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ORIGINAL ARTICLE

Why did the breast cancer lymph node status distribution improve in Denmark in the pre-mammography screening period of 1978–1994?

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Abstract

Background. Danish breast cancer patients diagnosed in 1978–1994 experienced a trend over time towards a more favourable distribution of lymph node status at time of diagnosis, which was not due to mammography screening. We investigated how this trend could be explained by patient characteristics at diagnosis: age (biological processes), calendar period (e.g. environmental changes), birth cohort (living conditions over a life time), post-menopausal status (a predictor of less favourable nodal status), and tumour diameter (a marker of detection time). *Material and methods*. The data set consisted of 22 955 patients aged 30–69 years at time of diagnosis with known lymph node status, known tumour diameter, known menopausal status, and clinically detected tumours, available from the Danish Breast Cancer Cooperative Group (DBCG). Age, period, cohort, menopausal status, and tumour diameter were used as predictors in generalised linear models with either node-positive status (at least one of the excised lymph nodes being tumour-positive) or severely node-positive status (at least half of the excised lymph nodes being tumour-positive) as outcomes. Lymph node status was assessed both empirically and estimated using an EM algorithm in order to reduce misclassification. *Results and discussion*. We found that the improved lymph node status distribution was most likely a period effect due to a combination of earlier detection of clinical tumours, explaining most of the trend in node-positive breast cancer and half of the trend in severely node-positive breast cancer, and some unknown factor affecting lymph node status but not necessarily other tumour characteristics.

Axillary lymph node status at time of diagnosis is the most important predictor of prognosis for breast cancer patients [1]. Danish breast cancer patients diagnosed in 1978–1994 experienced a trend over time towards a more favourable lymph node status distribution, the most conspicuous part being an almost halving of the fraction of patients in the category with the worst prognosis [2,3]. Altogether changes in lymph node status distribution explained half of the improvement in five-year relative survival for the studied patients [3].

Having established the importance of lymph node status on the improved prognosis, this study was undertaken to search for environmental and secular explanations for the improved lymph node status distribution. As our outcome we chose to study only lymph node status. This choice reflected that we found it more likely to be driven by a few factors than more complex staging measures such as TNM stage or Nottingham Prognostic Index, both of which synthesise several prognostic factors of a disparate nature. This choice also enabled us to bring in tumour diameter as an explanatory variable. Apart from being a prognostic factor in its own right, we considered a small tumour diameter a proxy for early detection, which a priori would be a likely explanation for part of the time trends in lymph node status distribution. To the extent that we had no specific a priori candidate explanations we would search for proxies in terms of age-, period- and cohort effects.

Denmark is well-suited for studying causes for changes in lymph node status distribution not related to mammography screening because mammography screening was only introduced in a few counties at the end of this period. Throughout this period, data on all incident cancer cases were available from the

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Danish Cancer Register and clinical data on lymph node status were available from the clinical database of the Danish Breast Cancer Cooperative Group (DBCG). The two files can be linked using unique personal numbers. Based on these data sources we studied the distribution of lymph node status at time of diagnosis in Danish breast cancer patients during the period 1978 to 1994 as a function of age, period, cohort, menopausal status and tumour diameter, in search for clues about what caused the improved lymph node status distribution.

Material and methods

The improvement in lymph node status distribution for Danish breast cancer patients was established in a data set containing all first incident breast cancers in Denmark diagnosed at age 30–69 in 1978–1994 [2]. The data set included 31 719 patients of whom 25 719 had a known lymph node status. We further excluded 788 patients whose cancers might have been detected in mammography screening programmes, as the screening could bias the lymph node status distribution in a favourable direction. These patients were characterised by living in counties having mammography screening programmes in place at the time of their breast cancer diagnosis and being in the target age group for that programme. We further excluded 17 patients due to unknown menopausal status. Finally we excluded 1 959 patients with unknown patho-anatomically assessed tumour diameter. Data on lymph node status of disease at time of diagnosis were then available for the remaining 22 955 patients. We considered the data for the 22 955 patients with known lymph node status to be representative for the whole group of 31 719 patients aged 30–69 years and diagnosed with breast cancer in Denmark in 1978–1994 [2]. Especially examination of Figure 1 in [2] and the survival patterns in the depicted subgroups do not suggest serious biases in the reported lymph node status distribution due to a varying fraction of breast cancer cases with known lymph node status. For completeness we have recorded malignancy grade in Table I, but did not use it in the analysis as a covariate since it was available only for patients with ductal carcinomas.

Lymph node status

We used both an empirical and an estimated lymph node status. The *empirical lymph node status* was a categorisation of the observed proportion of positive lymph nodes [2]. Breast cancer cases were divided into node-negative cases, moderately node-positive cases with $<50\%$ of excised lymph nodes being positive, and severely node-positive cases with at least 50% of the excised lymph nodes being positive. The relevance in the context of large variation in the number of excised lymph nodes and the improved prognostic performance of stage measures based on proportions of involved lymph nodes rather than numbers of involved lymph nodes have been demonstrated elsewhere [2–4].

Lymph node status based on less than 10 excised lymph nodes can be unreliable [5]. As the average number of excised lymph nodes has increased over time [2,3] the resulting misclassification may furthermore vary over time. Therefore, we used also an *estimated lymph node status*. For cases with at least 10 excised lymph nodes the estimated lymph node status equalled the empirical lymph node status. For cases with less than 10 excised lymph nodes we made an estimate of what the lymph node status would have been, if 10 lymph nodes had been excised. We assumed that lymph nodes actually excised always would be the first part of a hypothetical sample of 10. The first DBCG protocol (1978–1983) recommended that five lymph nodes be extracted and demanded that at least one lymph node was typed. Over time the recommendations and demands of the DBCG protocols were strengthened [6]. Folklore has it that the reported results were based on preferentially selected lymph nodes, which may bias the observed lymph node status towards the less favourable. This selection could be a consequence of not reporting node-negative findings in lymph nodes beyond the recommended number. It could also be a consequence of the procedure for axillary clearance itself, which calls for identifying enlarged (lymph) nodes [7,8]. To accommodate these phenomena and its changing impact over time it was assumed that the observed number of positive lymph nodes would be due to a mixture of two distributions, the first distribution corresponding to a random sample from the hypothetical sample of 10, the second distribution corresponding to drawing all the node-positive lymph nodes first if any was present. Establishing the relative contribution from each distribution was part of the estimation process. More precisely for every patient we estimated the contribution to each stratum (node-negative, moderately node-positive or severely node-positive) as the probability of being in that stratum. This probability only depended on the number of excised lymph nodes, the number of positive lymph nodes, and the time period (1978–1983, 1984–1989, 1990–1994). An EM algorithm [9] was used for the estimation, for details see the supplementary appendix to be found only online, at http//www.informaworld.com/(DOI: 10.3109/02841861003602074).

In order to compare and facilitate the discussion of the use of proportion-based lymph node status as opposed lymph node status based on absolute numbers we also calculated the average number of positive lymph nodes for different time periods, crude, adjusted

for age and adjusted for age and number of excised lymph nodes. This was done by multiple linear regression of the number of positive lymph nodes for each breast cancer case on time period and age and number of excised lymph nodes as needed, treating time period as a factor and the other predictors as linear trends. A constant was added to the time period effect estimates so that they had the same value as the crude estimate for the time period 1986–1987, to ease comparison.

Sentinel node sampling was introduced experimentally in 1998 and introduced nation-wide in the DBCG 2002 protocol [6,10], therefore it was not relevant for the present study.

Menopause

The proportion of breast cancer cases with localised disease (as opposed to breast cancer that had spread to axillary lymph nodes or to distant sites) diminishes after menopause [11], and we therefore included menopausal status in the analysis. The definition of menopausal status in the DBCG data changed during the study period.

In the period 1978–1989 patients were defined as postmenopausal if menostasia for more than five years, or prior hysterectomy or bilateral oophorectomy and 55 years or older, or menstruation during cyclic hormonal therapy and 55 years or older. All other patients were defined premenopausal [6].

In the period 1990–1994 patients were defined as postmenopausal if menostasia for 12 or more months, or prior bilateral oophorectomy or prior hysterectomy, or menstruation on cyclic hormonal therapy and 50 years or more. All other patients were defined pre-menopausal [6].

Obviously the determination of effect due to age and effect due to menopausal status depends heavily on observations in the age band where both pre-menopausal and post-menopausal status is common since they are otherwise heavily confounded. We looked at the fraction of node-positive and severely node-positive breast cancer cases by age and menopausal status in the two periods with different definitions of menopausal status (data on request). This suggested that the risk of being node-positive in post-menopausal patients increased up to a certain age after which it stabilised. In a supplementary analysis (available on request), we modelled this by a variable for menopausal status, which for post-menopausal women was modified by a covariate depending linearly on the distance from the age where the node-positive risk stabilised. This was set to 56 years in 1978–1989 and 48 years in 1990–1994, based on a subjective assessment of the data. In a sensitivity analysis all combinations of the values (48,50,52,54,56) for these two ages were tried out.

Tumour diameter

We used tumour diameter as a marker of how early clinical breast tumours are detected. From 1984 onwards tumour diameter was exclusively assessed patho-anatomically. In 1978–1983 a subset of patients also had or only had a surgically assessed tumour diameter. Since the two measurements differed somewhat in patients with both we decided only to use the patho-anatomical measure.

Age-period-cohort modelling

For both the empirical and the estimated lymph node status measures, we used standard age-period-cohort modelling [12,13] to investigate to what extent the changes in lymph node status distribution could be explained by age-, period-, or cohort effects. Age effects are those that affect all individuals in a given age group the same. This will usually represent biological processes in the subjects. Period effects are those that have the same effect on all individuals in a given period. This could represent e.g. environmental factors or changes in disease classifications. Cohort effects are those that have the same effect on all individuals born in the same calendar period. This could represent the effect of common exposures in childhood or any other stage of life prior to the age span studied.

Thus we modelled the lymph node status distribution as a function of age, period, cohort, menopausal status and tumour diameter at the time of diagnosis. We made two separate dichotomous analyses of the proportion of node-positive cases and the proportion of severely node-positive cases. Cases were aggregated into cells cross-classified by tumour diameter d, menopausal status m coded as 1 for post-menopausal and 0 for pre-menopausal, age a coded as 30, 32,.., 68 and period p coded as 1978, 1980,…, 1994 and creating (synthetic) birth cohorts $c = a - p$. For each cell we calculated the number of cases having lymph node status s, X_{sapmd}, and the total number of cases, n_{apmd}. When using the estimated lymph node status, the contribution from a case to each category of lymph node status was the estimated probability of belonging to that category. The proportion of cases having lymph node status s was then modelled in a generalised linear model [14] with age, period, cohort, menopausal status and tumour diameter as predictors. We used the same generalised linear model specification regardless of whether the outcome X_{sapmd} was calculated from the estimated or the empirical lymph node status measure. For the empirical lymph node status measure this specification was equivalent to logistic regression. The tumour diameter d was included with a linear and a quadratic term, i.e. a coefficient was estimated for both d and d^2. As expected both terms were extremely

significant, and the effect of the quadratic seems to be to counter-balance the non-linear link function and thereby provide a more linear relation between exposure and the probability of the outcome, as observed.

As it was not clear a priori how the time variables should be categorised we considered three predictors regarding age: linear age, age aggregated into 10-year categories, and age with 2-year age categories, and likewise for period and cohort. We used a stepwise strategy, with a 1% significance level as criterion, to identify which of these nine predictors were indispensable.

When using estimated lymph node status the imputation of expected values rather than actual outcomes (0 or 1) in some observations might cause the variability in the data to be lower than expected, thereby deflating the significance level of our tests. We therefore chose to estimate parameter variance robustly, using the technique in [15], and base confidence intervals (CIs) and significance tests (Wald tests) on the robustly estimated covariance matrix. All analyses were performed using SAS version 9.2.

Ethics

This register-based study did not include any contact with individual study subjects. The study was approved by the Danish Data Protection Agency.

Results

Features of the raw data

Table I shows that the average tumour diameter decreased from 33 mm in 1978–1979 to 24 mm in 1994, while little happened to the malignancy grade distribution of ductal carcinomas over time. The average number of excised lymph nodes increased from 5.67 in 1978–1979 to 11.41 in 1994. The average number of positive lymph nodes increased from 1.70 to 2.20 during the same period, and the percentage of patients with 4+ positive lymph nodes increased from 17% in 1978–1979 to 20% in 1994. Adjustment for age hardly mattered. When the average number of positive lymph nodes was adjusted for both age and number of excised lymph nodes (and for 1986–1987 set equal to the observed number) an opposite trend was seen with a decrease from 2.05 in 1978–1979 to 0.64 in 1994 showing that the trend in number of positive lymph nodes was very sensitive to the number of excised lymph nodes. The empirical data thus support the use of a proportion-based measure of lymph node status instead of the absolute number of positive lymph nodes for studies of time trends.

Detailed examination of Figure 1 showed evidence of the suspected preferential selection of node-positive lymph nodes when a small number of lymph nodes is reported. This was very pronounced for the period 1990–1994, however, less than 3% of all cases had three or less lymph nodes excised in this period, and so the only large deviation for this period concerned few persons (data not shown). For the other two periods the excess of node-positive lymph nodes among those with few reported lymph nodes excised was modest. These claims were substantiated by the fact that the best model fit for the estimated lymph node status was obtained using models that assumed 100% of the observed node-positive lymph nodes to be random samples of the hypothetical sample of the 10 first lymph nodes. So the estimated lymph node status was created using this assumption. The correspondence between the predicted and the observed distribution of number of positive lymph nodes for a given number of excised lymph nodes was statistically quite satisfactory in the first and the last protocol, and satisfactory for few excised lymph nodes in all the protocols (data not shown).

Table I. Prognostic characteristics by year of diagnosis for 22 955 breast cancer patients diagnosed in 1978–1994 in Denmark.

Period	1978–79	1980–81	1982–83	1984–85	1986–87	1988–89	1990–91	1992–93	1994
N	1138	2014	2567	2668	3083	3284	3160	3444	1597
Average tumor diameter (mm)	33	32	29	26	25	24	24	24	24
Ductal carcinoma (%)	89	84	84	81	83	84	82	82	81
Malignancy grade I* (%)	32	28	31	31	32	34	35	36	33
Malignancy grade II* (%)	51	54	52	49	48	47	45	43	47
Malignancy grade III* (%)	17	18	16	20	20	19	20	21	20
Average number of excised lymph nodes	5.67	6.05	6.24	6.66	6.83	7.80	9.56	10.57	11.41
Average number of positive lymph nodes	1.70	1.67	1.75	1.75	1.72	1.72	1.99	2.02	2.20
Do. adjusted for age	1.69	1.66	1.75	1.75	1.72	1.72	1.99	2.02	2.20
Do. adjusted for age and number of excised lymph nodes	2.05	1.93	1.95	1.80	1.72	1.39	1.06	0.75	0.64
1–3 positive lymph nodes (%)	31	30	30	29	29	29	28	28	28
4+ positive lymph nodes (%)	17	17	17	17	16	16	19	19	20

*Malignancy grade was defined for carcinomas with a ductal component as a slight modification of the Bloom and Richardson system where only the number of typical mitoses, and not hyperchromatic nuclei was evaluated as one of the three criteria [2]. WHO malignancy points 3–5 were graded as 1; 6–7 points as 2; and 8–9 points as 3.

Smoothness of temporal trends

Our starting models included period, cohort, menopausal status and tumour diameter as predictors. It is well known that due to the linear dependence between age, period and cohort any linear combination of the three can be represented by any two of them. So a forward inclusion model selection strategy from this starting point amounts to an assessment of the smoothness of the unknown temporal trends. This strategy added no predictors to the starting models when considering node-positive lymph node status as outcome. For the severely node-positive outcome the strategy suggested inclusion of time as a factor, either in groups of two or 10 years. Since the former includes the latter we included time in 2-year groups as a predictor. Starting from this model added no further predictors. For both outcomes and both lymph node status measures the linear cohort effect was not statistically significant, while the period effects in most cases were highly statistically significant. We therefore were able to simplify the models using period as the only temporal variate. The model search terminated here.

Effect estimates

Most effect estimates were very similar for the two lymph node status measures, with the odds ratio of being node-positive between successive years as the exception (Table II). Here the odds of being node-positive increased for the empirical lymph node status while it was stable for the estimated lymph node status. For illustration we have for each of the two lymph node status measures depicted the distribution of cases by lymph node status and calendar year (Figure 1). The adverse effect of being postmenopausal was strong when predicting the proportion of severely node-positive cases (OR=1.16; 95% CI 1.08 or 1.09 to 1.24), but seemingly absent when predicting the proportion of node-positive cases.

We note some of the consequences of this being a mutually adjusted model. Firstly the predicted net effect of increasing tumour diameter is increased risk of late stage disease over the full range of realistic tumour diameters (up till 11–12 cm). The effect of the negative coefficient for tumour diameter squared is to dampen the slope of the increase in risk of late stage disease with increasing tumour diameter. Secondly tumour diameter is a strong predictor of late stage disease, so in the case of the stable fraction of empirically node-positive tumours (Figure 2), the trend in tumour diameter distribution would predict a decreasing fraction of node-positive tumours. To compensate the model must postulate a strong underlying time trend towards more node-positive tumours (OR=1.026; 95% CI: 1.020–1.033). In contrast to this, the very modest time trend in the odds of estimated node-positive tumours (OR=0.998; 95% CI: 0.993–1.003) shows that the clearly decreasing fraction of node-positive tumours according to this measure (Figure 2), is mostly explained by the changing distribution of tumour diameters. The awkward looking time trend for the odds of severely node-positive tumours in Table II owes much to this interplay with the tumour diameter distribution, the

Table II. Odds ratios for node-positive and severely node-positive status of disease by menopausal status, tumour diameter, and year of diagnosis for 22 955 Danish breast cancer patients diagnosed in 1978–1994.

Outcome	Node-positive status[a]		Severely node-positive status[b]	
Method/measure Exposure	Estimated OR (95% CI)[c]	Empirical OR (95% CI)[c]	Estimated OR (95% CI)[c]	Empirical OR (95% CI)[c]
Post- vs. pre-menopausal	0.97 (0.92–1.02)	0.95 (0.90–1.00)	1.16 (1.09–1.24)	1.16 (1.08–1.24)
Tumour diameter, trend per cm	1.73 (1.67–1.79)	1.88 (1.81–1.95)	1.96 (1.89–2.04)	1.98 (1.90–2.06)
Tumour diameter squared, trend per cm^2	0.977 (0.974–0.980)	0.973 (0.970–0.976)	0.973 (0.969–0.976)	0.972 (0.969–0.976)
Year of diagnosis, trend per year	0.998 (0.993–1.003)	1.026 (1.020–1.033)		
Year of diagnosis, 1978–79			0.90 (0.77–1.05)	0.90 (0.76–1.06)
Year of diagnosis, 1980–81			0.83 (0.73–0.95)	0.83 (0.72–0.96)
Year of diagnosis, 1982–83			0.95 (0.84–1.07)	0.93 (0.82–1.06)
Year of diagnosis, 1984–85			0.95 (0.84–1.07)	0.95 (0.84–1.08)
Year of diagnosis, 1986–87			1 (ref)	1 (ref)
Year of diagnosis, 1988–89			0.84 (0.75–0.95)	0.83 (0.73–0.95)
Year of diagnosis, 1990–91			0.74 (0.66–0.84)	0.71 (0.62–0.81)
Year of diagnosis, 1992–93			0.66 (0.58–0.74)	0.61 (0.53–0.69)
Year of diagnosis, 1994			0.68 (0.58–0.79)	0.63 (0.53–0.74)

[a]Node-positive status: patients with any excised lymph nodes being positive.
[b]Severely node-positive status: patients with >50% of excised lymph nodes being positive.
[c]Mutually adjusted for menopausal status, tumour diameter, and year of diagnosis.

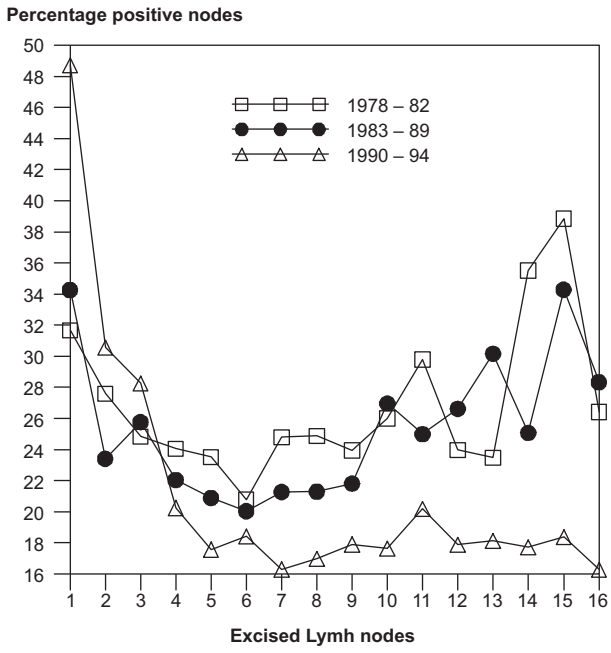

Figure 1. Fraction of node-positive lymph nodes by number of excised lymph nodes and time period for 22 955 Danish breast cancer patients 30–69 years of age diagnosed in 1978–1994.

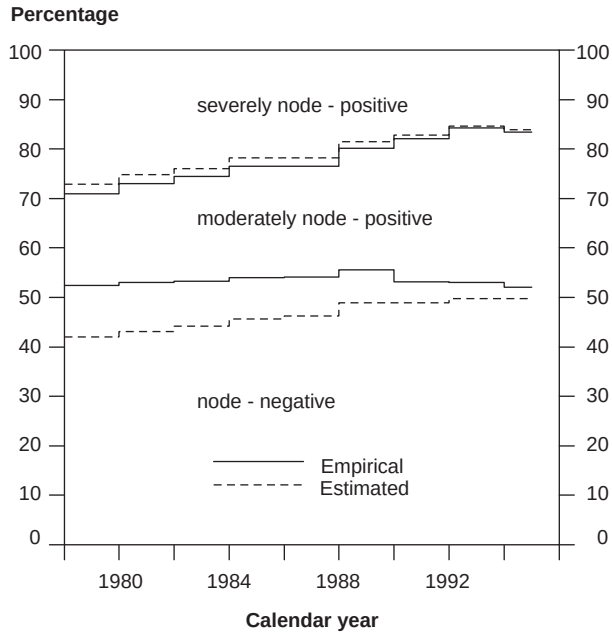

Figure 2. Distribution of lymph node status at time of diagnosis for 22 955 Danish breast cancer patients 30–69 years of age diagnosed in 1978–1994. Cumulative percentage.

time trends are much smoother without tumour diameter as a predictor (data not shown).

In order to get an idea about how much of the time trend was due to faster detection of tumours we fitted the end models with a linear period trend as the only temporal variate and then compared the linear period trends from these and the same models without tumour diameter as a predictor. This suggested that 48–54% of the trend in severely node-positive breast cancer and around 90% of the trend in node-positive breast cancer was explained by faster detection. The latter number is based on the estimated lymph node status only as the calculation was rendered meaningless for the empirical lymph node status by an almost zero trend without tumour diameter as a predictor. In a similar exercise regarding the role of menopausal status, comparing the models with and without menopausal status we found it to be of no import at all.

More advanced modelling of the effect of menopausal status, taking into account the variation by age and period of the effect of menopause, did not substantially change any of the above inferences (data available on request).

We have so far modelled the fraction of incident breast cancer cases with a certain lymph node status. To provide an alternative view of trends in lymph node status we approximated the trends in rates of the three lymph node statuses. We applied the lymph node status distribution in the study population to the population of all incident breast cancer cases aged 30–69 years, dividing by the person-years at risk (Figure 3). According to this the rate of severely node-positive disease decreased slightly over the period, while the increasing incidence of breast cancer was due to the increasing rates of node-negative and moderately node-positive breast cancer.

Discussion

The trend in the distribution of lymph node status among 30–69 year old incident Danish breast cancer cases diagnosed in 1978–1994 was adequately modelled by simple functions of tumour diameter, menopausal status, and period. We used proportion-based measures of lymph node status as we found no evidence in favour of using the traditional measure of lymph node status based only on the number of positive nodes in the present context of large variation between individuals and over time in the number of excised lymph nodes. We found evidence for a suspected preferential selection of node-positive lymph nodes when few excised lymph nodes were reported, but the effect of this phenomenon did not seriously affect this investigation. By design, the estimated lymph node status is likely to be less biased and less misclassified than the empirical lymph node status, e.g. the empirical lymph node status measure *is* biased because some true node-positives will be misclassified as node-negative, while the estimated lymph node status measure *may be* biased if the model assumptions do not hold. So undoubtedly the odds of being

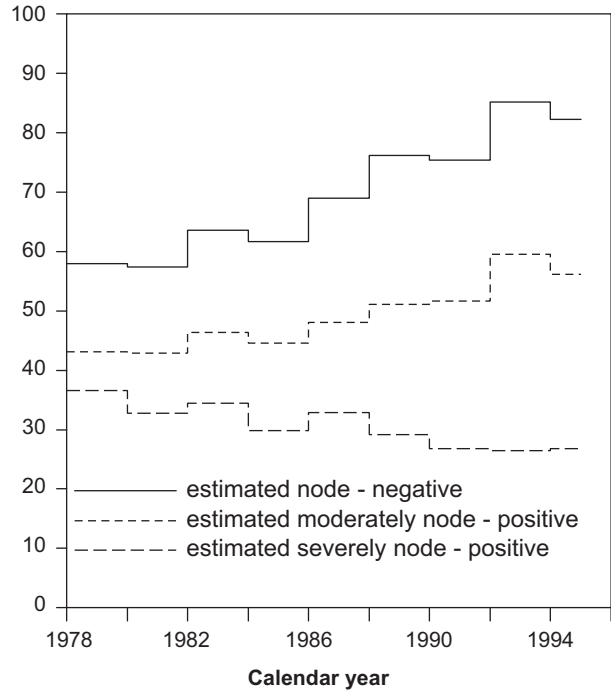

Figure 3. Projected incidence rates per 100 000 person-years of node-negative, moderately node-positive and severely node-positive breast cancer in Denmark in women 30–69 years of age in 1978–1994.

node-positive decreased over time as suggested by the analyses using the estimated lymph node status as outcome and especially the odds of being severely node-positive decreased over time as demonstrated by the analyses using either lymph node status measure as outcome. We see the stable fraction of empirically node-positive as the net result of two opposite tendencies – a decreasing fraction of true node-positive and an increasing probability of detecting the true node-positive.

In general, the trend in lymph node status distribution could be caused by earlier detection of tumours, in accordance with Hellman's spectrum theory [16], or changes in the distribution of risk factors favouring less aggressive tumour types. Faster detection explained most of the trend in node-positive breast cancer, and half of the trend in severely node-positive breast cancer. Changes in menopausal status had no impact on the trend, and the residual period effect in the models therefore represents changes in the distribution of unknown breast cancer risk factors favouring less aggressive tumour types.

We assume tumour diameter to be a perfect marker of the effect of earlier detection because it must be a smooth monotone function of time since tumour initiation and although some of the change over time in tumour diameter may be due to changes in risk factors or lifetime exposures, we consider this unlikely. We therefore interpret changes in the tumour diameter distribution over time as a specific period effect. Therefore the period effect in the model must represent changes in the distribution of risk factors favouring less aggressive tumour types exclusively.

It is not possible from the statistical tests to conclude that there was no cohort effect, because it is possible to reproduce exactly any effect of a linear period effect alone by a combination of a linear cohort effect and a linear age effect [12,13]. However, fitting models with linear age and linear cohort instead of linear period effect lead to unbelievably strong age effects, implying, for instance, that 68–69 year old patients should have odds of being severely node-positive around three times less than patients aged 30–31, everything else being equal. In practice assigning all the linear period effect to either a linear period effect or a linear cohort effect with the necessary compensating age effects represent the extreme positions in the balance between period and cohort effects as explanatory variables. There is no obvious biological reason why the lymph node status distribution should depend on age beyond what is a consequence of menopause. We therefore find the results suggestive of a period effect as the by far most important source of the time trend, and so we shall only elaborate on that contribution in the following.

Other studies have examined lymph node status and trends in the DBCG data, e.g. [8,17–20], but these have mainly been focused on breast cancer management or covers other time periods. They will therefore not inform this discussion.

Earlier detection of tumours

By design, the few tumours potentially detected in the organised mammography screening programs were excluded. Unlike in many other European countries opportunistic screening was not widespread in Denmark in the study period. The total number of clinical mammograms only increased from 37 000 in 1983 to 48 000 in 1991, and in 1991 still only about 5% of all 50–69 year old women had a clinical mammogram taken during two years [21]. In the absence of screening, most breast cancers are detected by the women themselves as a lump in the breast usually with no other symptom. One could therefore imagine secular trends, as increased breast awareness among women that would lead to earlier detection of clinical cancers, and a more prompt reaction from clinicians towards presented breast cancer symptoms. The crude calculations in the results section suggest that 48–54% of the trend in severely node-positive breast cancer, and around 90% of the trend in node-positive breast cancer are explained by earlier detection.

Menopause

We found no difference between pre- and post-menopausal women in the risk of node-positive tumours, but post-menopausal women had 16% higher risk of being severely node-positive than pre-menopausal women. Data from a meta-analysis on hormonal replacement therapy found that the proportion of breast cancer cases with localised disease (as opposed to breast cancer that had spread to axillary lymph nodes or distant sites) diminished after menopause [11], indicating that post-menopausal women had an approximately 20% higher risk of distant disease than pre-menopausal women. Our classification into node-negative and node-positive does not entirely correspond to the classification in the meta-analysis, nor do our definitions of menopausal status entirely correspond to the classification in the meta-analysis. These differences may explain why our results correspond with those of the meta-analysis for the severely node-positive tumours, but not for the entire groups of node-positive tumours.

Origin of the residual period effect in lymph node status distribution

The period effect in the model must represent changes in the distribution of risk factors favouring less aggressive tumour types exclusively, under the assumptions presented earlier.

Around 80% of the tumours were intraductal carcinomas. Only small changes were seen in the distribution of malignancy grade [2,3], which is a measure of the aggressiveness of intraductal carcinomas. Furthermore only small changes were seen in the distribution of tumours regarding morphology and topography (data not shown).

It is certainly possible that the distribution of some tumour characteristics change over a span of several years while others do not. This is illustrated by the low correlation between them. In our data we found the correlation between empirical lymph node status and tumour diameter to be 0.34, between lymph node status and malignancy grade to be 0.16, and between tumour diameter and malignancy grade to be 0.19 (data not shown). Thus we are searching for one or more explanatory factors affecting lymph node status, but not necessarily other important biological tumour characteristics. As we found no effect of age when menopausal status was controlled for, this exposure cannot be factors with vastly different impact in young and older women beyond the effect of menopausal status.

Due to the methodological problems in generalising from the study population with known lymph node status to all incident breast cancer cases in Denmark, we made only a simple attempt to translate the lymph node status distribution into lymph node status specific incidence rates, and the results should be interpreted cautiously. The speculative view on incidence trends suggested in Figure 3 is that the overall increasing incidence of breast cancer during the study period was essentially due to an increase in node-negative and moderately node-positive tumours, and that these tumours may somehow have an aetiology different from that of the severely node-positive tumours, the rate of which seemed to be only slightly decreasing.

Conclusion

The main source of the improved lymph node status distribution at time of diagnosis in Danish breast cancer patients diagnosed in the pre-mammography screening period of 1978–1994 is most likely a period effect, not depending on the birth cohort or age of the patients. Seemingly this period effect stems from earlier detection of tumours, supplemented with some unknown factor affecting lymph node status but not necessarily other tumour characteristics.

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Appendix

The EM algorithm used to compute the estimated lymph node status

This appendix describes the algorithm used to derive the estimated lymph node status. The following variables are used: S (lymph node status), N (number of excised lymph nodes), X (number of positive lymph nodes among the excised) and Z (the number of positive lymph nodes among the 10 first excised lymph nodes), a hypothetical intermediate. The estimated lymph node status is obtained from $P(S=s \mid N=n,X=x)$, and our goal is to estimate this probability. For $n \geq 10$ the estimated lymph node status coincide with the empirical lymph node status, i.e. we define the lymph node status to be node-negative for $x/n=0$, moderately node-positive for $0 < x/n < 0.5$ and severely node-positive for $x/n \geq 0.5$, when $n < 10$ the empirical x/n is replaced by $z/10$. Note that the estimated lymph node status becomes a distribution on the set of possible statuses when $n < 10$.

When $n < 10$ we assume $P(X=x \mid Z=z,N=n) = P(X=x \mid Z=z,N=n,S=s)$ and $P(S=s,Z=z) = P(S=s,Z=z \mid N=n)$ and $P(S=s \mid X=x,N=n)$ is obtained by use of Bayes' formula on

$$P(X=x \mid Z=z,N=n) \text{ x } P(Z=z \mid S=s) \text{ x } P(S=s).$$

$P(S=s \mid X=x,N=n)$ is then in turn used on the raw data to provide estimated counts of all possible values of S and thus an estimate of $P(S=s)$. This completes one cycle in our algorithm. The algorithm terminates when the maximal absolute change in the estimated cell counts moves below some threshold. When $P(X=x \mid Z=z,N=n)$ and $P(Z=z \mid S=s)$ are fixed this can be shown to be an EM algorithm.

$P(X=x \mid Z=z,N=n)$ was chosen to reflect that a random sample of N lymph nodes are selected out of a (hypothetical fixed) sample of 10 with Z lymph nodes positive. X of the chosen N lymph nodes is then observed to be positive. We assumed it to be a mixture of a hypergeometric distribution and an extreme distribution where all positive nodes would always be selected before the negative nodes. The fraction f of $P(N,X)$ due to a hypergeometric distribution was determined using a goodness-of-fit criterion on the combinations of X and N ($N<10$) on a grid of values for f. The best fit was always obtained with $f=1$.

$P(Z=z \mid S=s)$ was estimated from the data on women who had at least 10 lymph nodes excised. For each combination of N and X we determined the distribution of Z assuming it hypergeometric, then discarded values of Z inconsistent with the observed S and rescaled to obtain a distribution $P(Z=z \mid N=n,X=x,S=s)$ from which we found $P(Z=z \mid S=s) \propto \Sigma_{n,x} P(Z=z \mid N=n,X=x,S=s) P(N=n,X=x)$, where $P(N=n,X=x)$ is the empirical distribution on this restricted data set.

The complete fitting process was performed separately and independently for the time periods (1978–1983, 1984–1989 and 1990–1994). The algorithm converged to the same solution starting from any point on a grid of starting points for $P(S=s)$. A more realistic scenario (within time periods) is obtained when the distribution of S is allowed to vary with calendar period p (either linearly or as a factor), essentially replacing $P(S=s \mid N=n,X=x)$ and $P(S=s)$ with $P(S=s \mid N=n,X=x,P=p)$ and $P(S=s \mid P=p)$ in the above approach. This additional complexity did, however, not change the inferences substantially and was consequently abandoned.