Cancer Causes Control (2006) 17:1135–1144
DOI 10.1007/s10552-006-0055-1

ORIGINAL PAPER

Influence of alternative mammographic screening scenarios on breast cancer incidence predictions (Finland)

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Received: 9 December 2005 / Accepted: 22 June 2006

Abstract
Background A population-based early detection programme for breast cancer has been in progress in Finland since 1987. Recently, detailed information about actual screening invitation schemes in 1987–2001 has become available in electronic form, which enables more specific modeling of breast cancer incidence.
Objectives To present a methodology for taking into account historical municipality-specific schemes of mass screening when constructing predictions for breast cancer incidence. To provide predictions for numbers of new cancer cases and incidence rates according to alternative future screening policies.
Methods Observed municipality-specific screening invitation schemes in Finland during 1987–2001 were linked together with breast cancer data. The incidence rate during the observation period was analyzed using Poisson regression, and this was done separately for localized and non-localized cancers. For modeling, the screening programme was divided into seven different components. Alternative screening scenarios for future mass-screening practices in Finland were created and an appropriate model for incidence prediction was defined.
Results and conclusion Expanding the screening programme would increase the incidence of localized breast cancers; the biggest increase would be obtained by expanding from women aged 50–59 to 50–69. The impacts of changes in the screening practices on predictions for non-localized cancers would be minor.

Keywords Breast cancer · Incidence · Mass screening · Prediction

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Introduction

In Finland, a population-based early detection programme for breast cancer has been in place since 1987. Responsibility of conducting the mass-screening is borne by individual municipalities. There is a bylaw on public health regulating the invitation procedure by stating that organized, free of charge mammography screening should be offered every second year to women aged 50–59 years, while screening of 60–69 years old remains optional. Despite the bylaw, municipalities may also decide to invite women to screening using schemes that differ from the recommendations. The main reasons for these deviations are dissimilar order of priorities and lack of sufficient funding.

The extending of the Finnish programme is a frequent topic in public discussions, and information about the potential impacts of extending or cutting the screening programme on future cancer incidence rates is needed. Møller et al. [1, 2] have evaluated the effects of breast cancer screening on cancer incidence and produced incidence predictions on the country level for all Nordic countries by assuming that each municipality within a country follows the same, fixed mass-screening

pattern given by the official recommendations. The present work makes use of the actual observed year- and age-specific screening invitation schemes from Finnish municipalities, assembled from the files of the Mass Screening Registry, a part of the Finnish Cancer Registry. It is expected that modeling based on detailed municipal invitation data will result in more accurate predictions than those based on country level ignoring the deviations. Moreover, access to a database that includes year- and age-specific screening invitation data makes it possible to manage adequately the 2-year mass-screening cycle and to separate the years within a screening round from each other, leading to a very specific manner of coding the separate phases of the programme.

The most important indicator for the effectiveness of screening is a decrease in disease-specific mortality. Even so, the incidence of breast cancer is a more acute indicator than mortality in terms of required health care resources. The statistical methodology together with alternative incidence predictions presented in this article is aimed to provide health authorities with tools to back up health policy decisions. Moreover, the models presented can be generalized to other sites of cancer, for instance for colorectum or prostate, provided that appropriate data on screening will be available.

In this study, the first aim is to present an incidence model that includes historical municipality-specific schemes of mass screening. Secondly, the obtained estimates in combination with different future scenarios of screening are used to make alternative predictions for breast cancer incidence up to 2012.

Materials and methods

Database

For the study database, information on annual screening invitations was linked with the breast cancer data from the Finnish Cancer Registry and population count data received from Statistics Finland.

The observation period was restricted to 1987–2001. Data from pre-screening years 1975–1986 were used to investigate the age-incidence and cohort-incidence dependences. Analysis was restricted to age group of women between 40 and 74 years because that was the age range where screening invitation data were available. The linked database was grouped to the level of accuracy that corresponds to the screening invitation data: by municipality, calendar year, and woman's age at the end of the year of invitation.

The screening invitation data containing annual observed municipality-specific screening invitation schemes were assembled from the Mass Screening Registry files, where the registration of the Finnish screening programme for breast cancer is centrally maintained. The information about invitations to screening tests can be assumed to reflect the actual screening activity very well since the attendance rate is known to be very high. For instance, during the 1990s, the mean compliance among 50–64-years-old women was 90% at first screen and 93% at subsequent screens [3]. Invitation data from the entire time period since screening started in 1987 have been registered in the central files by municipalities that have an arrangement with one of the ten screening centres of the Cancer Society of Finland. These centres cover 267 out of 444 (60.1%) municipalities, and 59.0% of 40–74-years-old women in Finland (year 2001). A total of 67 (25.1%) municipalities offered voluntarily screening to women aged 40–49, and 19 (7.1%) to women aged 70–74. In general, minor deviations from the bylaw, such as short breaks in the screening programme and some irregularities in screening intervals were rather common among municipalities [4].

The breast cancer data were obtained from the Finnish Cancer Registry. Almost 100% coverage of all breast cancer cases is ensured by compulsory, independent reporting from physicians, pathological laboratories, and hospitals, combined with receiving death certificates. Accuracy of the registry data is very high [5]. Modeling and predictions were done separately for localized breast cancers (56.3% of all the cases), non-localized breast cancers (35.0%), and also for all stages combined. The analyses for all stages combined include also cases with unreported stage (8.7%). Ductal carcinoma in situ tumors were included in the data (3.7%).

Components of the screening programme

According to the bylaw, organized mammography screening is offered to women every second year in Finland, so one screening round in the Finnish programme lasts for 2 years. For incidence modeling and predictions the screening programme was divided into seven components. Every cohort in a certain year in a certain municipality was coded separately according to the invitation information. The codes for the components together with coding in three example cohorts are shown in detail in Appendix A.

The first year of the first screening round is the year of the first invitation (component 1). Separation of the first and second year of the screening rounds is

motivated by the idea that the incidence is not assumed to be constant during the whole 2-year round; the incidence increases during the first year when actual screening takes place, and then decreases below the baseline during the second year. The first round (components 1 and 2) was separated from the subsequent ones (components 3 and 4), and the post-screening period was divided into two components: the first 5 years after the programme (component 5) and the rest of the time until the age of 74 or the end of follow-up (component 6). The non-invited women served as a baseline (component 0).

Component 7 is defined as a break in a woman's screening programme. In principle, there is no upper limit for the duration of the break; the main point is that a woman has been screened at least once and will be screened again in the future. After a break of more than 4 years between invitations the coding starts with the year of the first invitation again, assuming that any carry-over effects of the last screening would have disappeared. It should be noted that, because of the time lag between invitation to screening test and the evaluation of the outcome, cancers diagnosed during the break in this setting do not meet the criteria of an 'interval cancer', defined as cancers diagnosed clinically between the screening rounds among those with negative results at screening [6].

Model for breast cancer incidence

The statistical modeling of breast cancer incidence during the observation period 1987–2001 was performed within a likelihood framework, using the general age-period approach presented by Clayton and Schifflers [7]. The incidence was modeled as a function of calendar time, numerical age, university hospital region, age group, component of screening programme, and interaction between age group and component of screening programme, using Poisson regression with a logarithmic link function. The university hospital region was used to describe the geographical differences that are known to exist in the baseline breast cancer incidence in Finland [8]. Based on a previous study, it was known that the effects of separate components of an invitational screening programme on breast cancer incidence are dependent on a woman's age [4]. Therefore, it was reasonable to add interaction terms between age group (40–49, 50–59, 60–74) and component of screening into the model. Inclusion of them improved the fit significantly in localized, advanced and all breast cancers combined. The formal mathematical model and more discussion of the modeling are presented in Appendix B.

Because there were such a large number of observations (140,175 municipality-year-age units) in the database and thus a large number of degrees of freedom for the deviance, the overall validation of the models was based on exploring graphics rather than deviance comparisons. Predicted values were plotted against the observed by all explanatory variables separately in order to ensure the goodness-of-fit of the models. Figure 1 displays the overall curves for model-based vs. observed incidence rates for years 1987–2001.

All programming was carried out with SAS Release 8.02 (PROC GENMOD for Poisson regression). Figures were produced with Origin version 7.5.

Screening scenarios for future

For future predictions up to 2012, five alternative scenarios of mass-screening practices for breast cancer were programmed by allowing the value of screening programme component indicator in a given municipality, calendar year and age to alter from one scenario to another. The scenarios were the following:

- Scenario A: continuing the current practice of inviting 50–59-year-old women every second year (but without any deviations, breaks etc.),
- Scenario B: expanding screening service from 50–59 to 50–65-years-old,
- Scenario C: expanding screening service from 50–59 to 50–69-years-old,

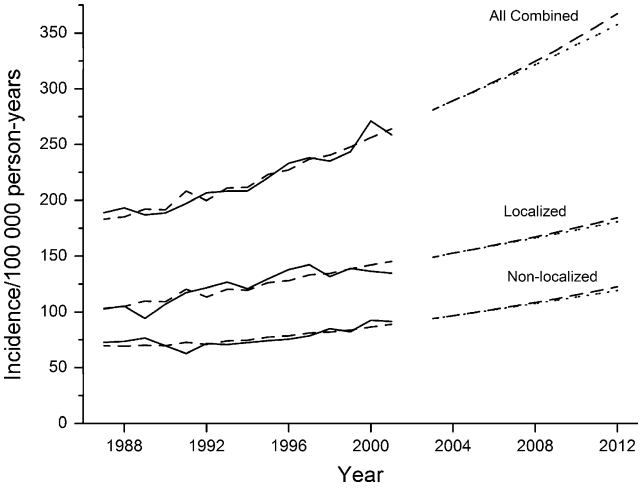

Fig. 1 Model-based and observed breast cancer incidence rates for localized cancers, non-localized cancers, and all cases combined, which also includes the cases with unreported stage. The solid line represents the observed values. The dashed line represents the fitted values based on the Poisson regression model during the observation period 1987–2001, and on prediction model 1 in the future (2003–2012). The dotted line illustrates the predicted rates based on prediction model 2. The predictions have been made under scenario A

- Scenario D: expanding screening service from 50–59 to 40–65-year-old women,
- Scenario E: stopping the screening service entirely.

Scenarios B and C are realistic and actually happening in several Finnish municipalities. To our knowledge, there are no plans to expand the mass-screening to women aged under 50 years in Finland, but scenario D was still thought to be of interest. Scenario E reflects the situation after stopping the programme: those women that have been screened just before 2005 are first coded to be in component 'up to 5 years after the last screening round', followed by 'more than 5 years after the last round.' Those who will become 50 in year 2005 or thereafter will be coded as 'not invited.' The youngest women that are screened before 2005 will become 74 in year 2028, so it would take 24 years to attain the situation where all the cohorts would have a pure 'not invited'-effect. This is, however, beyond the scope of this paper.

All changes in the screening practice were programmed to take place in the beginning of 2005. The transitional period 2002–2004 from current practice to the future scenarios was programmed to follow the bylaw without any deviations. As mentioned before, the observed schemes differed to some extent from one municipality to another. The major variations were accounted for when programming the transition period. For instance, if a municipality had invited women below 50 just before 2001, they were not coded to have their first year of the first round as they become 50, but the first year of a subsequent round etc.

Population forecast data from Statistics Finland were linked with each scenario in order to be able to derive predictions for the numbers of cancer cases.

Prediction model

Two different approaches for incidence prediction were used: A natural first choice was to use the same exponential model for predictions as for the observation period (Model 1). A basic problem with this widely applied cancer incidence prediction model is that it can give unrealistic exponential growth with calendar time in the incidence of a cancer site with an increasing trend like breast cancer. Møller et al. [9] have studied several alternative methods to modify the exponential growth. One way to level it off is to replace the exponential relationship between the incidence and calendar time with a linear one (Model 2). Since this approximation holds very well when the term for calendar time is small (then exp(calendar time term) $\approx$ (1 + calendar time term)), predictions obtained using model 2 will only slightly differ from model 1 in the near future. Model 2 was chosen to be the method for making the future predictions based on the alternative scenarios. The models are described in detail in Appendix C. Figure 1 shows the difference between predicted incidence rates made by using model 1 and model 2.

Results

The effect estimates for the components of the screening programme in each age group to be used in predictions are given in Table 1 as relative risks (RR) compared to the not invited in the same age group. In general, the RR goes up during the first years of the screening rounds when the invitation and also the mammography test takes place, and declines below the baseline during the second years. This effect is larger during the first round compared to the subsequent ones. During the first years of the screening rounds, RRs in localized breast cancers are higher compared to RRs in advanced cancers. They also increase with age, whereas for non-localized cases RR is at its highest in the age group of 50–59.

The predicted breast cancer incidence rates for localized and non-localized cancers based on the alternative mammographic mass-screening scenarios are illustrated in Fig. 2. In general, major changes in incidence rate levels take place during the first 3 years after 2005 when the changes in current practice are programmed to happen, stabilizing to be quite parallel towards the end of the prediction period. As an exception to this there is scenario E in localized cases (Fig. 2a), which reflects the situation after stopping the programme: the incidence first increases due to the elevated 'up to 5 years after' -risk in the age group 50–59 (RR 1.64, 95% CI 1.15–2.34), and after 5 years from stopping the service it decreases below the level of current practice (RR for age group 50–59 assumed to be 1 (no effect), RR for age group 60–74 0.91, 95% CI 0.80–1.03).

In localized cancers, expansions of the screening programme increase the incidence rates in the long run compared to continuing the current practice regularly, while stopping causes a decline (Fig. 2a). Expansion of the service from 50–59 (scenario A) to 10-years older women (scenario C) introduces the biggest increase, followed by expansions to 10-years younger and 5-years older (scenario D) and only to 5-years older women (scenario B). Table 2 shows that screening has an increasing effect also on the number of localized cancers; scenario C yields the biggest increase in

Table 1 Numbers of diagnosed breast cancer cases (N) and relative risk (RR) of breast cancer compared to non-invited women in the same age group provided with 95% confidence interval (95% CI) during each component of the screening programme (time period 1987–2001, 267 municipalities)

Component of screening programme	Age	Localized			Non-localized			All combined [a]		
		N	RR	95% CI	N	RR	95% CI	N	RR	95% CI
1st round/1st year	40–49	**68**	**2.15**	**(1.69, 2.74)**	**32**	**1.36**	**(0.95, 1.93)**	**106**	**1.82**	**(1.50, 2.21)**
	50–59	**1,048**	**2.49**	**(2.20, 2.83)**	**530**	**1.65**	**(1.41, 1.94)**	**1,722**	**2.17**	**(1.97, 2.39)**
	60–74	72	4.06	(3.19, 5.16)	22	1.58	(1.03, 2.43)	107	3.20	(2.63, 3.89)
1st round/2nd year	40–49	**18**	**0.86**	**(0.54, 1.37)**	**14**	**0.90**	**(0.53, 1.53)**	**32**	**0.83**	**(0.58, 1.17)**
	50–59	**278**	**0.71**	**(0.60, 0.83)**	**173**	**0.58**	**(0.48, 0.71)**	**490**	**0.66**	**(0.59, 0.75)**
	60–74	21	0.65	(0.42, 1.01)	14	0.56	(0.33, 0.95)	39	0.65	(0.47, 0.89)
Subseq. rounds/1st year	40–49	**140**	**1.63**	**(1.37, 1.94)**	**50**	**0.81**	**(0.61, 1.07)**	**205**	**1.32**	**(1.14, 1.52)**
	50–59	**2,082**	**1.93**	**(1.71, 2.18)**	**949**	**1.22**	**(1.05, 1.42)**	**3,365**	**1.67**	**(1.53, 1.83)**
	60–74	**577**	**2.28**	**(2.05, 2.55)**	**195**	**0.97**	**(0.82, 1.14)**	**846**	**1.74**	**(1.60, 1.90)**
Subseq. rounds/2nd year	40–49	**18**	**0.88**	**(0.55, 1.41)**	**9**	**0.62**	**(0.32, 1.20)**	**28**	**0.76**	**(0.52, 1.10)**
	50–59	**586**	**0.65**	**(0.56, 0.75)**	**405**	**0.63**	**(0.53, 0.74)**	**1,095**	**0.65**	**(0.59, 0.72)**
	60–74	**180**	**0.54**	**(0.46, 0.63)**	**104**	**0.39**	**(0.32, 0.48)**	**322**	**0.50**	**(0.44, 0.56)**
Up to 5 years after	40–49	–			–			–		
	50–59	**35**	**1.64**	**(1.15, 2.34)**	**12**	**0.83**	**(0.46, 1.49)**	**51**	**1.31**	**(0.98, 1.75)**
	60–74	**941**	**1.08**	**(0.99, 1.19)**	**554**	**0.80**	**(0.71, 0.89)**	**1,684**	**0.99**	**(0.92, 1.06)**
More than 5 years after	40–49	–			–			–		
	50–59	-[b]			-[b]			-[b]		
	60–74	**298**	**0.91**	**(0.80, 1.03)**	**191**	**0.75**	**(0.64, 0.87)**	**583**	**0.90**	**(0.82, 0.99)**
Break	40–49	35	0.85	(0.61, 1.19)	33	1.09	(0.77, 1.55)	72	0.95	(0.75, 1.20)
	50–59	111	1.56	(1.26, 1.94)	42	0.84	(0.60, 1.17)	161	1.23	(1.03, 1.47)
	60–74	56	1.31	(1.00, 1.72)	27	0.80	(0.55, 1.18)	92	1.12	(0.91, 1.38)
Not invited	40–49	2,231	Ref.		1,764	Ref.		4,311	Ref.	
	50–59	352	Ref.		246	Ref.		635	Ref.	
	60–74	2,603	Ref.		1,931	Ref.		4,907	Ref.	

The bolded estimates were used in predictions for years 2005–2012

[a] Includes cases with unreported stage

[b] Assumed to be 1 (no effect) in predictions based on scenario E

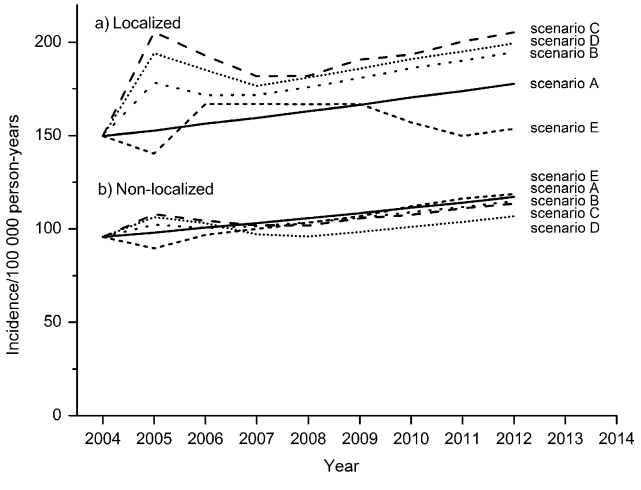

Fig. 2 Predicted breast cancer incidence rates based on alternative mammographic screening scenarios. In scenario A the current practice of inviting 50–59-years old women every second year is continued, in scenario B the screening service is expanded from 50–59 to 50–65, in scenario C to 50–69, and in scenario D to 40–65-years old women. In scenario E the screening service is stopped entirely. Changes in screening practice have been programmed to take place in year 2005

predicted number of cases (increase of 553 cases from 2001 to 2012).

When looking at the impact of changes in the screening practice on non-localized cancers, it appears that the effects are quite small. In the long run, only the biggest expansion, scenario D, gives somewhat lower predictions for both the rate level and number of non-localized cancers (Fig. 2 b, Table 2). Immediate effects in 2005 differ from the later prediction period; stopping the screening service in 2005 (scenario E) first decreases the incidence rate, but the level reaches the others after one screening round. The expansions of the service, scenarios B, C and D, first introduce a small increase in the incidence, which disappears after the first years.

Results were also calculated by 5-year age groups to enable a more detailed evaluation (Table 2). In localized cancers, screening increases the incidence rate and amount of cases in all age groups, and this effect also seems to reach the groups next to the screened ones. The biggest increase in incidence caused by expanding the programme, 47.4%, is in the age group 60–64 years.

Table 2 Numbers of breast cancer cases observed in year 2001 and predicted for year 2012 in 267 Finnish municipalities, and corresponding incidence rates (/100,000 person-years) by age group. The predictions are based on alternative mass-screening practice scenarios and bolded numbers represent the screened age groups

Age	2001		2012									
	Observed		Scenario A		Scenario B		Scenario C		Scenario D		Scenario E	
	Cases	Inc.	Cases	Inc.	Cases	Inc.	Cases	Inc.	Cases	Inc.	Cases	Inc.
Localized												
40–44	50	46.8	72	79.2	72	79.2	72	79.2	**101**	**110.7**	72	79.2
45–49	117	102.9	143	136.0	143	136.0	143	136.0	**170**	**161.1**	143	136.0
50–54	207	171.1	**272**	**256.5**	**272**	**256.5**	**272**	**256.5**	**251**	**236.7**	177	167.0
55–59	150	155.7	**234**	**212.1**	**234**	**212.1**	**234**	**212.1**	**234**	**212.1**	195	176.0
60–64	138	164.7	224	193.8	**330**	**285.6**	**330**	**285.6**	**330**	**285.6**	188	162.9
65–69	128	176.9	177	173.2	187	182.2	**241**	**235.7**	187	182.2	177	173.2
70–74	107	144.9	133	175.6	137	181.5	158	208.9	137	181.5	133	175.6
Total	897	134.3	1,255	177.5	1,375	194.3	1,450	205.1	1,410	199.4	1,085	153.4
Non-localized												
40–44	48	45.0	67	73.3	67	73.3	67	73.3	**57**	**62.4**	67	73.3
45–49	101	88.8	116	110.0	116	110.0	116	110.0	**81**	**76.4**	116	110.0
50–54	143	118.2	**154**	**145.9**	**154**	**145.9**	**154**	**145.9**	**143**	**135.2**	146	138.0
55–59	100	103.8	**131**	**118.7**	**131**	**118.7**	**131**	**118.7**	**131**	**118.7**	160	144.4
60–64	86	102.6	144	124.4	**134**	**115.6**	**134**	**115.6**	**134**	**115.6**	135	116.4
65–69	57	78.8	124	121.5	117	114.4	**104**	**101.3**	117	114.4	124	121.5
70–74	77	104.3	91	119.8	92	121.3	97	128.1	92	121.3	91	119.8
Total	612	91.6	827	116.9	811	114.7	803	113.6	755	106.8	839	118.6
All combined[a]												
40–44	106	99.3	156	171.0	156	171.0	156	171.0	**183**	**200.4**	156	171.0
45–49	241	212.0	293	277.3	293	277.3	293	277.3	**287**	**272.5**	293	277.3
50–54	396	327.3	**492**	**464.5**	**492**	**464.5**	**492**	**464.5**	**456**	**430.7**	362	341.5
55–59	285	295.8	**425**	**384.2**	**425**	**384.2**	**425**	**384.2**	**425**	**384.2**	396	358.0
60–64	264	315.0	426	368.4	**538**	**465.2**	**538**	**465.2**	**538**	**465.2**	390	336.7
65–69	217	299.8	367	358.2	356	347.1	**404**	**394.5**	356	347.1	367	358.2
70–74	216	292.6	270	357.2	275	363.2	296	390.9	275	363.2	270	357.2
Total	1,725	258.3	2,429	343.5	2,535	358.5	2,604	368.2	2,520	356.4	2,234	315.9

[a] Includes cases with unreported stage

Impacts of screening on non-localized cases are minor. If screening is started already at the age of 40, it has a protective effect especially in the age group 45–49.

The temporal development of predicted incidence rate and number of new cases by 5-year age groups for localized cancers according to scenario C are illustrated in Fig. 3. Expansion to 60–64- and 65–69-year-old women is clearly visible in both incidence rate and case number curves; there is a prevalence peak in 2005 when the scenario takes effect. The difference in later behavior between incidence and case number curves can be explained by the underlying fact that the number of women above 60 is growing in the near future compared to women below 60 in those 267 municipalities, as observed throughout Finland, see Fig. 4.

Discussion

Detailed screening invitation data were incorporated into modeling of breast cancer incidence by defining a screening variable that gives the component of the screening programme by municipality, year and age. Incidence rate during the observation period 1987–2001 was then modeled using a Poisson regression approach, giving maximum likelihood estimates for the parameters, including effects of the screening programme components in different age groups. These estimates, together with hypothetical scenarios of future screening policy, were then used in extrapolating the model into the future and calculating predictions for breast cancer rates up to 2012.

The effects of separate components of an invitational screening programme on breast cancer incidence in different ages have been estimated and discussed in more detail in a previous paper [4]. In that study, age from 50 to 74 was divided into 5-year groups when modeling the incidence. In this current paper, we chose for prediction purposes a more general (and robust) division of age into three categories, so the estimates presented in Table 1 serve more as one stage in a prediction process than final results for risk of breast

cancer. It should be emphasized that the high relative risk for being diagnosed with a localized breast cancer during the first 5 years after the programme in women aged 50–59 (RR 1.64, 95% CI 1.15–2.34) is based only on 35 cancer cases.

Strong assumptions concerning the screening data were made: First, only invitations to the screening test were known, not the real attendance activity. For extrapolations this means that a certain pattern of invitation is regarded to result in a certain level of attendance, and this effect is assumed to hold also into the future. On the other hand, the level of attendance is known to be very high among Finnish women, and there is no such a reason within sight that would change this behavior. Second, year of diagnosis together with birth year was used to link the cancer cases with the invitation data. Because there is some time lag between invitation to screening test and the (final) diagnosis, particularly women invited in the end of the calendar year might have their diagnosis not until the next year. There is no doubt this introduces some bias in the estimates, and one could think that the true differences in the screening effect sizes between the first actual screening year and the second year of the screening round are larger since the number of diagnoses is not evenly distributed over those 2 years.

When producing predictions, it would be pertinent to provide information about the amount of uncertainty related to predicted numbers. An appropriate way to measure this uncertainty could be to present prediction intervals that, in addition to confidence intervals, also take into account the variation in the future number of cases [10]. There are three sources of error associated with predictions made using model extrapolations: The variance of the parameter estimates in the model, the variation in the future number of cases, and the adequacy of the model. If the model fits well, the first, uncertainty in parameter estimates, decreases as the number of cases increases leading to narrow prediction intervals. Consequently, the uncertainty about the adequacy of the model starts to dominate, and then even relatively minor deviations in the assumptions can result in observed future rates lying outside the prediction interval. Such deviations could be, for example, that current trends do not continue exactly as assumed [11]. Moreover, the population forecasts used in calculating the incidence are also extrapolations, based on assumptions about future birth rates, death rates and migration patterns, and thus introduce a separate source of error when predicting future incidence rates. Hakulinen and Dyba used the delta method based on Taylor series expansion to approximate the variance of the future number

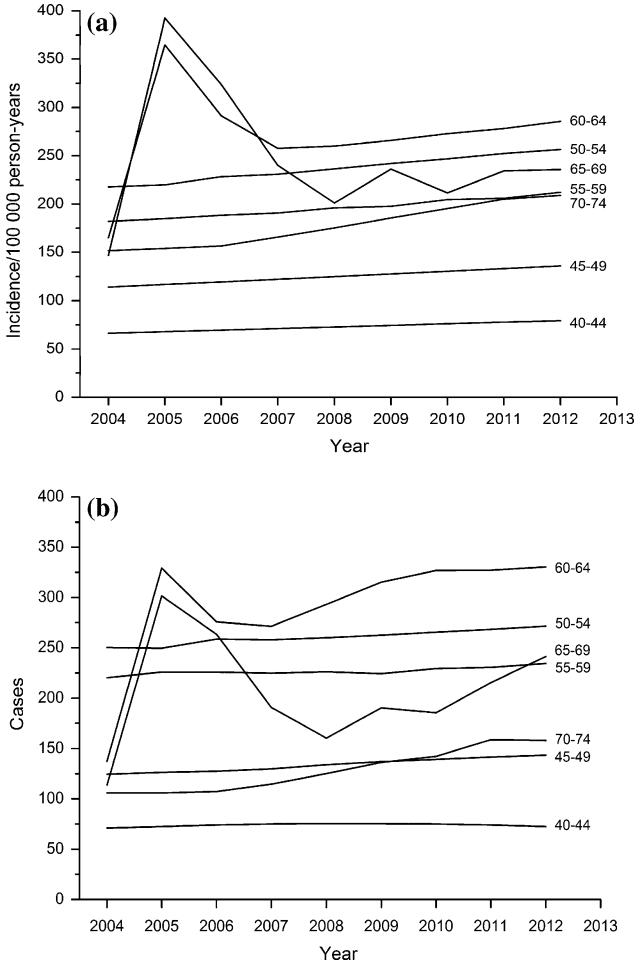

Fig. 3 Predicted breast cancer incidence rates (a), and predicted number of new cases (b) in 267 Finnish municipalities for localized cancers in 5-year age groups according to screening scenario C, where the mass-screening service is extended from 50–59 to 50–69-years old women in year 2005

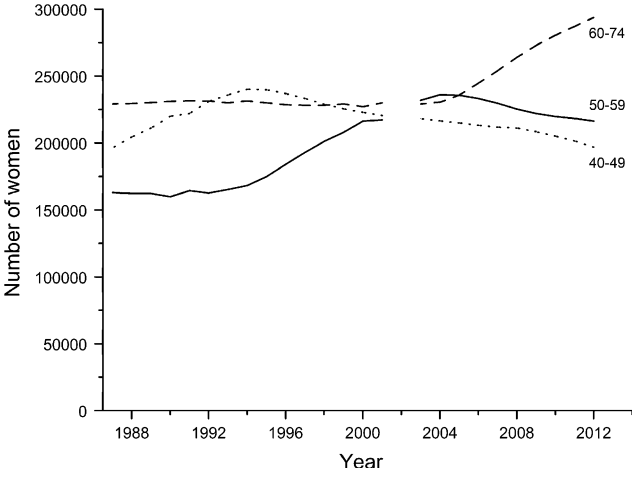

Fig. 4 Observed and predicted development of women's population size by age group in 267 Finnish municipalities

of cases that is needed to calculate the prediction interval [10]. However, the prediction model used in the present study includes 35 parameters, which makes this approximation technique less attractive. Bootstrapping or Bayesian approach could be useful [12].

A comparison between breast cancer incidence predictions presented in this paper and predictions presented before that account for mammographic mass-screening [2] is not straightforward: Previous predictions were based on more rough data, grouped into 5-year age groups and 5-year time periods. Our database on municipality-year-age-level allows for separating the different components of the screening programme in a more specific manner compared to the grouped data where it is not possible to manage adequately the 2-year mass-screening cycle. The observed invitation schemes that we used include also the information about apparently quite common deviations from the bylaw among municipalities. Taking them into account gives a more realistic picture of the true screening activities taking place in Finland than assuming fixed patterns. This all is likely to lead to more accurate effect estimates and hence improved incidence predictions, enabling also the evaluation of alternative future perspectives, which has to our knowledge never been done before.

Breast cancer is by far the most common type of cancer among women in Finland, but also in many other countries in Western Europe and North America. The fact that mammographic screening causes extra incidence is well known, and it has been explained by detection of the prevalence pool of breast cancers during the first round, and by advanced diagnosis during the subsequent rounds. However, by defining real extra incidence as cancers detected in a screening programme that would not have been detected during lifetime without the programme Boer et al. [13] suggest that the order of magnitude of true extra incidence that a screening programme causes is less than 2%.

The present paper outlines how to utilize detailed screening invitation data and make breast incidence predictions based on alternative screening patterns. There are known causal factors, for example reproductive behavior and hormonal replacement therapy that have an important role in the etiology of breast cancer [14, 15]. These factors have now been only implicitly taken into account in the models by the effects of calendar time, age and region. Accounting for causal factors in an explicit manner is beyond the scope of this study, but would be a challenging task demanding very specific data.

Current EU Council Recommendations on cancer screening [16] concern only the registration and management of screening data. In our opinion, to be able to make rapid and reliable predictions concerning whole populations, and thereby to guide the health policy, also recommendations on collecting and managing invitation data should be made.

Acknowledgments We thank M.Sc. Hanna Virkkunen for assembling the screening invitation data from the files of the Mass Screening Registry of Finland. This work was financially supported by the Cancer Society of Finland, Academy of Finland (MaDaMe project), and Doctoral Programs in Public Health/ Department of Public Health of the University of Helsinki, Finland.

Appendix A: Coding of the programme components

The table illustrates the coding of different programme components in three example cohorts. The components are the following: 1 = 1st year of the 1st screening round (year of the 1st invitation), 2 = 2nd year of the 1st screening round, 3 = 1st years of subsequent screening rounds (years of the subsequent invitations), 4 = 2nd years of subsequent screening rounds, 5 = up to 5 years after the last screening round, 6 = more than 5 years after the last round, 7 = break, 0 = not invited.

A cohort with a regular programme up to age 65

Age	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74
Round	1		2		3		4		5		6		7		8		Post screening period								
Coding	1	2	3	4	3	4	3	4	3	4	3	4	3	4	3	4	5	5	5	5	5	6	6	6	6

A cohort with a more than 4 years break between invitations and screening up to age 65

Age	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74
Round	1		2		Break					1		2		3		4		Post screening period							
Coding	1	2	3	4	7	7	7	7	7	1	2	3	4	3	4	3	4	5	5	5	5	5	6	6	6

A cohort with postponed start at age 55, two small breaks, and screening up to age 69

Age	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74
Round	Pre-screening					1		2		Break			3		Break		4		5		Post screening				
Coding	0	0	0	0	0	1	2	3	4	7	7	7	3	4	7	7	3	4	3	4	5	5	5	5	5

Appendix B: Model for breast cancer incidence

The statistical modeling of breast cancer incidence during the observation period 1987–2001 was carried out using a Poisson regression technique with logarithmic link function, where the logarithm of the breast cancer incidence I_{mya} in municipality m (m = 1, ..., 267) in calendar year y (y = 1987, ..., 2001) for women of age a (a = 40, ..., 74) is expressed as a sum of factors related to the incidence:

$$\log(I_{mya}) = \alpha + \beta y + \gamma_1 a + \gamma_2 a^2 + \gamma_3 a^3 + \gamma_4 a^4 + \rho_{r(m)} + \delta_{s(m,y,a)c(a)}.$$

Here *r(m)* is the region r (r = 1, ..., 5) to which municipality m belongs, *s(m,y,a)* is the screening component s (s = 0, ..., 7) in municipality m in calendar year y for women of age a, and *c(a)* is the age category c (c = 40–49, 50–59, 60–74) that includes age a. Calendar year and age are treated as numeral variables. Finland is divided into five university hospital regions, Helsinki, Turku, Tampere, Kuopio, and Oulu.

The dependence between age and incidence on one hand, and cohort and incidence on the other, was investigated using data from pre-screening period 1975 to 1986. This was to ensure that the data were not confounded by regular mass screening. For describing these dependencies, numerical functions for continuous age and cohort terms were looked for [17]. A polynomial describing the age-incidence curve was determined by first fitting a simple Poisson regression model including continuous calendar time and age as covariates. Then, one higher degree age term was added to the model at a time as long as they significantly improved the fit. Comparisons between models were done with log likelihood ratio tests (significance level 0.05). In conclusion, the polynomial describing the age effect was of fourth degree. The age function was examined separately for localized, non-localized and all breast cancers combined, result being the same form for all of them. After including the fourth degree age function to the model, the cohort effect was subjected to a similar procedure. The result was that there is no significant cohort effect left in either localized cancers, non-localized cancers or when combining all breast cancers, after controlling for calendar time and fourth degree polynomial age dependence. The birth cohort was calculated as the difference between calendar year and age.

APPENDIX C: Prediction model

Model 1

$$\hat{I}_{mya} = \exp(\hat{\alpha} + \hat{\beta} y + \hat{\gamma}_1 a + \hat{\gamma}_2 a^2 + \hat{\gamma}_3 a^3 + \hat{\gamma}_4 a^4 + \hat{\rho}_{r(m)} + \hat{\delta}_{s(m,y,a)c(a)}),$$

Model 2

$$\hat{I}_{mya} = (1 + \hat{\beta} y) \exp(\hat{\alpha} + \hat{\gamma}_1 a + \hat{\gamma}_2 a^2 + \hat{\gamma}_3 a^3 + \hat{\gamma}_4 a^4 + \hat{\rho}_{r(m)} + \hat{\delta}_{s(m,y,a)c(a)}),$$

where $\hat{I}_{mya}$ is the predicted incidence rate in municipality m in calendar year y (y = 2003, ..., 2012) for women of age a. The maximum likelihood estimates $\hat{\alpha}$, $\hat{\beta}$, $\hat{\gamma}_{1,\ ...,\ }\hat{\gamma}_4$, $\hat{\rho}_{r(m)}$, and $\hat{\delta}_{s(m,y,a)c(a)}$ were obtained as a result from modeling the breast cancer incidence during the observation period. The values of *s(m,y,a)* were programmed to differ between the alternative scenarios. The estimate for the component 'more than 5 years after' in the age group 50–59 needed for scenario E was set to be 0 (no effect).

The overall year-specific incidence rate predictions $\hat{I}_y$ were derived by first calculating the predicted municipality-year-age-specific cancer case numbers $\hat{c}_{mya} = \hat{I}_{mya}\hat{n}_{mya}$, where $\hat{n}_{mya}$ is the corresponding predicted number of person-years. These predicted numbers of cases and person-years were then summed over all municipalities and ages to obtain the respective year-specific figures: $\hat{c}_y = \sum_m \sum_a \hat{c}_{may}$ and $\hat{n}_y = \sum_m \sum_a \hat{n}_{may}$. Finally, the predicted year-specific incidence rates were calculated as $\hat{I}_y = \hat{c}_y/\hat{n}_y$.

Similarly, this method can be directly applied to get overall predictions by age (group), screening component or region, and any combination of these variables.

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