Hakama M. & Pukkal E. & Heinonen O.-P. (1999) The cost-effectiveness of nationwide breast carcinoma screening in Finland 1987–92. *Cancer* **86**, 638–646.

Lejeune C., Arveux P., Fagnani F., Bonithon-Kopp C. & Faivre J. (2003) A simulation model for evaluating the medical and economic outcomes of screening strategies for colorectal cancer. *European Journal of Cancer Prevention* **12**, 77–84.

van der Maas P.J., de Koning H.J., van Ineveld B.M. *et al.* (1989) The cost-effectiveness of breast cancer screening. *International Journal of Cancer* **43**, 1055–1060.

McCann J. & Stockton D. & Day N. (1998) Breast cancer in East Anglia. the impact of the breast cancer screening programme on stage at diagnosis. *Journal of Medical Screening* **5**, 42–48.

Moss S. & Blanks R. (1998) Calculating appropriate target cancer detection rates and expected interval cancer rates for the UK NHS Breast Screening Programme. *Journal of Epidemiology and Community Health* **52**, 111–115.

Moss S.M. & Ellman R. & Coleman D. & Chamberlain J. for the United Kingdom Trial of Early Detection of Breast Cancer Group. (1994) Survival of patients with breast cancer diagnosed in the United Kingdom trial of early detection of breast cancer. *Journal of Medical Screening* **1**, 193–198.

Norum J. (1999) Breast cancer screening by mammography in Norway. Is it cost-effective? *Annals of Oncology* **10**, 197–203.
Obuko I., Glick H., Frumkin H. & Eisenberg J.M. (1991) Cost-effectiveness analysis of mass screening for breast cancer in Japan. *Cancer* **7**, 2021–2029.
van Oortmarssen G.J. & Boer R. & Habbema J.D. (1995) Modelling issues in cancer screening. *Statistical Methods in Medical Research* **4**, 33–54.
Page D.L. & Dupont W.D. & Rogers L.W. (1984) Intra-ductal carcinoma of the breast: Follow-up after biopsy only. *Cancer* **49**, 751–758.
Plans P. & Casademont L. & Salleras L. (1996) Cost-effectiveness of breast cancer screening in Spain. *International Journal of Technological Assessment of Health Care* **12**, 146–150.
Royston G. (1999) Commentary: trials versus models in appraising screening programmes. *British Medical Journal* **318**, 360–361.
Schaffer P. & Renaud R. & Gairard B. & Guldenfels C. (1996) Le rôle des registres dans l'évaluation des campagnes de dépistage du cancer du sein. *Rev Epidém et Santé Publications* **44**, S15–S21.
Schaffer P., Gairard B., Guldenfels C. & Haehnel P. *et al.* (2000) Un système decentralisé de dépistage du cancer du sein: l'exemple du Bas-Rhin en France. [A decentralized breast cancer screening program in the French department of Bas-Rhin.] *Journal of Radiology* **81**, 845–857.
Schwartz M. (1980) Estimates of lead time and length biasing in a breast cancer screening program. *Cancer* **46**, 844–851.
Séradour B. & Allemand H. & Schaffer P. (1997) Programme français de dépistage du cancer du sein. Résultats de Cinq Départements 1989–94. *Bulletin Cancer* **84**, 822–828.
Sonnenberg F.A. & Beck J.R. (1993) Markov models in medical decision making: a practical guide. *Medical Decision Making* **13**, 322–338.
Tabar L., Fagerberg G., Duffy S.W. & Day N.E. (1989) The Swedish two county trial of mammographic screening for breast cancer: recent results and calculation of benefit. *Journal of Epidemiology and Community Health*, **43**, 107–114.
U.S. Congress Office of Technology Assessment. (1987) *Breast Cancer Screening for Medicare Beneficiaries: Effectiveness, Costs to Medicare and Medical Resources Required*. US Government Printing Office, Washington, DC.
Wait S. & Allemand H. (1996) The French breast cancer screening programme: epidemiological and economic results of the first round of screening. *European Journal of Public Health* **6**, 43–48.
Wait S., Schaffer P., Seradour B., Chollot M., Demay M. & Dejouhanet S. (1997) Le dépistage spontané du cancer du sein. [Opportunistic screening of breast cancer in France.] *Bulletin Cancer* **84**, 619–624.
Wait S., Schaffer P., Seradour B. *et al.* (2000a) Le coût du dépistage du cancer du sein en France.[The cost of breast cancer screening in France]. *Journal of Radiologie* **81**, 799–806.
Wait S., Schaffer P., Blanchard O. & le Bas-Rhin. J. (2000b) La prise en charge hospitalière du cancer du sein dans. *Econ Médicale* **18**, 85–100.
de Wolf C.J.M. & Perry N.M. (June 1996) *European Guidelines for Quality Assurance in Mammography Screening*, 2nd edn. European Commission.
Wright C. & Mueller C. (1995) Screening mammography and public health policy: the need for perspective. *Lancet* **346**, 29–32.