

# DEMOGRAPHIC AND CLINICOPATHOLOGIC FEATURES OF PATIENTS WITH PRIMARY BREAST CANCER TREATED BETWEEN 1997 AND 2010: A SINGLE INSTITUTION EXPERIENCE

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**SUMMARY** – Breast cancer accounted for 28% of all new cancers and 18% of female cancer deaths in Europe in 2010. It is the most common type of cancer in women in Croatia, with an incidence rate of 56.9/100 000 in the year 2010, and the highest number of newly diagnosed women aged between 60 and 64. Multiple factors are associated with an increased risk of breast cancer: advancing age, family history, exposure to endogenous and exogenous reproductive hormones, dietary factors, benign breast disease, and environmental factors. To assess demographic and clinicopathologic features of primary breast cancer, we retrospectively analyzed 870 patients treated in our institution between 1997 and 2010. Data were obtained from medical documentation and a printed questionnaire regarding life habits. Most of our patients presented with a breast lump and were self-diagnosed by breast examination. This fact highlights the need of regular breast self-examination, although it should also be taken into account that most of our patients did not attend regular mammography screening (only 31%). One of the most concerning facts is that the mean time from observing the first symptom to visiting a physician was 4 months. Previous studies have identified ignorance, fear and fatalistic attitudes, poor socioeconomic conditions, and illiteracy as important factors resulting in delay. Considering these facts, education and raising awareness about the disease in the general population is one of the key weapons for lowering breast cancer mortality.

**Key words:** *Breast neoplasms – pathology; Breast neoplasms – epidemiology; Breast neoplasms – diagnosis; Risk factors; Early detection of cancer; Patient education as topic*

## Introduction

Breast cancer is a major health problem for women throughout the world. In 2010, it was the most common type of cancer in Europe in women, accounting for 28% of all new cancers and 18% of female cancer deaths<sup>1</sup>. The lowest mortality rates from breast cancer have been reported in Bulgaria, Portugal, Spain and

Sweden, as well as Norway (<20/100 000 females), while the highest rates are in Belgium and Denmark (approximately 30/100 000 females)<sup>2</sup>. In 2011, 11191 men and 9319 women were diagnosed with invasive form of cancer in Croatia. Out of these 9319 women, 2094 had breast cancer, the most common type of cancer in women in Croatia, with a standardized incidence rate of 50.1/100 000, and the highest number of newly diagnosed women aged 60-64 in the year 2010. Data analysis from the Croatian National Cancer Registry shows that the number of new breast cancer cases in the 1998-2008 period increased from 1220 to 2472, and that the age-standardized inci-

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dence rate increased from 35.5 to 61.9/100 000. The number of deaths also increased from 670 to 902, but with no change in the age-standardized rate, which is approximately 18/100 000<sup>3</sup>. Considering the calendar period, there was a significantly increasing trend in the incidence, with estimated annual percent change (EAPC) of 2.6%, while it was -0.3% for mortality trend. The incidence increased in all age groups, most pronouncedly in women aged 60-69 in 2005, with EAPC of 14.2% for the 2005-2008 period. Mortality rate decreased in younger women aged 30-49, but increased in women older than 60. In women aged 50-59, mortality rate increased in the 1988-1999 period, but decreased afterwards<sup>4</sup>. Regarding breast cancer incidence and mortality, Croatia is among European countries with an intermediate incidence and mortality, with a comparable incidence increase in the 1990-2002 period as well. This increase could be the result of lifestyle changes (a higher number of obese women, higher alcohol consumption, increased age at first delivery, use of hormonal therapy, and implementation of the national screening program, launched in 2006).

Breast tumors are divided into invasive cancer (not otherwise specified (NOS)), special subtypes including invasive lobular, tubular, cribriform, medullary, adenoid cystic, and many others. The most common form of breast cancer is invasive carcinoma (NOS), which accounts for 70%-80% of all cases<sup>5</sup>. Lobular carcinoma is the second most common histologic type of breast cancer, and can be noninvasive or invasive. Other histologic types of breast cancer are Paget's disease, Paget's disease with intraductal carcinoma, Paget's disease with invasive ductal carcinoma, undifferentiated carcinoma, phyllodes tumor, angiosarcoma, and primary lymphoma. Non-ductal cancers account for approximately 20%-30% of invasive carcinomas; at least 90% of a tumor should demonstrate defining histologic characteristics of a special type of cancer to be designated as this histologic type<sup>5</sup>.

Multiple factors are associated with an increased risk of breast cancer: advancing age, positive family history, exposure to endogenous and exogenous reproductive hormones, dietary factors, benign breast disease, and environmental factors<sup>6</sup>. The majority of these factors convey a small to moderate increase in the risk for any individual woman.

## Patients and Methods

All patients with primary breast cancer treated in our institution between 1997 and 2010 were included in this study. A total of 870 patients were retrospectively analyzed. Data were obtained from medical documentation and a printed questionnaire regarding life habits. All patients gave their consent to participate in the study. Demographic characteristics included age at the time of diagnosis, personal and family history of cancer, menstrual history and reproductive behavior, occupation, and type of diet. Questions also addressed perception of the lump and time to medical treatment (i.e. delay in treatment). Clinicopathologic characteristics included tumor size, location, other features such as skin inflammation, retraction, fixation, and ulceration, then clinical stage, histologic type, lymph node metastases (number and group of lymph nodes, extracapsular spread), and hormonal receptor- and HER2/neu status. In a small percent of women, data were not available for some categories analyzed.

## Results

Eight hundred and seventy patients were analyzed. All patients were females. Demographic characteristics, menstrual history and reproductive findings are shown in Table 1. Mean age was 69 years, most women were perimenopausal with an average length of fertile life of 35 years. Only 8% (n=71) of women were exposed to exogenous hormones (i.e. oral contraceptives), most of them for less than 5 years. Some 15% of them were smokers, hardly any consumed alcohol (0.7%), and the preferred diet was mixed. Sixty-three percent of women were employed, more than half with a sedentary occupation. Fifteen percent of women were nulliparous, the mean number of children *per* woman was 1.6, and only 5% gave birth to their first child after the age of 35. Thirty percent had benign breast disease prior to breast cancer diagnosis. Mean age at diagnosis was 59 years, and only 31% of women had regular mammography screening prior to the breast cancer diagnosis.

Family history for breast and/or ovarian cancer was positive in 19% of patients, mostly for breast cancer (96%). Six percent of women had positive personal history, i.e. they had been previously treated for some other malignancy (Table 2).

Table 1. Demographic and reproductive characteristics (N=870)

Category	Number (%)
Employment	
Unemployed	281 (32.3%)
Employed	552 (63.4%)
Not analyzed	37
Occupation	
Sedentary	371 (67.2%)
Active	181 (32.8%)
Constitution	
Skinny	17 (2%)
Medium	313 (36%)
Fat	126 (14.5%)
Not analyzed	414
Breast size	
Small	101 (11.6%)
Medium	407 (46.8%)
Voluminous	347 (39.9%)
Not analyzed	15
Diet	
Meat	23 (2.6%)
Mixed	821 (94.4%)
Fat rich	10 (1.1%)
Vegetarian	2 (0.2%)
Not analyzed	14
Smoking	
Yes	127 (14.6%)
No	742 (85.3%)
Not analyzed	1
Alcohol	
Yes	6 (0.7%)
No	863 (99.2%)
Not analyzed	1
Use of oral contraceptives	
<5 years	44 (5.1%)
≥5 years	27 (3.1%)
No history of use	799 (91.8%)
Menstrual status	
Fertile	68 (7.8%)
Perimenopause	736 (84.6%)
Postmenopause	64 (7.4%)
Not analyzed	2

Most women had palpable tumor presenting as a breast lump, discovered in the majority of cases by patients themselves. In one-third of patients, breast lump was found by a physician, and in less than 1% it

Table 2. Personal and family history (N=870)

Category	Number (%)
Positive family history for breast and/or ovarian cancer	
Yes	168 (19.3%)
Breast cancer	162 (96.4%)
Ovarian cancer	6 (3.6%)
No	702 (80.7%)
Positive personal history	
Yes	50 (5.7%)
No	819 (94.1%)
Not analyzed	1

was an accidental finding on ultrasound or mammography. Average time from self-diagnosis to first visit to a physician was around 4 months (Table 3).

In 95% of women, there were no physical findings other than breast lump. In the rest, the most common physical finding was skin ulceration. Primary tumor was mostly localized in the upper lateral quadrant, with a mean size of 2.5 cm. The most common histology was invasive carcinoma (NOS), of which 66% of tumors were moderately, 21% poorly, and 13% well differentiated. Cancer cells were ER and PR positive in 62% and 55% of women, respectively. Only 8% of women had HER2/neu positive tumors, but in more than half of women HER2/neu receptor status was not analyzed (Table 4). The mean number of evacuated lymph nodes was 11.32, mean number of posi-

Table 3. Diagnosis (N=870)

Category	Number (%)
Palpable tumor	
No	13 (1.5%)
US, mammography	3 (23.1%)
Other	10 (76.9%)
Yes	856 (98.4%)
Self-diagnosed	577 (67.4%)
Physician	279 (32.6%)
Not analyzed	1
Mean time from self-diagnosis to first visit to physician (months)	4.28

US = ultrasonography

Table 4. Clinico-pathological characteristics of primary tumor (N=870)

Category	Number (%)
Primary tumor location	
Upper lateral quadrant	457 (52.5%)
Lower lateral quadrant	78 (9%)
Upper medial quadrant	86 (9.9%)
Lower medial quadrant	35 (4%)
Areolar	97 (11.1%)
Multilobular	8 (0.9%)
Multicentric	63 (7.2%)
Not analyzed	46
Histology	
Not otherwise specified (NOS)	742 (85.3%)
Lobular	55 (6.3%)
Inflamed	4 (0.5%)
Papillary	7 (0.8%)
Tubular	9 (1%)
Medullary	14 (1.6%)
Mucinous (gelatinous)	14 (1.6%)
Cribriform	4 (0.5%)
Adenocarcinoma	3 (0.3%)
Paget's disease	4 (0.5%)
Neuroendocrine	3 (0.3%)
Histiocytoma	1 (0.1%)
Sarcoma	1 (0.1%)
Squamous cell carcinoma	4 (0.5%)
Not analyzed	5
Receptor status	
Estrogen receptors (ER)	
Positive	541 (62.2%)
Negative	215 (24.7%)
Not analyzed	114
Progesterone receptors (PR)	
Positive	477 (54.8%)
Negative	212 (24.4%)
Not analyzed	181
HER2/neu receptors	
Positive	72 (8.3%)
Negative	328 (37.7%)
Not analyzed	470

tive lymph nodes 2.64, and extracapsular spread was found in 6% of patients. The mean size of the largest node was 1.64 cm. At the time of diagnosis, distant metastases were found in only 32 (3.7%) women, with bones being the most common site of distant spread (Table 5).

Table 5. Distant metastases (N=870)

Distant metastases at the time of diagnosis	Number (%)
No	837 (96.2%)
Yes	32 (3.7%)
Bones	18 (56.3%)
Lung	0
Liver	4 (12.5%)
Brain	0
Skin	3 (9.4%)
Lymph nodes	2 (6.3%)
Multiple	3 (9.4%)
Other	2 (6.3%)
Not analyzed	1

Table 6. Treatment (N=870)

Category	Number (%)
Surgery	
Radical	407 (46.8%)
Breast conserving	460 (52.9%)
Inoperable	1 (0.1%)
Not analyzed	2
Radiotherapy	
Primary	2 (0.2%)
Adjuvant	812 (93.3%)
None	50 (5.7%)
Not analyzed	6
Chemotherapy regimens	
Applied - Adjuvant	392 (45.1%)
CMF	54 (13.8%)
FEC	259 (66.1%)
FAC	33 (8.4%)
AC	44 (11.2%)
EC	2 (0.5%)
Not applied	477 (54.8%)
Not analyzed	1
Applied - Neoadjuvant	13 (1.5%)
CMF	3 (23.1%)
FEC	9 (69.2%)
FAC	1 (7.7%)
Not applied	856 (98.4%)
Not analyzed	1
Hormonal therapy	
No	405 (46.6%)
Yes (tamoxifen)	463 (53.2%)
Not analyzed	2

CMF = cyclophosphamide, methotrexate and 5-fluorouracil; FEC = 5-fluorouracil, epirubicin and cyclophosphamide; FAC = 5-fluorouracil, doxorubicin and cyclophosphamide; AC = doxorubicin and cyclophosphamide; EC = epirubicin and cyclophosphamide

The most common surgical procedure was breast conserving therapy (53%), and 93% of women received adjuvant radiotherapy. Adjuvant chemotherapy was administered in 45% of patients, most commonly FEC (5-fluorouracil, epirubicin and cyclophosphamide) regimen. More than half of patients (53%) were treated with hormonal therapy as well (Table 6).

## Discussion

Our analysis showed the mean age at diagnosis to be 69, which is in accordance with the results from other European countries<sup>2</sup>. As in many other malignant tumors, age is an important and independent risk factor for breast cancer as well<sup>6</sup>. Less than 2% of our patients were younger than 35, and the youngest one was 25 years old.

Considering lifestyle factors, physical activity reduces the risk of breast cancer by approximately 25%<sup>7</sup>. Most of our patients had sedentary occupation and spent most of their daily hours inactive, so there was no protective effect that any kind of regular, daily physical activity could ensure. Regarding other habits, it is known from the literature that there appears to be a positive association between alcohol consumption and breast cancer risk, with the risk increasing linearly with the amount of alcohol consumed<sup>8</sup>. Surprisingly, only a very small percent of our study patients declared themselves as smokers (15%) and alcohol consumers (0.7%). Since these numbers are not even close to the percentage of smokers and especially alcohol consumers in the Croatian general population, it is likely that most women did not want to admit their habit, probably because of shame, judgment, fear, or some other reasons. Obesity is also associated with an increased risk of both breast cancer development in postmenopausal women and increased breast cancer mortality<sup>6</sup>. According to one survey<sup>9</sup>, the prevalence of obesity in Croatian people, both men and women, was 11% and of overweight 46%, with the critical age at getting overweight from 35 to 49 years. Only 14% of our patients were overweight and obese, and had an increased risk of breast cancer as a result of their adiposity.

The observation that there is large international variation in breast cancer incidence, with countries with high fat diets having higher rates of breast cancer than those with diets lower in fat, suggests that high

fat intake might be associated with an increased breast cancer risk. However, pooled analysis of seven prospective epidemiological studies failed to identify an association between fat intake and breast cancer risk in adult women in developed countries<sup>10</sup>. In our analysis, most women practiced balanced diet with adequate amounts of all nutrients, and only 1.1% consumed fat rich diet. According to the literature, there may be a moderate protective effect of high vegetable consumption, but results for fruit, fiber and meat consumption are inconclusive.

Epidemiological studies have identified a number of breast cancer risk factors associated with increased exposure to endogenous estrogens<sup>11</sup>. Early age at menarche, nulliparity, late age at first full-term pregnancy, and late age at menopause increase the risk of developing breast cancer. In postmenopausal women, obesity and postmenopausal hormone replacement therapy, both of which are positively correlated with plasma estrogen levels and plasma estradiol levels, are associated with an increased breast cancer risk<sup>12,13</sup>. Age at menarche and regular ovulatory cycles are strongly linked to breast cancer risk<sup>6</sup>. Earlier age at menarche is associated with an increased risk of breast cancer; there appears to be a 20% decrease in breast cancer risk for each year that menarche is delayed. In our analysis, the mean age at menarche was 13.7 years, which is according to the literature considered to be similar to the general population (13.3 years)<sup>14</sup>. Additionally, late onset of menarche results in a delay in regular ovulatory cycles. From these data, it seems that total duration of exposure to endogenous estrogen is an important factor in breast cancer risk. Mean age at menopause in our patients was 48.8 years, which taken together with mean age at menarche resulted in the mean duration of fertile life of 34.7 years, which is similar to the general population. Based on epidemiological studies, women whose first full-term pregnancy occurs after age 30 have a two- to fivefold increase in breast cancer risk in comparison to women who have first full-term pregnancy before age 18<sup>15</sup>. Our data showed that 5% of women gave birth to their first child after the age of 35. Nulliparous women are also at an increased risk of developing breast cancer, with a relative risk of about 1.4. Most of our patients were multiparous, while 15% of women were nulliparous.

Positive family history was observed in 19% of patients; when analyzed for breast and ovarian cancer family history, 96% of these patients had a relative with breast cancer. The impact of family history as a risk factor depends on the number of relatives with breast cancer, the exact relationship, the age at diagnosis, and the number of unaffected relatives. North American investigators with special interest in familial breast cancer have described positive family history (first- or second-degree relatives) in up to one-third of patients<sup>16</sup>. Only 5% to 10% of women with BRCA1 and BRCA2 gene mutations have a true hereditary predisposition<sup>17</sup>.

Most of our patients presented with a breast lump and were self-diagnosed by breast examination. This fact highlights the need of regular breast self-examination, although it should also be taken into account that most of our patients did not attend regular mammography screening. If so, greater part of these tumors would have probably been found and diagnosed at an earlier stage of the disease. In contrast to developed countries, where a high percent of women after the age of 50 have yearly mammograms<sup>18-20</sup>, in our study only 31% of women attended regular mammography screening prior to breast cancer diagnosis. Hopefully, these unfavorable results will change since the national screening program for breast cancer was introduced in 2006. One of the most concerning facts is that the mean time from observing the first symptom to visiting a physician was 4 months. Previous studies have identified ignorance, fear and fatalistic attitudes, poor socioeconomic conditions, and illiteracy as important factors resulting in delay<sup>21-23</sup>. In this analysis, information about the reasons for delayed seeking medical advice was not discussed in detail with patients, but one can conclude that it was a matter of dissimulation and fear. Considering these facts, education and raising awareness about the disease in the general population is one of the key weapons for lowering breast cancer mortality. Failure to visit a physician promptly has surely led to a higher disease stage at diagnosis in some patients; more than one-third were diagnosed with locally advanced disease, i.e. metastases in axillary lymph nodes. Fortunately, only 4% had distant metastases at the time of diagnosis. The mean number of evacuated lymph nodes was 11.32 and the mean number of positive lymph nodes was 2.64. Extracapsular spread was found in only 6% of patients. The most common histology was ductal carcinoma (86%), whereas no unusual incidence was recorded for other types. Cancer was most often localized in the upper lateral quadrant of the breast. Less than one-third of patients had tumor cells negative for hormonal receptors. Only 8% had positive HER2 tumors, but our analysis was insufficient here because information about HER2/neu receptor status was unknown in 54% of patients; in a small percent of these patients, supplementation of histopathologic diagnosis was not available at the time of recruitment, but in the majority of them probably not performed due to the fact that immunohistochemical analysis for HER2/neu receptor was not a routine procedure in Croatia until 2003. Data regarding Ki-67 proliferation index were not available.

The most common surgical procedure performed on these patients was breast conservation followed by adjuvant radiotherapy. However, a significant percent of women (47%) underwent radical mastectomy. When analyzed chronologically, radical mastectomy was the most common type of surgery until 2002 and most of these women were operated in that period. After 2002, breast conserving surgery has become a standard. Ninety-four percent of patients received adjuvant radiotherapy, which can be explained by the above mentioned locally more advanced disease, as well as the type of surgery. Considering chemotherapy, it was applied in 405 (46.6%, mostly in adjuvant setting) women and consisted mostly of 5-fluorouracil, epirubicin and cyclophosphamide (FEC regimen), most often used in other countries as well.

In conclusion, our data show that patients with breast cancer treated in our institution from 1997 to 2010, when compared to their European counterparts, more often presented with locally advanced disease at the time of diagnosis, with T2 primary tumor and N2 lymph node stage. There was no apparent change in lifestyle throughout the years that would significantly increase the risk of breast cancer (smoking, alcohol, obesity), but the number of sedentary professions was higher in the last decade. Considering surgical and oncologic treatment, our patients were treated according to current standards. The most important information obtained was the one about the time from self-diagnosis to seeking physician's advice, which was as

long as 4 months. It is a major social and healthcare problem, and reduces the possibility of complete recovery. In order to improve the outcome of these patients, it is essential to understand the reasons behind delayed presentation and to take appropriate remedial measures. More intensive health promotion and education is needed. There is a great need to additionally increase public awareness and make the most of the national screening program.

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## Sažetak

## DEMOGRAFSKA I KLINIČKO-PATOLOŠKA OBILJEŽJA BOLESNICA S PRIMARNIM RAKOM DOJKE LIJEČENIH U RAZDOBLJU OD 1997. DO 2010. GODINE: ISKUSTVO JEDNE KLINIKE

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U europskoj populaciji rak dojke činio je 2010. godine 28% svih novodijagnosticiranih zloćudnih tumora te bio uzrokom smrti u 18% žena oboljelih od raka. Prvi je po učestalosti zloćudni tumor u žena u Hrvatskoj, s incidencijom od 56,9/100.000 (2010. godine), a najveći broj bolesnica dijagnosticira se u dobi između 60 i 64 godine. Rizični čimbenici za rak dojke su višestruki: dob, pozitivna obiteljska anamneza, izloženost endogenim i egzogenim hormonima, prehrana, dobroćudna bolest dojke te okolišni čimbenici. Radi procjene demografskih i kliničko-patoloških značajka primarnog raka dojke retrospektivno smo analizirali 870 bolesnica koje su liječene u našoj ustanovi između 1997. i 2010. godine. Podaci su prikupljeni iz medicinske dokumentacije te formuliranog upitnika koji se odnosio na životne navike. U većine bolesnica se bolest prezentirala kao čvor u dojci te su bolest dijagnosticirale same. Ova činjenica naglašava potrebu redovitog samopregleda, iako također treba uzeti u obzir činjenicu da je tek manji broj bolesnica redovito pohađao kontrolne mamografske preglede (31%). Zabrinjava podatak da je prosječno vrijeme od prvog simptoma bolesti do javljanja liječniku bilo čak 4 mjeseca. Prema ranijim studijama najvažniji razlozi odgode javljanja liječniku su neznanje, strah i fatalistički odnos prema bolesti, niži socioekonomski status te nepismenost. U skladu s dobivenim rezultatima, izobrazba i podizanje svijesti o bolesti u općoj populaciji među ključnim su metodama za snižavanje smrtnosti od raka dojke.

Ključne riječi: *Dojka, tumori – patologija; Dojka, tumori – epidemiologija; Dojka, tumori – dijagnostika; Čimbenici rizika; Rano otkrivanje tumora; Bolesnik, edukacija kao tema*