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ORIGINAL RESEARCH

Association of carcinoembryonic antigen (CEA) and cancer antigen 15-3 (CA 15-3) with socio-demographic factors and metastases site in women with metastatic breast cancer in Albania

Adrian Hoti[1], Edmond Gashi[1], Fationa Kraja[1], Agim Sallaku[1]

[1] Oncology Service, University Hospital Centre "Mother Teresa", Tirana, Albania.

Corresponding author: Dr. Adrian Hoti
Address: Rr. "Dibres", No. 370, Tirana, Albania;
Telephone: +355672024078; E-mail: dr.ahoti@yahoo.com

Abstract

Aim: The aim of our study was to assess the association of carcinoembryonic antigen (CEA) and cancer antigen 15-3 (CA15-3) with socio-demographic factors and metastases site in women diagnosed with metastatic breast cancer in post-communist Albania.
Methods: A case-series study was carried out during the period January 2010 – September 2017 including 110 female patients diagnosed with breast cancer with metastases at the Oncology Service of the University Hospital Centre "Mother Teresa" in Tirana, the Albanian capital. Of these, 57 (51.8%) patients had evidence of hepatic metastases, whereas the reaming 53 (48.2%) patients had metastases in the bones and/or in the lungs. CEA and CA15-3 were measured at the time of diagnosis for all study participants. In addition, information on socio-demographic factors was collected. General linear model was used to assess the relationship of CEA and CA15-3 with covariates.
Results: There was evidence of a significant correlation between CEA and CA15-3 levels (Spearman's rho=0.59, P<0.001). Upon simultaneous adjustment for all covariates, mean values of CEA and CA15-3 were significantly higher in patients with metastases in the bones and/or in the lungs compared with their counterparts with metastases in the liver. Also, CA15-3 levels were significantly higher in younger patients compared with their older counterparts.
Conclusion: This study provides valuable evidence on selected correlates of CEA and CA15-3 in Albanian female patients diagnosed with metastatic breast cancer. Oncologists and other health professionals in Albania, as well as decision-makers and policymakers should be aware of the burden and risk factors of breast cancer among women in this transitional society.

Keywords: Albania, bone metastases, breast cancer, cancer antigen 15-3 (CA15-3), carcinoembryonic antigen (CEA), hepatic metastases, lung metastases, oncology, tumours, tumour markers.

Conflicts of interest: None.

Introduction

Breast cancer is a serious issue and an important public health problem in all countries worldwide. It has been convincingly documented that breast cancer leads to death of more women than any other type of malignant tumours (1). A recent systematic review reported that, at a global scale, breast cancer is the most frequently diagnosed cancer and the leading cause of cancer mortality among women (1). It has been reported that the incidence of breast cancer increases by 5% each year in low- and middle-income countries representing an increasingly urgent public health problem in these countries, similar to the situation observed in higher income countries (1-3). Many studies on this matter have addressed several risk characteristics (etiological factors) for breast cancer including reproductive characteristics, growth, obesity, and postmenopausal hormones (1,4). Nonetheless, these putative etiological factors are responsible only for a small proportion of breast cancer risk (1,4). The prognosis of breast cancer depends on a wide range of factors and circumstances including tumour biology, histology, peritumoural vascular invasion, tumour size, lymph node involvement, receptor status and presence of distant metastasis (5). Furthermore, it has been indicated that the skeleton is the most frequent site of metastasis in breast cancer patients (5).

Cancer antigen 15-3 (CA15-3) and, to a lesser degree, carcinoembryonic antigen (CEA) are the tumour markers most strongly related to recurrence in asymptomatic breast cancer patients (6,7). Yet, these antigens lack specificity, and the American Society of Clinical Oncology (ASCO) does not recommend their use in routine follow-up of patients treated for breast cancer (8). In addition, it has been argued that an increase in these tumour markers does not predict the number of involved sites or their localization (9).

According to the Global Burden of Disease (GBD) Study, the mortality rate from breast cancer in Albania was estimated at 15.2 deaths per 100,000 females in the year 2016 (10). On the other hand, for the same year, the Disability-Adjusted Life Years (DALYs) for breast cancer were estimated at about 441 per 100,000 (10). According to the GBD estimates, there has been a steady increase in the mortality rate and the burden of breast cancer in Albanian women for the period 1990-2010, which was followed by a plateau during the past few years (10). However, the validity of such estimates is questionable and open to criticism.

On the other hand, according to the most recent World Health Organization (WHO) report released in 2017 (11), the estimated breast cancer incidence in females in Albania is 30.8 per 100,000 population. The WHO European Region average is 106.7 per 100,000 population, which is substantially higher than in Albania. As a matter of fact, the incidence rate of breast cancer in Albanian females is lower than in all countries of the South Eastern European region. The highest incidence rate in this region is evident in Slovenia (125.0 per 100,000 population) followed by Croatia (116.1 per 100,000 population) and Montenegro (114.9 per 100,000 population) (11).

In any case, to date, the available scientific evidence about the burden of breast cancer in the general female population in Albania is scarce. Likewise, there are no scientific reports about the main risk factors or determinants related to breast cancer occurrence among Albanian females during the transition period in the past two decades.

In this framework, the aim of this study was to assess the association between CEA and CA15-3 with socio-demographic factors and metastases site in women diagnosed with metastatic breast cancer in post-communist Albania, a country characterized by a particularly rapid transition towards a market-oriented economy which is associated with tremendous changes also in lifestyle patterns of the adult population.

Methods

A case-series study was carried out in Tirana during the period January 2010 – September 2017. This study involved 110 female patients diagnosed with breast cancer with metastases at the Oncology Service of the University Hospital Centre "Mother Teresa" in Tirana, the Albanian capital city.

The different sites of metastases were dichotomized in the current analysis into: liver metastases vs. bones and/or lungs metastases.

CEA and CA15-3 levels were measured for each study participant at the time of diagnosis.

In addition, a structured questionnaire was administered to all the female patients in order to collect information on socio-demographic characteristics including age (which in the analysis was dichotomized into: ≤50 years vs. ≥51 years), district of current residence (dichotomized into: Tirana vs. other districts of Albania), place of residence (urban areas vs. rural areas), educational attainment (trichotomised in the analysis into: 0-8 years, 9-12 years and ≥13 years of formal schooling), economic level (also trichotomised into: low, middle, high) and employment status (nominal variable: employed, unemployed, retired).

Spearman's correlation coefficients were used to assess the association between CEA, CA15-3, age, and educational attainment (introduced as the number of years of formal schooling).

On the other hand, general linear model was employed to assess the associations of CEA and CA15-3 with socio-demographic characteristic and metastases site of female patients diagnosed with metastatic breast cancer. From a methodological point of view, the general linear model procedure provides regression analysis and analysis of variance for one dependent variable by one or more factors (referred to as variables). Using the general linear model procedures one can test the null hypothesis about the effects of other variables on the means of various groupings of a single dependent variable. In the current analysis, this feature of the general linear model was used in order to compare the mean values of CEA and CA15-3 by different categories of socio-demographic factors (age-group: ≤50 years vs. ≥51 years; district of residence: Tirana vs. other districts of Albania; place of residence: urban vs. rural areas; educational level: 0-8, 9-12, ≥13 years; economic level: low, middle, high; employment status: employed, unemployed, retired) and metastases site (liver vs. bones and/or lungs). Initially, age-adjusted mean values and their respective 95% confidence intervals (95%CIs) were calculated. Subsequently, multivariable-adjusted (simultaneous adjustment for: age-group, district of residence, place of residence, educational attainment, income level, employment status and metastases site) mean values and their respective 95%CIs were calculated.

SPSS (Statistical Package for Social Sciences, version 17.0), was used for all the statistical analyses.

Results

Overall, mean age of the study population was 57.1±11.9 years (median age: 57.5 years; interquartile range: 48.0-66.0 years; age range: 26-83 years).

Of 110 women included in this study, 57 (51.8%) patients had evidence of hepatic metastases, whereas the reaming 53 (48.2%) patients had metastases in the bones and/or in the lungs.

On the whole, 38% of participants had a low educational level; about 32% reported a low economic level; and 36% of participants were unemployed (data not shown in the tables).

Table 1 presents the distribution of CEA and CA15-3 levels in the sample of female patients with breast cancer included in this study.

Mean (SD) value of CEA was 19.1±23.9 ng/ml (median value: 12.9 ng/ml; interquartile range: 4.7-22.1 ng/ml).
On the other hand, mean (SD) value of CA15-3 was 167.2±205.2 U/mL (median value: 94.7 U/mL; interquartile range: 27.5-219.5 U/mL). Of note, both CEA and CA15-3 values displayed a highly skewed distribution as evidenced in Table 1 by their respective measures of dispersion (that is standard deviation).

Table 1. Distribution of CEA and CA15-3 in the study population

PARAMETER	CEA (ng/ml)	CA15-3 (U/mL)
Mean (±SD)	19.1±23.9	167.2±205.2
Median (IQR)	12.9 (4.7-22.1)	94.7 (27.5-219.5)
Range	1.7-133.2	6.1-1026.0

There was evidence of a significant correlation between CEA and CA15-3 levels (Spearman's rho=0.59, P<0.001) [Table 2]. Furthermore, there was evidence of a significant inverse linear association between CA15-3 and age (rho= - 0.43, P<0.001), but a positive relationship with education which was only borderline statistically significant (rho=0.42, P=0.1).
Interestingly, there was a significant inverse correlation between age and educational attainment (rho= -0.52, P=0.02).

Table 2. Correlational matrix of CEA, CA15-3 and socio-demographic characteristics

VARIABLE	CEA	CA15-3	Age
CA15-3	0.59 (<0.001)*	-	-
Age	-0.04 (0.704)	-0.43 (<0.001)	
Years of formal schooling	0.36 (0.109)	0.42 (0.097)	-0.51 (0.023)

* Spearman's correlation coefficients and their respective p-values (in parentheses).

Table 3 presents the association between CEA and socio-demographic characteristics and metastases site. In age-adjusted general linear models, there was evidence of a borderline statistically significant association of CEA with age-group (mean CEA level was higher among younger participants) and district of residence (mean CEA level was lower among Tirana residents).
Furthermore, mean CEA level was higher among the low-educated female patients compared with their high-educated counterparts (overall P=0.06). In particular, mean CEA level was considerably higher in patients with metastases in the bones and/or lungs compared with those with metastases in the liver (27.2 ng/ml vs. 13.5 ng/ml, respectively; P<0.01).
Upon simultaneous adjustment for all covariates, there was no evidence of significant associations of CEA with any socio-demographic factors, whereas the strong and significant relationship with metastases site persisted (mean CEA level was 24.5 ng/ml in patients with bones and/or lungs metastases compared with 11.9 ng/ml in those with liver metastases; P<0.01).

Table 3. Association of CEA with socio-demographic characteristics and metastases site; age-adjusted and multivariable-adjusted mean values from the General Linear Model

VARIABLE	Age-adjusted			Multivariable-adjusted*		
	Mean	**95% CI**	**P**	**Mean**	**95% CI**	**P**
Age-group:						
≤50 years	24.3	17.0-31.6	0.081	20.7	10.9-30.4	0.401
≥51 years	16.0	10.4-21.7		15.7	8.8-22.6	
District of residence:						
Tirana	18.7	11.3-26.0	0.072	15.6	7.3-23.8	0.267
Other districts	21.2	15.2-27.1		20.8	13.8-27.8	
Place of residence:						
Urban areas	17.9	12.1-23.7	0.206	17.4	10.3-24.5	0.759
Rural areas	23.8	16.5-31.1		18.9	10.5-27.4	
Education:			**0.056 (2)**†			**0.247 (2)**
0-8 years	26.4	19.1-33.7	0.068	24.6	15.2-33.9	0.268
9-12 years	18.3	11.7-24.9	0.615	18.1	5.0-31.3	0.877
≥13 years	11.2	0.3-22.2	-	11.9	0.5-23.3	-
Economic level:			**0.363 (2)**			**0.991 (2)**
Low	24.7	16.8-32.7	0.628	18.8	8.4-29.2	0.994
Middle	18.1	12.0-24.3	0.991	17.8	8.1-27.5	0.997
High	16.2	2.8-29.6	-	18.0	2.6-33.3	-
Employment status:			**0.716 (2)**			**0.607 (2)**
Employed	20.9	12.7-29.1	0.913	21.3	12.9-29.7	0.691
Unemployed	21.7	14.1-29.3	0.805	18.8	10.4-27.3	0.846
Retired	16.8	7.0-26.7	-	14.4	3.4-25.4	-
Site of metastases:						
Liver	13.5	7.4-19.6	0.002	11.9	4.3-19.6	0.008
Bones and/or lungs	27.2	20.9-33.5		24.5	16.9-32.0	

* This model was simultaneously adjusted for age-group (≤50 years vs. ≥51 years), district of residence (Tirana vs. other districts of Albania), place of residence (urban vs. rural areas), educational level (0-8, 9-12, ≥13 years), economic level (low, middle, high), employment status (employed, unemployed, retired) and metastases site (liver vs. bones and/or lungs).

† Overall p-values and degrees of freedom (in parentheses).

Table 4 presents the association between CA15-3 and socio-demographic characteristics and metastases site. In age-adjusted general linear models, there was an inverse and statistically significant association of CA15-3 with the age and educational attainment of study participants (mean CEA level was higher among the younger and the low-educated individuals). In addition, mean CA15-3 level was significantly higher in patients with metastases in the bones and/or lungs compared with those with metastases in the liver (235.7 U/mL vs. 150.4 U/mL, respectively; P<0.01). In multivariable-adjusted general linear models, there was evidence of a significant association of CA15-3 with the age-group (mean level was 246.6 U/mL in younger patients compared with 84.9 U/mL of their older counterparts; P<0.01) and metastases site (mean level was 203.6 U/mL in patients with bones and/or lungs metastases compared with 128.0 U/mL in those with liver metastases; P=0.04) [Table 4].

Table 4. Association of CA15-3 with socio-demographic characteristics and metastases site; age-adjusted and multivariable-adjusted mean values from the General Linear Model

VARIABLE	Age-adjusted			Multivariable-adjusted*		
	Mean	**95% CI**	**P**	**Mean**	**95% CI**	**P**
Age-group:						
≤50 years	289.9	233.3-346.4	<0.001	246.6	170.1-323.1	0.001
≥51 years	94.2	50.6-137.8		84.9	31.2-138.7	
District of residence:						
Tirana	188.7	131.9-245.5	0.881	153.9	89.1-218.7	0.519
Other districts	194.2	148.2-240.3		177.8	123.1-232.3	
Place of residence:						
Urban areas	177.8	132.9-222.7	0.303	161.7	106.1-217.3	0.834
Rural areas	214.9	158.4-271.4		169.9	103.6-236.1	
Education:			**0.055 (2)**†			**0.249 (2)**
0-8 years	235.6	179.5-291.7	0.052	220.2	146.9-293.6	0.314
9-12 years	184.6	133.8-235.5	0.388	150.8	47.8-253.7	0.982
≥13 years	113.5	29.3-197.6	-	126.4	37.1-215.6	-
Economic level:			**0.323 (2)**			**0.733 (2)**
Low	219.9	158.8-281.1	0.360	171.2	89.7-252.8	0.926
Middle	186.8	139.7-234.0	0.672	194.2	118.2-270.1	0.818
High	129.6	26.2-233.1	-	132.0	11.7-252.2	-
Employment status:			**0.637 (2)**			**0.506 (2)**
Employed	197.1	134.0-260.1	0.893	189.8	124.3-255.2	0.620
Unemployed	207.1	148.3-265.9	0.719	177.5	111.3-243.7	0.680
Retired	163.0	87.3-238.7	-	130.1	43.8-216.5	-
Site of metastases:						
Liver	150.4	102.5-198.4	0.014	128.0	68.0-188.0	0.039
Bones and/or lungs	235.7	186.6-284.8		203.6	144.7-262.5	

* This model was simultaneously adjusted for age-group (≤50 years vs. ≥51 years), district of residence (Tirana vs. other districts of Albania), place of residence (urban vs. rural areas), educational level (0-8, 9-12, ≥13 years), economic level (low, middle, high), employment status (employed, unemployed, retired) and metastases site (liver vs. bones and/or lungs).

† Overall p-values and degrees of freedom (in parentheses).

Discussion

Main findings of the current analysis include a higher mean value of both CEA and CA15-3 levels in Albanian female patients with breast cancer metastases in the bones and/or lungs compared with their counterparts with metastases in the liver. Furthermore, mean CA15-3 level was considerably higher in the younger patients. There was a significant linear association between CEA and CA15-3 levels. It should be noted that the current analysis of both CEA and CA15-3 values relates to the time of diagnosis and not the subsequent treatment which certainly causes alterations of the CEA and CA15-3 values.

Breast cancer is the most frequent cancer in women from Western countries (9) and it is increasing in low- and middle-income countries as well (1-3). In Western countries, the incidence of breast cancer has progressively increased in the past 30 years, whereas the specific mortality rate is relatively stable (9,12). It has been argued that this is a result of both extensive screening and great therapeutic strides (9,13).

In the current study conducted in Tirana, two important tumour markers were measured in all study participants at the time of diagnosis. However, to date, measurement of CA15-3 and CEA serum levels are not recommended in the follow-up of breast cancer, in light of their lack of specificity (9,14). Yet, some previous studies have indicated that the likelihood of discovering recurrence of breast cancer is influenced by the CA15-3 serum level and its doubling time (15,16).

The current analysis may have some limitations related to the inclusion of study participants and the data collection procedures. Regarding the possibility of selection bias, it should be noted that this study involved all patients with metastatic breast cancer diagnosed and treated over a seven-year period at the Oncology Service of the University Hospital Centre “Mother Teresa”, which is currently the only tertiary care institution in Albania. Based on this fact, the Oncology Service of the University Hospital Centre “Mother Teresa” in Tirana is the only public institution in Albania offering specialized services and most of the Albanian female patients are assumed to be diagnosed with breast cancer and subsequently treated in this medical centre. Therefore, the female patients included in our analysis comprise a representative sample of breast cancer patients for the whole period study period. As for the possibility of information bias, the diagnosis of breast cancer and the location of metastases were based on the best clinical protocols and contemporary examination techniques used in other countries. In any case, we cannot entirely exclude the possibility of information bias at least for the socio-demographic information which was collected through interviews. Yes, seemingly, there is no plausible reason to assume a differential reporting of socio-demographic factors between women with different clinical characteristics or stage of disease progression.

In conclusion, this study provides valuable evidence on selected correlates of CEA and CA15-3 levels in Albanian female patients diagnosed with metastatic breast cancer. Oncologists and other health professionals in Albania, as well as decision-makers and policymakers should be aware of the burden and risk factors of breast cancer among women in this transitional society.

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