LETTER TO THE EDITOR

Minimal Breast Cancer in Split Region of Croatia on the Eve of the National Mammographic Screening Program

To the Editor:

As a result of the worldwide use of screening mammography, many breast biopsies are now performed for small, usually nonpalpable, mammographically detected abnormalities. The breast biopsies of screened abnormalities contain a large number of so-called minimal breast cancers. This term includes all non-invasive cancers (Tis) and invasive cancers up to 1 cm in diameter (minimal invasive cancers, T1a,b) (1,2). In our previous work on the minimal breast cancers in Split region (period 1997–2001), the proportion of Tis and T1a,b cancers was 2.78% and 15.16%, respectively (3). These low proportions were concordant to the proportions of detected minimal breast cancers in developed countries in the prescreening period. Therefore, we advocated the introduction of regional and national breast cancer early detection programs (3).

The national breast cancer early detection program started in Croatia in the second half of 2006 under the auspices of Ministry of Health and Social Affairs. The screening method consists of mammography in 50–69-year-old women, with 2-year screening interval. The main goals of this program are reduction in breast cancer mortality for 25% over a 5-year period starting with the introduction of the program, detection of higher percentage of cancers at an early stage, and improvement of the life quality of the patients with breast cancer (4).

We wanted to explore basic pathohistologic characteristics of the breast cancer detected in Split region before the introduction of screening program, particularly the presence of the minimal breast cancers that are expected to be increasingly detected during screening program. Therefore, the results presented here may be used in future evaluation of screening success.

The pathohistologic data of 2,141 consecutively operated breast carcinomas in Clinical Hospital Center Split in the period from 1997 to 2006 were retrieved from the data base of Institute of Pathology and Cytology, Clinical Hospital Split, Croatia. The data (tumor size, histologic types of invasive and non-invasive tumors, differentiation grade, axillary lymph node status, and hormonal receptor expression) were collected over two 5-year periods (1997–2001/2002–2006), and statistically correlated to explore possible changing trends. According to the greatest diameter, the invasive tumors were divided in the following groups: the tumors with the diameter of ≤2 cm, 2–5 cm, and >5 cm. The cancers with the diameter of ≤2 cm were additionally divided in T1a,b tumors (diameter of ≤1 cm; microinvasive carcinomas (T1mic) are also included in this group), and T1c tumors (diameter of 1.1–2 cm) (5). Invasive and non-invasive tumors were histologically classified according to the WHO Classification of breast tumors (5). The grade of invasive tumors was assessed according to Elston and Ellis, and the grade of non-invasive ones according to the classification proposed by a group of European pathologists (6,7). The patients with one or more tumor positive lymph nodes were considered node positive (N+). Estrogen (ER) and progesterone receptor (PgR) status were determined mainly biochemically in the period 1997–2001, using the dextran-coated charcoal method (DCC) with cut-off level of 5 fmol/mg of protein for ER, and 10 fmol/mg of protein for PgR. In the period 2002–2006, the hormonal status was determined immunohistochemicaly using the standard avidin-biotin complex method. ER and PgR were considered positive, if there was nuclear staining in more than 10% of neoplastic cells.

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Statistical analysis was made using chi-squared test and *t*-test, and the significance of the differences was calculated as a p-value. In statistical analysis, only probabilities lower than 5% ($p < 0.05$) were considered significant. Statistical analysis was performed with the Statistical Package for Social Sciences, version 15.0 for Windows (SPSS, Chicago, IL).

Out of an overall number of 2,141 surgically removed breast cancers, 937 cases were detected in the period 1997–2001, while the remaining 1,204 cases were detected in the period 2002–2006 ($p < 0.001$). The mean and median tumor sizes of all invasive cancers are shown in Table 1. The distribution of all operated cancers according to the tumor's diameter is shown in Table 2. In the group of invasive tumors, 41.62% of the cancers was lymph node positive. The percentage of the lymph node positive T1a,b cancers was 17.42%. Among the invasive cancers, the commonest histologic types were ductal and lobular ones (69.7% and 11.4%, respectively), with the predominance of the grade II tumors (43.5%). The percentage of hormone positive cancers increased from 72.5% to 81.4% during the correlated periods ($p < 0.001$). The ductal type of Tis was predominant (69%), with commedo and cribriphorm forms as the commonest histologic subtypes, and with equal distribution of the grade II and grade III tumors.

Table 1. Mean and Median Tumor Size of All Invasive Cancers

Period	Mean (±SD) tumor size (cm)	Median (range) tumor size (cm)	p*
1997–2001	2.65 ± 2.146	2.0 (0.2–20)	0.018
2002–2006	2.43 ± 1.860	2.0 (0.3–25)	
1997–2006	2.54 ± 1.998	2.0 (0.2–25)	

*t-test.

Table 2. Distribution of Breast Cancers According to the Greatest Diameter (TNM)

T	Total (%)	1997–2001 (%)	2002–2006 (%)	p*
Tis	113 (5.28)	26 (2.78)	87 (7.23)	<0.001
T1a,b (≤1 cm)	333 (15.55)	142 (15.16)	191 (15.86)	0.653
T1c (1–2 cm)	705 (32.93)	312 (33.3)	393 (32.64)	0.748
T2 (2–5 cm)	756 (35.31)	353 (37.63)	403 (33.46)	0.043
T3 (>5 cm)	131 (6.12)	70 (7.47)	61 (5.08)	0.021
Unknown	103 (4.81)	34 (3.62)	69 (5.73)	0.024

*Chi-squared test.

The presented data (mean diameter of invasive cancers of 2.54 cm, small percentage of minimal breast cancers, and 41.62% of lymph node positive cancers) confirm the need for the introduction of the population-based mammographic screening program. However, we noticed a significant decrease in the mean tumor size during the two compared periods (2.65 cm to 2.43 cm, $p = 0.018$), probably because of better public awareness with higher number of the women with performed mammography or breast ultrasound exams (opportunistic screening). We also noticed a significant increase in detected Tis during these periods (2.78% to 7.23%, $p < 0.001$), mainly because of the introduction of digital mammography with stereotactic equipment for biopting lesions with microcalcifications during the second period. The performed stereotactic biopsies mostly showed non-invasive carcinomas pathohistologically, confirmed later on the excisional surgical biopsies.

The expected increase in the number of detected minimal cancers during the future screening may cause some diagnostic problems. Pathohistologic interpretation of minimal cancers, particularly of non-invasive types, and of the other borderline-screened abnormalities needs experienced pathologists, well trained in the field of breast pathology (8,9). Except the basic education in breast pathology during the residency program, additional educational programs are rare in Croatia. Additionally, despite the facts that the nationally standardized diagnostical and therapeutic procedures proposed by Croatian Senologic Society exist, they are not always followed in routine practice. The aforementioned problems might seriously hamper established screening goals. The Global Summit Early Detection Panel suggests that screening in the countries with low or medium level resources could be implemented within centralized cancer facilities in which the best practice breast cancer diagnosis and treatment is available. This institution-based screening could be a pilot program for the future one, which would cover the entire population, give an opportunity for an insight into the problems and raise the consciousness of the screening importance in population (10). As we expect low response rate to the screening invitations and problems with radiologic and surgical part of screening program, it would be ideal to introduce such pilot program in the large regional Croatian centres with the best practice health care institutions as the first step, rather than to implement the screening program in the whole country at once.

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