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Original article

Reduction in advanced breast cancer after introduction of a mammography screening program in Tyrol/Austria

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ABSTRACT

Background: We analysed all female breast cancer (BC) cases in Tyrol/Austria regarding the shift in cancer characteristics, especially the shift in advanced BC, for the group exposed to screening as compared to the group unexposed to screening.
Methods: The analysis was based on all BC cases diagnosed in women aged 40–69 years, resident in Tyrol, and diagnosed between 2009 and 2013. The data were linked to the Tyrolean mammography screening programme database to classify BC cases as "exposed to screening" or "unexposed to screening". Age-adjusted relative risks (RR) were estimated by relating the exposed to the unexposed group.
Results: In a total of about 145,000 women aged 40–69 years living in Tyrol during the study period, 1475 invasive BC cases were registered. We estimated an age-adjusted relative risk (RR) for tumour size $\geq$ 21 mm of 0.72 (95% confidence interval (CI) 0.60 to 0.86), for metastatic BC of 0.27 (95% CI 0.17 to 0.46) and for advanced BC of 0.83 (95% CI 0.71 to 0.96), each comparing those exposed to those unexposed to screening, respectively.
Conclusion: In our population-based registry analysis we observed that participation in the mammography screening programme in Tyrol is associated with a 28% decrease in risk for BC cases with tumour size $\geq$ 21 mm and a 17% decrease in risk for advanced BC. We therefore expect the Tyrolean mammography programme to show a reduction in BC mortality.

1. Introduction

Breast cancer (BC) is the leading cancer type in women. For the year 2012, IARC estimated worldwide about 1.7 million new BC cases and 522,000 deaths due to BC. In Europe, this involved a total of 464,000 new BC cases [1].

It has been shown in randomised trials that mammography screening brings about a reduction in BC mortality [2] although the size of the reduction has been a matter of debate during the past decade, see for example [3,4]. The most accepted estimate of the BC mortality reduction as a result of invitation to screening is between 20% and 25% with greater reductions found in observational studies, see for example [5,6].

In Tyrol (Austria) mammography screening (called MST) was

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offered to all women aged 40–69 years between June 2008 and December 2013. The target population included all women aged 40–69 years living in Tyrol who were covered by compulsory medical insurance, as are more than 98% of the population (personal communication from insurance companies). Women aged 40 to 59 were invited annually, and women aged 60 to 69 biennially, based on the official list of insured persons. Women were invited via a personal letter and were free to attend screening at a time of their own choice. The main difference between EU guideline-compliant mammography programmes [7] and MST was that in Tyrol supplemental hand-held ultrasound (US) was offered free of charge at the radiologist's decision and performed in about 70% of participants. Recently, we reported good intermediate performance parameters for this programme with supplemental US, while keeping the adverse effects of US such as increased recall and biopsy rates comparable to those in screening programs using mammography only [8,9].

However, all these quality parameters are intermediate quality measures, and BC mortality reduction – the primary aim of mammography screening - does not occur before several years after a mammography screening programme is launched [10].

One of the main reasons for mortality reduction following mammography screening is stage shift: mammography screening leads to a shift towards earlier BC stages and women with an earlier stage experience better survival than do those with advanced stage [11]. Recently, Tabar et al. [12] reported an inverse association between the proportion of advanced BC cases detected in a screening programme and the expected mortality reduction as a consequence of participating in a mammography screening programme, thus enabling estimation of future BC mortality reduction at a rather early point in time after programme start.

In order to estimate whether our programme could result in a BC mortality reduction, we used the advanced cancer rates in the exposed and unexposed to screening groups as a surrogate measure of the forthcoming mortality reduction. We were able to link the database of all incident BC cases diagnosed in Tyrol and the screening database. This allowed us to characterise all incident BC cases diagnosed in Tyrol between January 1, 2009 and December 31, 2013 as exposed to screening versus unexposed to screening.

We therefore aimed to analyse for all incident female BC cases in Tyrol aged 40–69 years and diagnosed between 2009 and 2013 the shift in cancer characteristics, especially the shift in advanced BC for the group exposed to screening as compared to the group unexposed to screening.

2. Methods

The analysis was based on all BC cases in the female population of Tyrol aged 40–69 years and diagnosed between January 1, 2009 and December 31, 2013, who were registered by the Cancer Registry of Tyrol (CRT). The CRT registers all cancer cases in Tyrol with a high level of completeness [13,14]. The CRT registers amongst other data information on tumour size (diameter in mm), pathological TNM staging (clinical TNM for a few cases where pathological TNM was missing), and histologic malignancy grade.

Concerning MST data, all screening units registered basic data on screening visits for every participant and this information was transferred to a central MST database. More details have been described elsewhere [15]. The overall biennial participation rate was 60.2% (63.2%, 63.6% and 50.1% in age groups 40 to 49, 50 to 59 and 50–69 years, respectively) [16]. CRT data were linked to the MST database after both databases were pseudonymised. The study was approved by the local ethics committee.

All BC cases diagnosed among women attending screening were defined as cancers diagnosed among women "exposed to screening", i.e. all screening-detected and interval cancers combined. All other BC cases were defined as diagnosed among women who were "unexposed to screening".

We analysed tumour size in categories 1–20 mm and ≥21 mm (following TNM classification T_1 versus $T_{2\text{-}4}$), N stage in categories $N_{0/1mic}$ (lymph node-negative) and $N_{1\text{-}3}$ (lymph node-positive), and M stage with distant metastases present (M_1) or absent (M_0) at the time of diagnosis. Advanced BC was defined as tumour size ≥21 mm or lymph node-positive or metastatic disease according to AJCC/UICC staging ≥ II [17,18]. Bloom-Richardson histologic malignancy grading was categorized as well/moderately/poorly differentiated (Grades 1–3).

For estimation of age-adjusted incidence rates and relative risks (RR) [19], we followed a cohort approach while taking into account the fact that the group exposed to screening was a dynamic population. The number of cancers diagnosed (980 cases in the exposed and 629 in the unexposed group) served as the numerator when calculating the incidence rates and estimating the RRs. The denominator for the group exposed to screening was the number of person-years between first and last screening mammography visit plus 24 months (this was the follow-up period for interval cancer cases) for each woman, but not later than December 31, 2013. For women with diagnosis of BC, time exposed ended at date of diagnosis. In addition, for cases with a known screening history before 2009 we defined beginning of exposure as January 1, 2009. For the unexposed group the total number of person-years was estimated as the remaining number of person-years for the 40- to 69-year-old female population in Tyrol between January 1, 2009 and December 31, 2013, taking into consideration that for women with BC time of exposure ended at date of diagnosis. The resulting person-years totalled 369,432 for the exposed and 347,704 for the unexposed to screening group, see Table 1. Then the RR for advanced BC, comparing the groups exposed versus unexposed to screening, was estimated by dividing the incidence rate of advanced BC for the exposed group by that of the unexposed group and reported with the 95% confidence interval (CI). We estimated age-adjusted RRs by applying weights according to the Mantel-Haenszel approach. The same method was applied for the various other BC tumour characteristics.

Statistical significance was established at $P < 0.05$. All statistical analyses were performed using STATA, version 13 [20].

3. Results

During the study period January 1, 2009 to December 31, 2013, 1,609 incident BC cases were registered in women aged 40–69 years living in Tyrol (142,307 in year 2009 and 146,441 in year 2013). Of these cases, 32%, 32% and 37% were in the age groups 40 to 49, 50 to 59 and 60–69 years, respectively, without differences in the age distribution between cases exposed and unexposed to screening (see Table 2). The proportion of ductal carcinoma in situ (DCIS) was 11% (N = 106) in women exposed and 4% (N = 28) in women unexposed to screening. The combined DCIS and invasive BC incidence rate was 171, 215 and 314 per 100,000 person-years in the age groups 40 to 49, 50 to 59 and 60 to 69 years, respectively;

Table 1
Numbers of person-years exposed and unexposed to screening, by age group and screening status.

	Exposed to screening	Unexposed to screening	Total
40–49	144,372 (39.1%)	150,591 (43.3%)	294,963 (41.1%)
50–59	129,255 (35.0%)	105,209 (30.3%)	234,464 (32.7%)
60–69	95,805 (25.9%)	91,904 (26.4%)	187,709 (26.2%)
Total	369,432 (100.0%)	347,704 (100.0%)	717,136 (100.0%)

Table 2
Breast cancer cases (N = 1609) by year of diagnosis, age group, and proportion of DCIS.

	Exposed to screening N (%)	Unexposed to screening N (%)	Total
Year of Diagnosis			
2009	159 (16.2)	122 (19.4)	281 (17.5)
2010	211 (21.5)	102 (16.2)	313 (19.5)
2011	209 (21.3)	115 (18.3)	324 (20.1)
2012	216 (22.0)	130 (20.7)	346 (21.5)
2013	185 (18.9)	160 (25.4)	345 (21.4)
Age			
40–49	313 (31.9)	194 (30.8)	507 (31.5)
50–59	311 (31.7)	196 (31.2)	507 (31.5)
60–69	356 (36.3)	239 (38.0)	595 (37.0)
Proportion of DCIS in age group			
40–49	34 (10.9)	16 (8.2)	50 (9.9)
50–59	37 (11.9)	4 (2.0)	41 (8.1)
60–69	35 (9.8)	8 (3.3)	43 (7.2)

the incidence rate for DCIS was 17 per 100,000 person-years in the age groups 40 to 49 and 50 to 59 and 23 per 100,000 person-years in the age group 60 to 69. Of all 1609 BC cases, 980 cases were diagnosed in women exposed to screening and 629 cases in women unexposed to screening.

The total number of invasive BC cases was 1475 in the two groups. Comparing BC exposed versus unexposed to screening, RR for advanced BC was 0.83 (95% CI 0.71 to 0.96). In addition, RR was significantly reduced for tumour size ≥21 mm (RR 0.72, 95% CI 0.60 to 0.86) and for BC with metastatic disease (RR 0.27, 95% CI 0.17 to 0.46). Further details on BC characteristics and RRs are shown in Table 3.

4. Discussion

In this population-based registry study of women aged 40–69 years we compared the characteristics of BC cases diagnosed in those women who attended the screening programme (exposed to screening group) and in women who were unexposed to screening. Statistically significantly less advanced BC, fewer BC cases with tumour size ≥21 mm, and fewer metastatic BC cases were found in the exposed to screening group.

Table 3
Characteristics of invasive breast cancer cases (N = 1475) and age-adjusted relative risk for exposed to screening versus unexposed to screening.

	Exposed to screening N	Unexposed to screening N	Age-adjusted relative risk (95% CI)
Tumour size			
<21 mm	647	289	2.09 (1.82–2.41)
≥21 mm	215	280	0.72 (0.60–0.86)
Missing	12	32	
TNM-N[a]			
N_0	680	393	1.62 (1.43–1.83)
N_{1-3}	188	194	0.91 (0.74–1.11)
Missing	6	14	
TNM-M			
M_0	851	529	1.50 (1.35–1.68)
M_1	19	65	0.27 (0.17–0.46)
Missing	4	7	
Advanced BC[b]			
No	544	226	2.25 (1.92–2.62)
Yes	323	367	0.83 (0.71–0.96)
Missing	7	8	
Grading			
1–2	723	446	1.51 (1.35–1.70)
3	121	124	0.92 (0.71–1.18)
Missing	30	31	
Overall Total	874	601	1.36 (1.23–1.51)

[a] N_{1mic} was defined as lymph node-negative.
[b] Advanced breast cancer was defined according to AJCC/UICC ≥ II as tumour size ≥21 mm or lymph node-positive (N_{1mic} was defined as lymph node-negative) or metastatic disease.

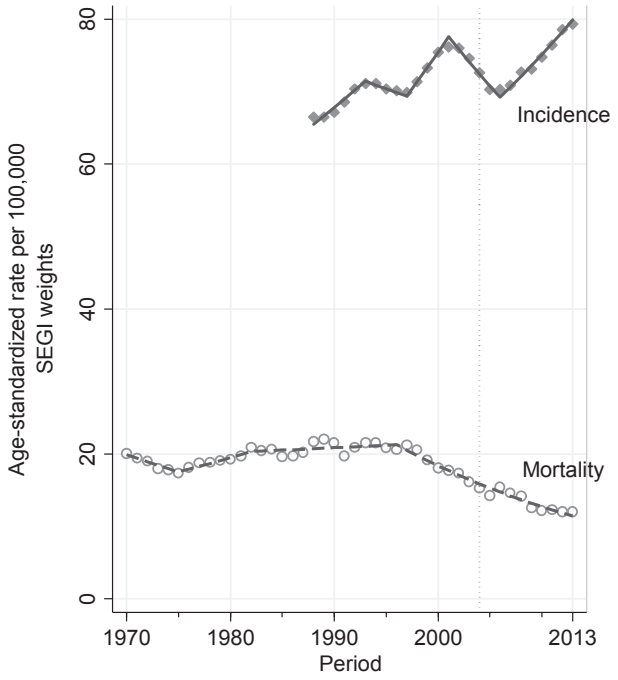

Fig. 1. Time trend of age-standardised breast cancer incidence and breast cancer mortality rates in females living in Tyrol, all age groups. Incidence data not available before 1988.

Voluntary mammography screening was already offered free of charge to all women aged 40–69 years in Tyrol in the early 1990s. There are no data available for the pre-screening period, because CRT did not register cancer cases before 1988. When looking at the time trend for overall breast cancer incidence in Tyrol presented in Fig. 1, we observed a steeper increase around 2000 and around 2008 that seem to be related to intensified screening activities (in 2000 the spontaneous screening programme in Tyrol was intensified [21], and in 2008 the organised programme (MST) was rolled out [15]). This complex time trend of cancer incidence and the lack of data for a pre-screening period prevented us from conducting a temporal trend analysis. On the other hand, we were able to link the MST database to the cancer registry's database. We compared the tumour characteristics of BC cases in two groups of women: in those who attended screening and in those who were not exposed to screening. Our purpose was to relate the differences to participation in the screening programme. Obviously, this study of the two groups exposed and unexposed to screening is an observational study entailing all problems related to this type of study design, both selection and information bias as well as confounding. It is well known that screening attendants and non-attendants differ in health attitudes, socio-demographic characteristics and in other prognostic factors. Therefore, interpretation of our results concerning shift in stage calls for caution.

To estimate relative risks and/or incidence rates we followed a cohort approach. Our definition of entry could have caused the person-years to be underestimated, because part of the women attended their first screening before June 1, 2008; this was not registered in the screening database (which started in June 2008) and therefore was not available for analysis. On the other hand,

there could also have been an overestimation of person-years for the women who underwent a screening mammography at least twice between January 1, 2009 and December 31, 2013 with an interval of more than two years between the two consecutive screening visits. We treated such women as exposed to screening for the whole period between screening visits. However, we estimate both deviations are fairly small.

Several studies [12,22–24] found a strong relationship between a lower rate of advanced BC cases detected in a screening programme and future breast cancer mortality reduction. Tabar et al. [12] argued that screening trials in which advanced-stage disease was reduced by 20% or more showed a 28% reduction in mortality, which should correspond to an approximately 40% reduction in mortality in women who actually underwent screening. Our estimates for relative risk reduction of 17% fewer advanced BC cases, 28% fewer BC cases with tumour size ≥21 mm and 73% fewer metastatic BC cases obtained by comparing cases exposed versus unexposed to screening lead us to anticipate a future reduction in BC mortality.

Our results show a remarkable difference in RR for BC with tumour size ≥ 21 mm (corresponding to $T_{2\text{-}4}$ according to AJCC/UICC [17,18]) at 0.72 and for advanced BC defined as staging according to AJCC/UICC ≥ II at 0.83. The reason for that difference is the proportion of lymph node-positive BC. Over the last fifteen years, the sentinel lymph node (SLN) technique was introduced in many breast cancer centres and it is well known that SLN has led to an upstaging of patients who would have been diagnosed as lymph node-negative in the pre SLN era [25]. However, the optimal technique remains the subject of discussion [26,27]. The period we cover comes after the introduction of SLN in our country, and analysis of the combination of T stage and N stage shows that the proportion of lymph node-positive BC cases is about 10% for T_{1a} (tumour size ≤5 mm) and increases to 30% for T_{1c} (tumour size between 11 and 20 mm), data not shown in detail. This observation can help explain the difference in RR between BC with tumour size ≥21 mm and advanced BC, the latter reflecting all three components, namely tumour size, lymph node status and metastatic BC.

We defined N_{1mic} as lymph node-negative. The RR for lymph node-positive BC was at 0.91 (not significant) and increases to 1.03 when we count N_{1mic} as lymph node-positive. However, this has no influence on our main result concerning advanced BC, because for the definition of advanced BC we strictly followed the AJCC/UICC definition for stage ≥ II.

Tabar [28] reported problems caused by digit preference, meaning that tumour size in millimetres is not perfectly recorded but is instead given in multiplies of 5 and 10; for example, the number of BC cases with tumour size exactly 15 mm or 20 mm is inflated. He therefore suggested that advanced BC be defined as ≥ 20 mm. We did a sensitivity analysis and the resulting relative risk of 0.76 differed only slightly from our result of 0.72, data not shown.

A number of studies have been published that cover various aspects of BC characteristics associated with mammography screening. Most of these analyses compared estimates of the number of early breast cancer cases between a pre-screening period and a screening period, see for example [29]. Such studies of temporal patterns of incidence of early- or late-stage BC are prone to a number of methodological challenges, especially those dealing with the underlying time trend in BC incidence in the absence of screening, the participation rate of the screening programme, the length of observation period, the stage migration bias, and the statistical methods [30]. Therefore, as expected, some of the previous studies of the time trend of advanced BC incidence demonstrated a decrease in advanced BC incidence between 10% and 20%, for example in the USA [31], Italy [30], the UK [32], Finland [33], the Netherlands [34], Australia [35] and Münster/Germany [36]. In contrast, a number of studies showed a relatively stable time trend for incidence of advanced BC, for example in the Netherlands [37], Switzerland [38], and some Norwegian counties [39].

The main strength of our study is the fact that we were able to link register and screening data on a personal basis and consequently categorise all incident BC cases by screening attendance. A second strength is the cancer registry's full coverage and the fact that nearly complete data on cancer characteristics was obtained.

However, an important limitation was the lack of data needed to adjust for confounding and various potential biases, especially lead time bias because our analysis was restricted to a time window of the first five years of an organised mammography screening programme following a period of about fifteen years of spontaneous screening. Also, data on histologic subtypes were not available, which prevented us from examining whether the proportion of triple-negative or HER2-positive cases might partly explain the observed effects. In order to deal with this last question we plan to collect more detailed data on BC characteristics, mainly histology and hormonal status, to be able to assess the aggressiveness of tumours in the two screening exposure groups.

5. Conclusions

In conclusion, in our registry analysis we observed that participation in the mammography screening programme in Tyrol was associated with important risk reductions for advanced BC by 17%, for BC with tumour size ≥21 mm by 28%, and for metastatic BC by 73%. We therefore expect that the Tyrolean mammography programme will lead to a relevant reduction in BC mortality.

Ethical approval

The Ethics Committee of the Medical University of Innsbruck confirmed in writing that no formal ethics committee approval was required for this retrospective analysis.

Conflict of interest

The authors declare that they have no conflicts of interest.

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