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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%)