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Modelling the effect of breast cancer screening on related mortality using French data

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ABSTRACT

Introduction: This study aimed at modelling the effect of organized breast cancer screening on mortality in France. It combined results from a Markov model for breast cancer progression, to predict number of cases by node status, and from relative survival analyses, to predict deaths. The method estimated the relative risk of mortality at 8 years, in women aged 50–69, between a population screened every two years and a reference population. *Methods*: Analyses concerned cases diagnosed between 1990 and 1996, with a follow-up up to 2004 for the vital status. Markov models analysed data from 3 screening programs (300,000 mammographies) and took into account opportunistic screening among participants to avoid bias in parameter's estimates. We used survival data from cancers in the general population (n = 918, 7 cancer registries) and from screened cancers (n = 565, 3 cancer registries), after excluding a subgroup of screened cases with a particularly high survival. Sensitivity analyses were performed. *Results*: Markov model main analysis lacked of fit in two out of three districts. Fit was improved in stratified analyses by age or district, though some lack of fit persisted in two districts. Assuming 10% or 20% overdiagnosed screened cancers, mortality reduction was estimated as 23% (95% CI: 4, 38%) and 19% (CI: −3, 35%) respectively. Results were highly sensitive to the exclusion in the screened cancers survival analysis. Conversely, RR estimates varied moderately according to the Markov model parameters used (stratified by age or district). *Conclusion*: The study aimed at estimating the effect of screening in a screened population compared to an unscreened control group. Such a control group does not exist in France, and we used a general population contaminated by opportunistic screening to provide a conservative estimate. Conservative choices were systematically adopted to avoid favourable estimates. A selection bias might however affect the estimates, though it should be moderate because extreme social classes are under-represented among participants. This modelling provided broad estimates for the effect of organized biennial screening in France in the early nineteen-nineties. Results will be strengthened with longer follow-up.

1. Introduction

The main objective of breast cancer screening is to reduce breast cancer mortality [1]. Overviews of randomized trials suggested regular screening would reduce breast cancer mortality

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by 25–30% in screened women [1–3]. Some authors, however, contested conclusive evidence from these trials [4]. Evaluating the effect of breast cancer service screening on mortality is a crucial issue for health authorities. Evaluation is difficult though outside the experimental context and a variety of methods have been used [5–18]. In France, pilot programs were first initiated in a few districts (*départements*) in 1990; a national program was later initiated and finally extended to all districts in 2004. Opportunistic screening is common and has developed in parallel to service screening programs. This study aimed at evaluating the effect of breast cancer screening on related mortality in France, comparing a screened population to an unscreened control group. We revised a method initially proposed by Chen and Duffy [13,14].

2. Material and methods

The method combines results from a Markov model for the progression of cancer and from relative survival analyses, using node status as prognostic factor. It requires survival from cancers diagnosed at screening and from a reference population. The Markov model is used to predict the numbers of cases and relative survival to predict deaths. The method estimates the relative risk (RR) of mortality between a population screened every two years and a reference population.

There is no proper control group in France to use as reference population, due to the concomitant development of opportunistic screening. We thus considered two alternatives: either cancers from the general population, but some were screened cancers outside the program, or clinical cancers diagnosed due to symptoms, but they represent a specific population (essentially women not undergoing opportunistic screening), that we will name "unscreened reference population". These two references, however, provide bounds for the RR we want to estimate, comparing a screened population to an unscreened control group.

2.1. Data and population

Analyses concerned invasive breast cancers in women aged 50–69. The study period was restricted to 1990–96 to ensure 8-years follow-up in the survival analyses. The data sources are presented in Tables 1 and 2. The Markov model analysed data from screening programs (detection rates at first and subsequent screens and interval cancer rates). Three districts involved in the pilot programs, covered by a cancer registry or with exhaustive monitoring of interval cancers, could be analyzed (Bas-Rhin, Isère, Rhône). Data pertained to 180,000 women and 300,000 mammography episodes (one-view, double-reading). Screening targeted women aged 50–69, except in Bas-Rhin (aged 50–64), and women were invited every 2, 2.5 and 3 years respectively in Bas-Rhin, Isère and Rhône.

For each reference population (general population or unscreened population), only one source provided adequate data: a sample of cases diagnosed in 1990 issued from the French cancer registries network (Francim-breast) and cases from the cancer registry of Loire-Atlantique, which monitored detection mode and identified cancers detected on clinical signs (clinical cancers).

2.2. Multi-state Markov model for the progression of cancer

We used a 5-state homogeneous Markov model to describe the natural progression of breast cancer, from no disease to preclinical asymptomatic phase and finally to clinical phase, according to node status. Women start without disease (state 1, no disease). Cancers not detectable by screening are assimilated to the 'no disease state'. Women enter in state 2 (preclinical cancer, node negative) when they get a cancer detectable by screening. From state 2, the cancer can either spread to lymph node staying asymptomatic (sate 3, preclinical, node positive) or become symptomatic (state 4, clinical, node negative). From state 3, the node positive cancer will finally become symptomatic (sate 5, clinical, node positive). The parameters of this model are the transition rates $\lambda_{i,j}$ from state i to state j. $\lambda_{1,2}$ represents the incidence rate of the preclinical disease. Markov model implies that sojourn times in the two preclinical states (node negative and node positive) both follow an exponential distribution and that they are independent. Let's first consider a screening program in the absence of opportunistic screening. Tumours may be detected by screening or diagnosed symptomatically between rounds of screening (interval cancer). Observed data consists of detection rates at first and subsequent screens and interval cancer rates, by node status. Screened cancers are assumed in preclinical states while interval cancers are assumed in clinical states. Screening rhythm must be specified for each district. Observations depend both on the transition rates (natural history of the cancer) and on the sensitivity of the mammography, which are estimated jointly by maximum likelihood. Cancers with unknown node status are integrated in the likelihood assuming that unknown node status is independent of the true node status.

Table 1
Data analyzed in Markov models (sources screening management centers). Node status according to detection mode.

District	Cancers at first screen			Cancers at subsequent screens			Interval cancers		
	N[a]	%pN−[b]	%pNx[c]	N[a]	%pN−[b]	%pNx[c]	N[a]	%pN−[b]	%pNx[c]
Bas-Rhin	216	74	10	154	69	9	157	59	15
Isère	206	76	4	54	63	8	130	71	7
Rhône	491	71	2	185	72	2	514	64	2

[a] Number of cancers with known node status.
[b] Proportion of node negative cancers among cancers with known node status.
[c] Proportion of cancers with unknown node status.

Table 2
Data analyzed in relative survival analyses[a,b] (sources cancer registries). Population, age and node status distribution.

Population	Sources	Period	Age class (%)		Node status	Number of cases
			50–59	60–69	%pN−	
Screened cancers	Bas-Rhin, Isère, Hérault	1990–96	42	58	72	731
General population	7 registries[c]	1990	46	54	58	918
Clinical cancers[d]	Loire-Atlantique	1991–95	47	53	52	811

[a] Node status (pN) was replaced by the clinical node status (N) for women without curage. In addition, pN status for cancers node negative after adjuvant chemotherapy in Loire-Atlantique were also replaced by the clinical node status N.
[b] End points between 2002 and 2004 according to data; analyses censored to 8 years.
[c] Bas-Rhin, Isère, Hérault, Calvados, Doubs, Somme, Tarn.
[d] Cancers diagnosed due to clinical signs or symptoms ("unscreened population").