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COMMUNICATION

Breast Cancer under 40 Years of Age: Increasing Number and Worse Prognosis

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Abstract Breast cancer at a relatively young age with a poor prognosis is currently exhibiting an increasing incidence. In a retrospective cohort analysis of early breast cancer cases after surgery from our institutional patient registry, 141 patients aged ≤40 years constituted the younger group, with 300 randomly selected patients aged >40 years as controls. A significant and steady increase was found in the relative number of younger cases during the years 2004–2009. The histological type and grade and the lymph node status of the cancers differed significantly between the two groups, with more aggressive biological behaviour, a more advanced stage and a worse prognosis in the younger group. Half of the cancers in the younger cohort were ER-negative, while two-thirds in the control group were ER-positive. Comparatively more tumours were PR-positive and HER2-negative in the control group than in the younger group. The rates of triple-negative cases were 25% and 13% in the younger age and the control group, respectively (p=0.026). Significantly higher mastectomy and axillary block dissection rates were observed in the younger age group, and more chemotherapy was administered than in the control group. Our findings demonstrate the significance of breast cancer in cases aged <40 years, and draw attention to the need for appropriate care in these cases.

Keywords Age · Breast cancer · Incidence · Predictive factors · Prognostic factors

Abbreviations

ER	oestrogen receptor
HER2	human epidermal growth factor receptor type 2
pN	pathological lymph node status
pT	pathological tumour size
PR	progesterone receptor
DCIS	ductal carcinoma in situ
IDC	invasive ductal carcinoma
ILC	invasive lobular carcinoma

Introduction

An increasing incidence of breast cancer at a comparatively young age has recently been demonstrated in many countries worldwide [1–3]. Among women aged <40 years, breast cancer is the most frequent form of cancer, accounting for 30–40% of all malignancies [4], with reported breast cancer incidences of 4–7% in different populations [5–7].

Breast cancer at a young age has been shown to be associated with a poor prognosis, in part because of the generally more aggressive nature and the more advanced stage in younger than in older women [8–10]. Most studies have revealed an increased proportion of high-grade, rapidly proliferating tumours accompanied by vascular invasion and regional lymph node involvement in younger patients [8–10]. Genomic analysis suggests a distinct

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biological entity with less frequent hormonesensitivity and a greater HER1-2 dependence [11]. An age <35 years has itself been demonstrated to be an independent unfavourable prognostic factor [4].

The National Cancer Registry indicates that, the incidence of breast cancers in women aged <40 years in Hungary is about 5% (Fig. 1). Our impression that we were seeing increasing numbers of young breast cancer patients in our everyday practice led us to perform an analysis on the proportions of such patients at our department, in conjunction with the tumour- and treatment-related features extracted from the available patient registry data. As a cut-off point for the analysis, we chose the age limit of 40 years similarly to most other investigators in the literature [2, 4, 6, 8, 12].

Materials and Methods

A retrospective cohort analysis was performed on the early breast cancer cases after surgery, retrieved from the institutional patient registry. Patients aged ≤40 years (141 women had attended our department between January 1998 and August 2009) constituted the younger group, with 300 randomly selected patients aged >40 years (treated between January 2004 and August 2009) as controls. The annual distribution of the younger cases and various clinical data were collected: the age of the patient at the time of surgery, the types of breast and lymph node surgery, the histological type and grade of the tumour, the pathological tumour size (pT) and lymph node status (pN), the hormone receptor (oestrogen receptor (ER), progesterone receptor (PR) and the human epidermal growth factor receptor type 2 (HER2) status of the tumour, and the nature of the systemic therapy. Tumour characteristics were determined by standardized methods that did not significantly change over the study period.

Statistical analyses were performed with Fisher's exact probability test and linear regression analysis. A p value of<0.05 was regarded as statistically significant.

Results

The mean (± standard deviation) ages of the 141 younger and the 300 control cases were 35.1±3.7 (23–40) and 58.9±9.9 (41–84) years, respectively. After a level state in years 1998–2003, we found a steadily increasing relative number of new breast cancer in to the younger group between 2004 and 2009 (p=0.035). The proportion of younger cases reached 13% by 2009, clearly different from the respective data registered in the national database throughout the same time period (Figs. 1 and 2).

The rates of mastectomy in the younger and control groups were 41.7% and 31.4%, respectively (p=0.046), those of axillary block dissection were 80% and 67%, respectively (p=0.007), and those of sentinel lymph node biopsy only were 19.8% and 33.1%, respectively (p=0.007).

The most common histological type in both age groups was invasive ductal carcinoma (IDC) (Table 1). Significantly more medullary cancers occurred in the younger group than in the control group, while in the control group, in contrast with the younger patients, the second most frequent histological type was invasive lobular carcinoma (ILC). Poorly-differentiated high-grade tumours occurred significantly more frequently in the younger group, whilst well-differentiated and moderately-differentiated cancers were significantly more frequent among the controls (Table 1). No difference was observed in the pT status of the tumours. Significantly more pN0 tumours were noted in the control group, while the number of pN2 cases was significantly higher among the younger patients. Half of the cancers in the younger cohort were ER-negative, while two-thirds of those in the control group were ER-positive (p< 0.001). Comparatively more tumours were PR-positive and HER2-negative in the control group than in the younger group. The proportion of ER- and PR-positive tumours was, however, significantly higher in the young age than in the control group (p=0.006). The rates of triple-negative

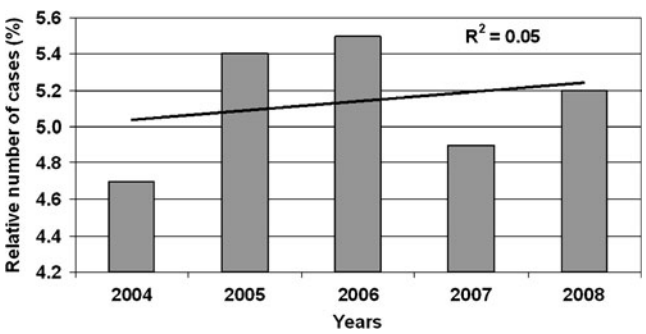

Fig. 1 Annual number of new breast cancer patients aged ≤40 years in proportion to the total number of all breast cancer cases in Hungary in 2004–2008 according to the National Cancer Registry (courtesy of Dr. István Gaudi)

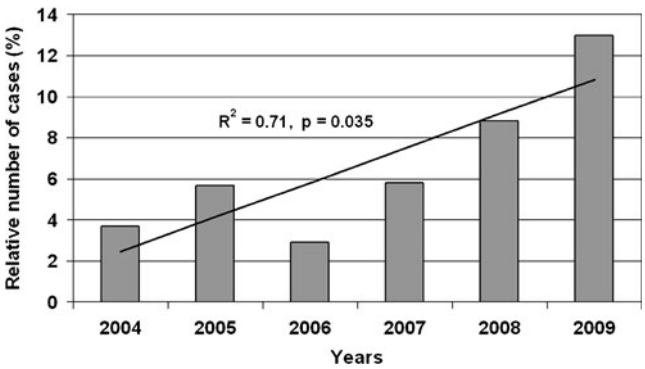

Fig. 2 Annual number of new breast cancer patients aged ≤40 years in proportion to the total number of all breast cancer cases at the Department of Oncotherapy, University of Szeged, in the period 2004–2009

Table 1 Pathological features of breast cancers in the younger and the control groups

Tumour features		Patients ≤40 years (n=141)		Patients >40 years (n=300)		p
		%	n	%	n	
Histolo-gical type	DCIS	4.3	6	8.7	26	0.116
	IDC	75.9	107	71.3	214	0.359
	medullary	4.3	6	1.0	3	0.033
	ILC	3.5	5	13.0	39	0.002
	other	12.0	17	6.0	18	0.037
pT	1–9 mm	9.9	14	14.3	43	0.225
	10–14 mm	21.3	30	23.0	69	0.715
	15–20 mm	22.7	32	24.7	74	0.720
	>20 mm	40.4	57	38.0	114	0.675
	unknown	5.7	8	0	0	–
pN	pN0	58.9	83	74.3	223	0.001
	pN1	16.3	23	17.3	52	0.892
	pN2	14.9	21	5.00	15	0.001
	pN3	6.4	9	3.4	10	0.206
	unknown	3.5	5	0	0	–
Grade	Grade 1	5.7	8	15.7	47	0.003
	Grade 2	29.8	42	43.3	130	0.007
	Grade 3	53.9	76	40.3	121	0.010
	Grade unknown	10.6	15	0.7	2	<0.001
ER	ER-positive	48.2	68	71.7	215	<0.001
	ER-negative	45.4	64	28.0	84	0.001
	ER unknown	6.4	9	0.3	1	<0.001
	proportion of ER-positive cells in ER-positive tumours (mean±SD)	61.0±22.55		74.0±17.69		0.070
PR	PR-positive	56.7	80	67.3	202	0.034
	PR-negative	38.3	54	32.0	96	0.198
	PR unknown	4.96	7	0.7	2	0.006
	proportion of PR-positive cells in PR-positive tumours (mean±SD)	67.0±19.52		70.3±19.51		0.761
HER2	HER2-negative	69.5	98	81.7	245	0.007
	HER2 2/3+	22.7	32	18.0	54	0.249
	HER2 unknown	7.8	11	0.3	1	<0.001
ER, PR and HER2-negative		25.2	31/123	13.5	40/297	0.026
ER-positive and PR-negative		6.6	9/136	16.1	48/298	0.006

cases in the younger and control groups were 25% and 13%, respectively (p=0.026) (Table 1). No significant differences were detected in the number of ER- and HER2-positive or grade 3 and ER-positive cases between the studied groups. Significantly more of the younger patients received chemotherapy (86.4% vs. 47.4%, p< 0.001), and a taxane-based chemotherapy (48.2% vs. 12.5% of all chemotherapies, p<0.001), whereas significantly more control patients received hormone therapy (64.1% vs. 50.4%, p=0.014). While 16 patients in the young age group received neoadjuvant chemotherapy, no such therapy was given in the control group.

Discussion

Our analysis confirmed a steady relative increase in the attendance at our department of breast cancer patients aged ≤40 years. Prognostic factors relating to biological behaviour, such as the histological type, grade, ER/PR status or stage, including the lymph node status, indicate more aggressive biological behaviour and a more advanced stage, with a worse overall prognosis, among these patients as compared with those >40 years.

An increase in the incidence of breast cancer at a comparatively young age has recently been demonstrated in

both well-developed and developing countries [1–3]. During the period 2004–2009, we found a roughly 50% yearly increase in the relative number of breast cancer patients aged ≤40 years attending our institute. On the basis of the data of the Geneva Cancer Registry, Bouchardy et al. reported an increase of the same magnitude in breast cancer cases among those aged ≤40 years in 2002–2004, after a steady state in the previous years. A major limitation of our analysis is that it is based on service data rather than population-based data, and thus no firm conclusions may be drawn on the changes in the incidence of the disease in this subgroup of women.

It has been suggested that, while the prognostic factors are poor in young breast cancer patients [4], the mortality rates are improving, probably as a result of the earlier diagnosis due to better breast-awareness and modern, more efficient therapy [13]. Although we did not analyse the outcome, the overall prognosis and the biological features of the breast cancers clearly differed between the cases in the younger and the control groups. The tumour characteristics were consistent with the findings of other studies [4, 6, 8, 10, 14], though mention should be made of the retrospective analysis by McAree et al., in which many of the pathological features were similar to those we observed, but medullary cancers were absent, and the high rate (76.8%) of ER-positive and the low rate (10.5%) of triple-negative breast cancers were striking among those aged <40 years [6]. In one group of breast cancer patients diagnosed under the age of 35, the proportion of "basal-like" breast cancers was 23% [12]. Since the rates of medullary and triple-negative cases were outstanding among the younger cases in our database, it may be speculated that BRCA1 mutation carriers were possibly over-represented, but no information on the genetic background of the patients was available. The differences between the two groups as regards surgical and medical therapy reflected the differences in stage and the biological features of the tumours.

Our findings demonstrate that breast cancer is not rare before the age of 40 years, and can then demonstrate particularly aggressive behaviour and a poor prognosis. Vigilance is needed to ensure its recognition and the provision of appropriate therapy.

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