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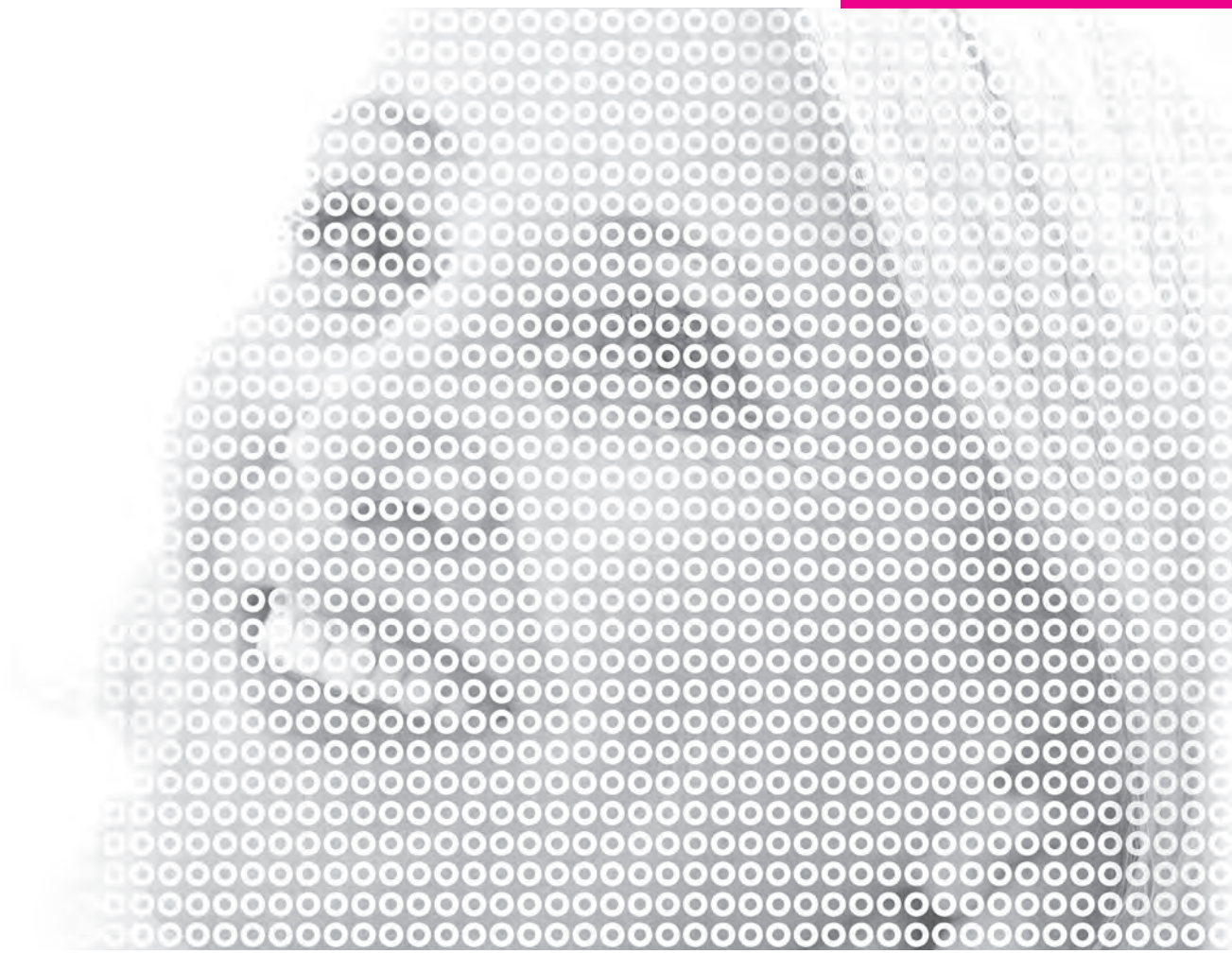

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Direction des systèmes de soins et services et maladies chroniques

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AUTHORS

Jacques Brisson
Unité Programmes de dépistage, génétique et lutte au cancer, Direction des systèmes de soins et services et maladies chroniques, Institut national de santé publique du Québec
Unité de recherche en santé des populations (URESP), Centre hospitalier affilié universitaire de Québec
Département de médecine sociale et préventive, Université Laval

Nathalie Vandal
Unité Programmes de dépistage, génétique et lutte au cancer, Direction des systèmes de soins et services et maladies chroniques, Institut national de santé publique du Québec

Jean-Marc Daigle
Unité Programmes de dépistage, génétique et lutte au cancer, Direction des systèmes de soins et services et maladies chroniques, Institut national de santé publique du Québec

Nicole Hébert-Croteau
Unité Programmes de dépistage, génétique et lutte au cancer, Direction des systèmes de soins et services et maladies chroniques, Institut national de santé publique du Québec

Isabelle Théberge
Unité Programmes de dépistage, génétique et lutte au cancer, Direction des systèmes de soins et services et maladies chroniques, Institut national de santé publique du Québec

Thierry Duchesne
Unité de recherche en santé des populations (URESP), Centre hospitalier affilié universitaire de Québec
Département de médecine sociale et préventive et Département de mathématiques et de statistique, Université Laval

Diane Major
Unité Programmes de dépistage, génétique et lutte au cancer, Direction des systèmes de soins et services et maladies chroniques, Institut national de santé publique du Québec
Unité de recherche en santé des populations (URESP), Centre hospitalier affilié universitaire de Québec
Département de médecine sociale et préventive, Université Laval

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ABSTRACT

Effect on breast cancer mortality of a mammography screening program initiated in 1998 was assessed. Two effect estimates were obtained for each of three groups: participants, eligible women and all women of the target age group including those with prior breast cancer diagnosis. Methods: Four approaches were used: 1) observed and projected breast cancer mortality trends for 1998-2004 were compared, 2) breast cancer mortality in the first five years of the program (1998-2003) was compared to mortality for the five years prior to program initiation (1992-1997) restricting numerators of rates to breast cancer deaths occurring among incident cases, 3) observed number of breast cancer deaths among 523,830 program participants was compared to expected number based on breast cancer incidence and survival of non-participants, 4) nested case-control study (873 cases, 8730 controls) was done within the 1,054,620 women eligible for screening. Results: Among participants, estimates of breast cancer mortality reduction associated with screening were 35% (95% confidence interval (CI): 23% to 48%) and 41% (95% CI: 28% to 52%). Among eligible women, estimates were 11% (95% CI: 1% to 21%) and 7% (95% CI: 1% to 13%). Among all women of the target age group, estimates were 3% (95% CI: -1% to 15%) and 3% (95% CI: -1% to 6%). Conclusion: The four approaches used provided effect estimates that were consistent within and between groups studied. Effect estimates and their consistency support the view that initiation of this screening program led to a significant reduction in breast cancer mortality within five years of its initiation.

A population-based mammography screening program was initiated in Québec, Canada, in 1998. This program invites by letter all women aged 50-69 for biennial screening mammography in designated screening centers. Such community screening programs have been associated with a reduction of breast cancer mortality using a variety of epidemiologic methods that have different strengths and limitations.[1-16] Possible variation in extent of residual bias of these methods could lead to differences and non-comparability of estimates of screening effects. Thus, in order to estimate the possible effect on breast cancer mortality of the Québec program in the first five years after its initiation, we carried-out four comparisons that provided two estimates of effect for each of three groups of women. Two estimates were obtained for women who participated in the program (*participants*). These are the only women whose breast cancer mortality can be affected directly by program screening. Among participants, the expected breast cancer mortality reduction associated with screening could reach 35%.[17] Two estimates were also obtained for women who were eligible to the program (*eligible women*). This group which includes participants as well as non-participants, is of interest because it is the one targeted by the program. The aim of this screening program was to reduce breast cancer mortality in eligible women by 25% after 10 years of operation.[18] Finally, two estimates were obtained for the entire population of women in the target age group (*all women of the target age group*). This group is of interest because screening is expected to be reflected in overall population age-specific breast cancer mortality statistics.[19] This group includes eligible women as well as women in the target age group who already had a breast cancer diagnosis before program initiation or before becoming eligible to the program once the program had started. Women with prior diagnosis of breast cancer will be responsible for a substantial proportion of breast cancer deaths in the first years after program initiation.

MATERIAL AND METHODS

OBSERVED AND EXPECTED MORTALITY TRENDS

This approach, based on the examination of population breast cancer mortality trends, provided an estimate of the effect of screening among all women of the age targeted by the program. Trends in breast cancer mortality rates observed after the introduction of the program (1998/2004) in all women aged 50 to 74 years were compared with trends expected during this period under the hypothesis that changes in breast cancer mortality seen prior to the introduction of the program had persisted. This analysis focused on the age group 50 to 74 because screening women 50 to 69 could affect breast cancer mortality up to the age of 74 in the five years studied. Observed trends were estimated by weighted loess smoothing applied to the logarithm of age standardized mortality rates observed between 1975 and 2004. Weights were defined as the square of standardized rates divided by their variances. Expected breast cancer mortality trends were obtained by weighted Joinpoint analysis[20] in which weights were the same as those used for

loess smoothing. Joinpoint analysis was first applied to logarithm of age standardized mortality rates from 1975 to 1998 to identify any major changes in breast cancer mortality that might have occurred prior to 1998 and to estimate the trend in breast cancer mortality in the period immediately preceding 1998. Expected mortality in 2004 was obtained by projecting this Joinpoint trend seen in the period prior to 1998 to the subsequent five years. The ratio of breast cancer mortality in 2004 obtained by loess smoothing to the projected mortality obtained by Joinpoint analysis was estimated. The variance of the logarithm of this ratio was calculated as the sum of the variances of the logarithm of the predicted rates minus twice their covariance which itself was set at its largest possible value (minus the square root of the product of the variances of the logarithm of the two predicted rates). The 95% confidence limits of the logarithm of this ratio were then obtained based on its variance. These limits were exponentiated to obtain corresponding confidence limits for the mortality rate ratio.

PRE AND POST MORTALITY RATES

This approach, used by Tabar et al.,[11] provided an estimate of the effect of screening among eligible women. The breast cancer mortality rate in the first five years of the program (1998-2003) was compared to the rate observed in the preceding five years (1992-1997). According to this approach, the numerators of the rates include only breast cancer deaths that occur among cases diagnosed in the period under consideration. This restriction implies elimination from the calculation of deaths that occur among women diagnosed before the beginning of the period under consideration. Ideally, the denominators of the rates should also be corrected to exclude women who had a diagnosis of breast cancer before the beginning of the period under consideration because these women are not eligible for screening. However, such women represent only a relatively small proportion of the entire population and this correction would not affect rates materially. All breast cancer deaths that occurred in Québec women in 1992-2003 were identified using the Québec mortality database. Linkage with the Québec Tumour Registry allowed identification of the year of their breast cancer diagnosis. Québec demographic data were used to estimate the denominators of the rates. The ratio of age adjusted breast cancer mortality rate in 1998-2003 to mortality rate in 1992-1997 was estimated for women aged 50-69.

The above mentioned breast cancer mortality rate ratio in women 50-69 years needed to be corrected for secular improvement in treatment and survival to better isolate the effect of screening. A “corrected” rate ratio was obtained by using the breast cancer mortality rate ratios observed among women aged 20-49 and 70 years or more. Such correction is based on the idea that the mortality reductions observed in these women reflects the effects of treatment improvement that would also be expected at age 50-69. The “corrected” rate ratio intended to better reflect the effect of screening on breast cancer mortality among women aged 50-69 was estimated by dividing the rate ratio observed in this age group by the pooled rate ratio seen in the other age groups. The pooled rate ratio was obtained by calculating the weighted average of the logarithm of the rate ratios for women aged 20-39, 40-49 and ≥ 70 using as weights the inverse of the variances of the logarithm of the rate ratios. The variances of the logarithm of rate ratios in each age group were those obtained by Poisson regression. The variance and 95% confidence limits of the logarithm of the “corrected” ratio were then obtained as well as, by exponentiation, the corresponding 95% confidence limits of the “corrected” ratio itself.

OBSERVED AND EXPECTED BREAST CANCER DEATHS

This approach (*incidence-survival approach*)[1,21] provided estimates of effect in our three groups of women: participants, eligible women and all women of the target age group. The observed number of breast cancer deaths that occurred among participants was compared to the expected number of breast cancer deaths derived from the breast cancer incidence and breast cancer specific survival among non-participants. The ratio of observed to expected deaths provided an estimate of effect of the program on breast cancer mortality among participants. The difference between observed and expected number of breast cancer deaths also provided an estimate of the absolute number of breast cancer deaths that may have been avoided through screening among participants. This absolute number of deaths possibly prevented could then be used to estimate the effect of the program in the two other groups of women.

This analysis was based on the cohort of women who have been considered eligible for the program between 13 May 1998 and 31 December 2003. Women were eligible if they were residents of Québec, were aged 50 to 69 and had no prior diagnosis of breast cancer. All eligible women were considered non-participants from the moment they became eligible to the program until the date of their first program participation defined as having a screening mammogram within the program accompanied by signed consent to program participation. In the first five years of the program, 93% of screened women consented to program participation. At the date of their first program participation women became participants and remained so until the end of follow-up.

Five data bases were used to create this cohort. The Québec universal health insurance data base identified all Québec women who were 50 to 69 years between 1997 and 2003. The screening program information system data base identified all women who had at least one screening mammogram sometime between 1998 and 2003. This database also identified women who at the time of their screening mammography consented to program participation. The Québec Tumour Registry data base identified women newly diagnosed with breast cancer between 1984 and 2003 in Québec. The completeness of the Québec Tumour Registry for breast cancer registration has been estimated at 98.8%.[22] This allowed identification of women who had a diagnosis of breast cancer prior to initiation of the screening program as well as afterwards. The Québec mortality database was used to identify all deaths (and their causes) that occurred within the study period. Finally, a data base among the Québec universal health insurance databases was used to identify women who left Québec for a substantial period of time. All theses files were linked using a unique identifier (the health insurance number), the name and date of birth of women.

The initial cohort included 1,112,208 women. Of these women, 57,588 were excluded because they had ceased to be eligible for the universal health insurance of Québec or because insufficient information was available to verify admissibility (table 1). The final cohort included 1,054,620 women among whom 523,830 had at least one screening mammography within the program, 14,699 women had a diagnosis of breast cancer and 1,142 women died of this disease.

TABLE I

Number of women excluded from the cohort according to reasons for exclusion

Reason for exclusion	Number excluded
Date of birth unknown	2,545
Age 70 or more on 13 May 1998	11,439
Eligible to the program after 31 December 2003	1
Screening mammography before age 50	70
Breast cancer (invasive *or in situ*) diagnosis prior to potential program eligibility	21,939
Death prior to potential program eligibility	1,783
Period of ineligibility to health insurance coverage prior to potential program eligibility	19,811
Total	**57,588**

The observed number of breast cancer deaths that occurred among the 523,830 program participants was obtained directly from their follow-up through linkage. The expected number of breast cancer deaths among these women was estimated using the breast cancer incidence and breast cancer specific survival seen among non-participants during the same period. Breast cancer incidence rates among non-participants were calculated by age and year of diagnosis. Survival among women who had breast cancer diagnosed while they were non-participants was modeled using semi-parametric Cox regression. The model included age at diagnosis (50-54, 55-59, 60-64, 65-69 and 70-75) and year of diagnosis (1998-1999 and 2000-2003).

The ratio of observed to expected breast cancer deaths provided an estimate of the effect of screening among participants. The variance of this ratio was calculated by postulating, first, that the observed number of breast cancer deaths was a Poisson variable with mean equal to the expected number of deaths and, second, that the variation in the expected number of deaths was negligible. Given the variance of the ratio, its 95% confidence limits were calculated.

The ratio of observed to expected number of deaths among eligible women and among all women of the target age group could also be calculated. In each group, the observed number of breast cancer deaths was obtained through follow-up. The expected number of deaths in each group was obtained by adding to the observed number the estimated number of breast cancer deaths possibly prevented by screening. The number of deaths possibly prevented was given by the difference between observed and expected number of deaths among participants. The variance of the ratio of observed to expected deaths among eligible women and among all women of the target age group was then calculated using the same postulates as above. This variance, in turn, allowed calculation of confidence limits of the ratio.

NESTED CASE-CONTROL STUDY

This approach provided an estimate of the effect of screening among participants.[23] The nested case-control study was conducted within the 1,054,620 women eligible to the program between 1998 and 2003. Cases were women who died of breast cancer and whose date of diagnosis could be identified. Among the 1,142 breast cancer deaths, 873 had a full date of diagnosis available. For each of these 873 cases, 10 controls were selected randomly among women who were alive at the time of the death of the case. Controls were also matched to cases by age and year when they became eligible to the program. Classification of cases and controls as to their participation to the program was measured at the date of diagnosis for cases or the equivalent date for controls. The odds ratio was obtained by conditional logistic regression. The odds ratio obtained from this analysis corresponds to the ratio of breast cancer mortality rate among participants to that among non-participants. The 95% confidence limits of the odds ratio were obtained from the conditional logistic regression model.

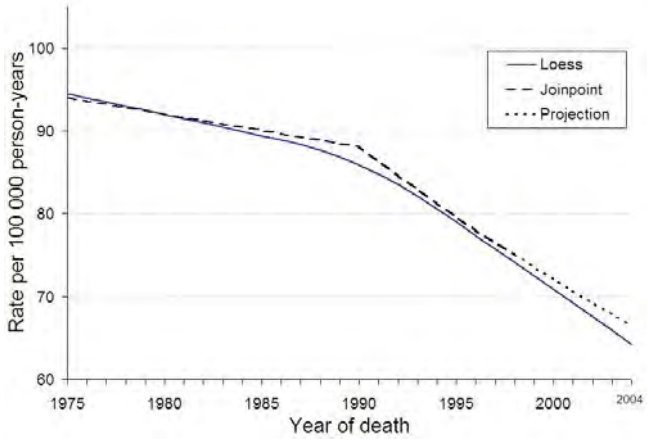
RESULTS

OBSERVED AND EXPECTED MORTALITY TRENDS

Observed and expected trends in breast cancer mortality rates among women aged 50 to 74 are presented in figure 1. The Joinpoint analysis showed that breast cancer mortality trend changed around 1990 (p-value= 0.035). From 1975 to 1990, average annual reduction in breast cancer mortality was 0.4%. From 1990 to initiation of the program in 1998, reduction was 2% annually (p-value= 0.0056). Thus, the program was started at a time when breast cancer mortality was already decreasing. Joinpoint projection of breast cancer mortality from 1998 to 2004 estimated that the breast cancer mortality rate in 2004 would have been 65 per 100,000 women-years if trends seen in 1990-1998 had persisted. In contrast, observed smoothed mortality rate, for 2004 was 63 per 100,000 women-years. The ratio of the observed smoothed mortality rate to the Joinpoint projected rate was 0.97 (95% confidence interval: 0.85 to 1.11) which suggests that the program was associated with a reduction of breast cancer mortality of 3% (95% confidence interval: -11% to 15%) among all Québec women aged 50 to 74.

FIGURE I

Observed and projected breast cancer mortality trends, Québec, 1975-2004



PRE AND POST MORTALITY RATES

Among women aged 50 to 69, 14,645 new cases of breast cancer were diagnosed between 1998 and 2003 (table 2). Among these new cases, 879 died of breast cancer in 1998-2003 which corresponds to a breast cancer mortality rate of 18.8 per 100,000 person-years. This rate is substantially lower than the one observed in 1992-1997 (rate ratio: 0.73; 95% confidence interval: 0.67 to 0.80; P<0.0001) suggesting a reduction in breast cancer mortality rate in eligible women of this age group of 27%.

TABLE 2

Breast cancer mortality by age at diagnosis, Québec, 1992-1997 and 1998-2003

Age and year of diagnosis and death	Incidence of breast cancer		Mortality from breast cancer	
	Person-years	Number (rate per 10^5)	Number (rate per 10^5)	Rate ratio (95% CI)
20-39 years				
1992-1997	6,802,772	1,507 (22)	149 (2.2)	1
1998-2003	6,245,324	1,509 (24)	100 (1.6)	0.73 (0.57;0.94)
40-49 years				
1992-1997	3,319,965	4,518 (136)	295 (8.9)	1
1998-2003	3,701,386	5,024 (136)	267 (7.2)	0.81 (0.69;0.96)
50-69 years				
1992-1997	4,213,144	11,212 (266)	1,050 (24.9)	1
1998-2003	4,845,844	14,645 (302)	879 (18.1)	0.73 (0.67;0.80)
≥ 70 years				
1992-1997	2,083,682	7,403 (355)	1,276 (61.2)	1
1998-2003	2,432,868	8,439 (347)	1,243 (51.1)	0.83 (0.77;0.90)

In the other age groups, breast cancer mortality in 1998-2003 was also lower than that observed in 1992-1997 even though, in these age groups, breast cancer screening within the program was not offered. The weighted average of mortality rate ratios in the age groups 20-39, 40-49 and 70 years or more reached 0.82. This reduction in mortality mostly reflects secular improvements in breast cancer treatment. Thus, dividing the breast cancer mortality rate ratio observed in the 50 to 69 year age group (rate ratio = 0.73) by the one observed in the other age groups (rate ratio = 0.82) allowed some correction for the effect on breast cancer mortality of factors other than screening. The "corrected" rate ratio was 0.89 (0.73/0.82 = 0.89: 95% confidence interval: 0.79 to 0.99) suggesting that, among eligible women, the reduction in mortality associated with the screening program reached 11% (95% confidence interval: 1% to 21%).

OBSERVED AND EXPECTED BREAST CANCER DEATHS

The cohort of 1,054,620 women who, from 1998 to 2003 became eligible to the program, cumulated 5,003,225 person-years of observation (table 3). These 1,054,620 women cumulated 3,354,199 person-years as non-participants and the 523,830 women who had at least one screening mammogram in the program contributed 1,649,026 person-years of observation as participants. According to the Québec Tumour Registry and the Québec mortality database, 14,699 new cases of breast cancers were diagnosed in this cohort and 1,142 women died of breast cancer. Among the 14,699 women with a diagnosis of breast cancer, 123 were excluded either because their diagnosis was made on the last day of follow-up (31 December 2003) or because the date of diagnosis of their breast cancer according to the Québec Tumour Registry was the same as their date of death and such dates of diagnosis were considered likely to be erroneous. Among the remaining 14,576 cases of breast cancer with follow-up, 873 died of their disease.

The incidence rate of invasive breast cancer among non-participants reached 259 per 100,000 person-years. Breast cancer specific survival at five years was 86.8%. Survival estimates were obtained among the 8,569 new breast cancer cases with follow-up diagnosed among non-participants and the 730 breast cancer deaths identified among theses cases.

Observed and expected cumulative probabilities of breast cancer death among participants are presented in figure 2. The observed cumulative probability of breast cancer death five years after first program participation was 6.4 per 10,000. The expected probability of death from breast cancer based on the incidence and survival seen among non-participants reached 9.8 per 10,000. In the first year after participation, the observed and expected probabilities of breast cancer death were comparable. Afterwards, the observed probability of breast cancer death was lower than that expected. The absolute difference between the observed and the expected cumulative probabilities of breast cancer death increased with time up to the end of the five years of follow-up.

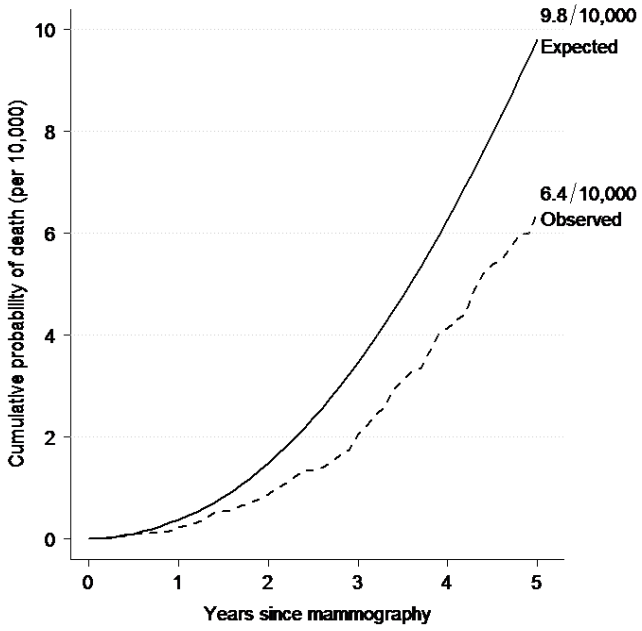
TABLE 3

Experience of eligible women, Québec, 1998-2003

Group	Person-years	Number of new cases		Number of deaths from breast cancer	
		Total	With follow-up	Total	Among newly diagnosed cases with follow-up
Participants	1,649,026	6,023	6,007	160	143
Non participants	3,354,199	8,676	8,569	982	730
Total	**5,003,225**	**14,699**	**14,576**	**1,142**	**873**

FIGURE 2

Observed and expected cumulative probability of breast cancer death among PQDCS participants



The total number of breast cancer deaths occurring among participants reached 160 while 247 were expected (table 4). Thus, participants experienced 87 fewer breast cancer deaths than expected based on incidence and survival of non-participants. The ratio of observed to expected number of breast cancer deaths reached 0.65 (95% confidence interval: 0.52 to 0.77). This estimate suggests that breast cancer mortality reduction associated with screening reached 35% (95% confidence interval: 23% to 48%) among participants. Among eligible women, 1,142 breast cancer deaths were observed and 87 more deaths were expected which results in a total of 1,229 expected breast cancer deaths. Thus, among eligible women, the program was associated with a breast cancer mortality reduction of 7% (87/1229; 95% confidence interval: 1% to 13%). Among all Québec women of the target age group, 3,050 breast cancer deaths were observed although 3,137 were expected which yields an estimate of breast cancer mortality reduction of 3% (87/3137=3%; 95% confidence interval: -1% to 6%).

TABLE 4

Observed and expected breast cancer mortality among participants, Québec, 1998-2003

Age at first screening mammography (years)	Person-years	Number of breast cancer deaths		Mortality rate ratio (95% CI)
		Observed	Expected	
50-59	1,075,509	75	134	0.56 (0.39;0.73)
60-69	573,516	85	113	0.75 (0.57;0.93)
Total	**1,649,026**	**160**	**247**	**0.65 (0.52;0.77)**

TABLE 5

Observed and expected number of breast cancer deaths among participants, eligible women and all women of the targetage group, Québec, 1998-2003

Group of women	Person-years	Number of breast cancer deaths		
		Observed	Expected	Difference
Eligible women				
Participants	1,649,026	160	247	87
Non participants	3,354,198	982	982	0
Total	5,003,224	1,142	1,229	87
Non eligible	45,783	1,908	1,908	0
All women	5,049,007	3,050	3,137	87

NESTED CASE-CONTROL STUDY

In the cohort of 1,054,620 eligible women, there were 873 breast cancer deaths for whom the date of diagnosis was known. Among these 873 women, 16.4% had had at least one screening mammogram within the program prior to their diagnosis. Among their matched controls, the corresponding percentage was 23.5%. The odds ratio (interpreted as the breast cancer mortality rate ratio) associated with at least one screening examination within the program was 0.59 (95% confidence interval: 0.48 to 0.72). Thus, this nested case-control study suggests that breast cancer mortality rate among participants was reduced by 41% (95% confidence interval: 28% to 52%) compared to non-participants.

TABLE 6

Program participation and breast cancer mortality, nested case control study among eligible women, Québec, 1998-2003

Program participation	Cases		Controls		Odds ratio (95% CI)
	Number	(%)	Number	(%)	
No	730	(83.6%)	6,677	(76.5%)	1
Yes	143	(16.4%)	2,053	(23.5%)	0.59 (0.48;0.72)

DISCUSSION

In the first five years after its implementation, the mammography screening program was associated with a reduction in breast cancer mortality rate. The two estimates of breast cancer mortality reduction in all three population groups were consistent (table 7). Among participants, the two estimates of breast cancer mortality reduction were 35% and 41%. Among eligible women, including participants as well as non-participants, our two estimates of breast cancer mortality reduction were 7% and 11%. Finally, among all women in the target age group, including eligible women as well as women who had breast cancer diagnosis prior to the moment when they would have become eligible for the program, the two estimates of mortality reduction were 3%. The comparison of observed and expected breast cancer deaths based on the incidence-survival approach[1,21] provided an estimate of program associated mortality reduction among participants. Such an estimate was also obtained through the nested case-control study. These two methods compare the experience of participants to that of women who either participate eventually or who never participate within the study period. For instance, in the incidence-survival approach,[1,21] person-years of all women are initially included among non-participant person-years. Only when women participate in the program are their person-years included in the participants' experience.

TABLE 7

Estimation of breast cancer mortality rate reduction (95% confidence interval) associated with program initiation by population group and study method

Group	Method			
	I[1]	II[2]	III[3]	IV[4]
All women	3% (-11;15)	-	3% (-1;6)	-
Eligible women	-	11% (1;21)	7% (1;13)	-
Participants	-	-	35% (23;48)	41% (28;52)

1 Comparison of observed and projected breast cancer mortality trends for 1998-2004;

2 Comparison of breast cancer mortality rate in first five years of the program (1998-2003) to mortality in five years before program initiation (1992-1997) restricting numerators of rates to breast cancer deaths occurring among incident cases;

3 Comparison of observed number of breast cancer participants to expected number based on breast cancer incidence and survival of non-participants;

4 Nested case-control study among eligible women.

Similarly, in the case-control study, exposure of controls is determined at the time of diagnosis of matched cases and will be considered unexposed if they have not yet been screened at that time even if they were later screened. Inclusion of the experience (person-years) of women who eventually participate, in the non-participant experience is necessary in order to avoid, at least in part, healthy screenee[24] and immortal time[25] biases.

Given such similarities in concept, these two methods also suffer from a number of comparable potential biases especially confounding. However, the direction and strength of such biases, if present, are difficult to determine. On one hand, women at high risk of breast cancer, such as those who use hormone replacement therapy, have a family history of breast cancer or have a personal history of benign breast disease, tend to participate more than those without such risk factors.[26,27,28] Thus, participants tend to have a higher underlying risk of breast cancer which, in turn, could lead to underestimation of screening effect. On the other hand, in some randomised trials, breast cancer mortality tended to be higher in women who had been randomised to screening but did not participate within the observation period compared to those who had been randomised to no screening.[29] However, in this study, these potential biases which are in different directions should dilute one another since the non-participant experience used for comparison includes not only that of women who chose not to participate throughout the observation period but also that of women who eventually chose to participate. Adjustment for confounders would have been preferable. Although detailed information on characteristics of participants was available, adjustment for potential confounders was limited by the paucity of information on characteristics of women who did not participate during the study period. Finally, in this analysis, participants were defined as women who had at least one screening mammogram within the program and also consented to program participation. Thus, 8% of women who had a screening mammogram but did not sign a consent form were considered non-participants. This definition of participation may lead to some underestimation of the effect of screening.

The incidence-survival approach[1,21] also allowed examination of the evolution over time of the difference in observed and expected cumulative probability of breast cancer death among participants. Such information permits estimation of the interval after a first screen when the effect of screening becomes apparent and of the manner in which this possible effect evolves over time. In this program, a difference in cumulative mortality became apparent in the second year after first program screen and the difference in cumulative mortality was clear five years after first screen. A few previous studies have provided information to which our data can be compared. Differences in cumulative breast cancer mortality curves comparing women offered screening to those not offered screening became apparent in the second year after entry in the HIP trial (age 40-64 at entry),[30] in a combined analysis of Swedish trials (age at entry 50-59 and 60-69)[9] and in women aged 60-69 in the Two-County trial.[4] In contrast, the difference in cumulative mortality became apparent in the sixth year after entry in the Two-County trial (age 50-59). In the Breast Cancer Detection Demonstration Project where women screened were compared to those who had not been screened, the difference in cumulative mortality appeared in the fourth year after first screen (age 50-74).[1] After five years of follow-up, all studies showed a reduction in cumulative breast cancer mortality in women offered screening (or screened) except in the Two-County study among women aged 50-59 at entry where this reduction was seen only later.

The incidence-survival approach[1,21] allowed estimation, among participants, of the absolute number of breast cancer deaths that might have been avoided because of the program. Given such an estimate, it was then possible to evaluate the relation of the screening program to breast cancer mortality among eligible women as well as among all women in the target age group. This was possible because only participants can benefit directly from screening. Any change in breast cancer mortality seen in eligible women and in all women of the target age group must be due essentially to that experienced by participants.

Among eligible women, the estimate (7%) based on the incidence-survival approach[1,21] can be compared to that derived by the approach proposed by Tabar et al.[11] (11%). In contrast to the first approach[1,21] the second one[11] does not suffer from non comparability of characteristics of participants and non-participants. Moreover, apart from age which has been taken into account, it appears unlikely that characteristics of women in Québec have evolved rapidly enough over the 10 years studied (1992-2003) to bias substantially the comparison of the two time periods. However, the approach proposed by Tabar et al.[11] may suffer from other types of biases. For instance, factors other than the screening program, most likely effectiveness of breast cancer treatment, appear to have evolved rapidly in Québec over the 10 years studied as reflected by changes in breast cancer mortality seen in women aged 20-39, 40-49 and 70 years or more. Thus, differences in breast cancer mortality between the two time periods seen among women aged 50-69 may be attributable at least in part to factors other than the screening program. We have used the experience of women younger and older than 50-69 to correct for such a bias. However, changes, such as improvement in treatment, in the age group 50-69 may have been different from those experienced in younger or older women. Thus, the correction may have resulted in over- or under-adjustment for such secular trends. Despite these differences in potential biases, the estimates of mortality reduction obtained by the incidence-survival approach[1,21] and the Tabar et al. method[11] are consistent.

Among all women of the target age group, the mortality reduction estimate obtained by the incidence-survival approach[1,21] (3%) can be compared to that obtained using analysis of breast cancer mortality trends (3%) although neither estimate is statistically significant. While potential errors in estimation based on analysis of secular trends in breast cancer mortality are different from those based on the incidence-survival approach,[1,21] estimates of mortality reduction were similar. As expected, the overall effect of screening in the entire population of women of the target age group during the first years after program implementation is quite small because, during that period, a large proportion of breast cancer deaths occur among women who had a diagnosis of breast cancer before program implementation.

In conclusion, despite differences in potential biases, the various approaches used provided effect estimates that were consistent within our three study groups as well as between groups. This consistency suggests that bias is unlikely to explain entirely the observed association between program initiation and breast cancer mortality reduction. In order to explain entirely our findings, the direction and strength of residual biases of all four methods used would need to be similar. Thus, while this screening program was started at a time when breast cancer mortality was already decreasing, the program appears to have led to a further significant breast cancer mortality reduction within the first five years after its initiation.

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