

Breast Cancer in Italy: Stage and Region Distribution

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Purpose: Describe breast cancer in Italy by age, geographical area, stage and sites of metastases. In addition, incident and prevalent cases by region are provided.

Patients and Methods: This population-based study included all female patients with histologically confirmed breast cancer diagnosed in Italy between 2013 and 2019 in the eight participating Cancer Registries. Cases were described by geographic area (north, center, south), age group (<50, 50–69 and 70+) and site of metastases. In addition, the study also provided an estimate of the cases of metastatic breast cancer per single region.

Results: Of the total 5731 cases, the number of unknown stage cases (eliminated from our analyses) was 545 (10.5% of cases); therefore, the study was conducted on 5186 cases. Overall, 333 (6.5%) of tumors were metastatic at diagnosis but the distribution by geographical area was different: 5.1% in the north, 7.4% in the center and 7.8% in the south. Related to age, 5.6% were diagnosed before the age of 50 and 5.6% within the screening target group (50–69 years), while in elderly women the percentage rose to 8.1%. As regards the site of the metastases, 27.1% developed metastasis to the bone, 12.4% to the liver, 8.6% to the lung and 2.6% to the brain; in 34.9%, multiple sites were already present at the beginning of the cancer. Overall, 3520 cases of incident mBC are estimated in Italia every year (520 in Lombardy in northern Italy, 350 in Lazio in the center, followed by 330 in Campania in the south), and finally they are out of 52,000 prevalent cases.

Conclusion: A greater possibility of treating and living with the disease for a long time now requires careful monitoring of these tumors.

Keywords: breast cancer, metastatic, incidence, Italy

Introduction

Breast cancer (BC) is the most common cancer in women, with approximately 55,000 new diagnosed cases per year in Italy and 13,000 deaths,¹ most of which are due to metastatic breast cancer (MBC).² Although advanced forms include both locally advanced and metastatic tumors, in this study we refer only to MBC.³

Unfortunately, there is a certain variability in defining the percentage of MBC: about 5–10% of breast tumors present metastases at diagnosis⁴ but the percentage varies from 8% in developed countries to 20–30% in developing countries.⁵ In the United States, this percentage is low, at 3–6%;⁶ in Italy a recent population study showed that 6% of cancers are diagnosed in the metastatic phase,⁷ confirmed by recent data,^{8,9} also existing in men.¹⁰

Although the percentage of MBC is low, the number of incident cases of breast cancer in Italy is high and constantly increasing, and consequently also the percentage of metastatic forms is significant. Furthermore, although MBC is characterized by low survival (30–40% after 5 years⁸), there are several variables related to the biology, the site and the number of metastases that can affect the prognosis.¹¹ Additionally, the availability of new drugs for advanced forms prolongs the survival of these patients, so currently a diagnosis of metastatic cancer does not always mean fatal cancer.^{12,13}

In addition to *ab initio* metastatic forms, it is estimated that 20–30% of early stage breast cancers will develop metastatic disease during the history of the disease.¹⁴

The aim of this study is to describe metastatic breast cancer in Italy by age, geographical area, and the sites of metastases. In addition, it provides a region-by-region estimate of incident and prevalent cases of metastatic cancer giving stakeholders and patient organizations a more comprehensive overview for disease management.

Patients and Methods

This population-based study included all female patients with histologically proven BC diagnosed in Italy between 2013 and 2019 in the participating registries. This work has not been submitted for approval by an Ethics Committee. In fact, they are epidemiological data collected routinely by the Italian Cancer Registries (CRs). No additional information was collected, they are retrospective data: no patients were contacted and no medical records were reviewed for this study.

Cases were described by geographical area, age group, and site of metastasis and an estimate of incident and prevalent mBC cases was provided by single regions, using data already published in Italy.¹⁵

The study involved eight Italian Cancer Registers (CRs), representing all areas of the country, which provided data covering about 5,000,000 inhabitants, ie 15% of the areas covered by Cancer Registries in Italy. CRs were divided into three areas: north (Bolzano, Parma and Reggio Emilia), center (Tuscany) and south (Taranto, Syracuse, Ragusa and Caltanissetta). Of the total 5731 cases, the number of unknown stage cases, which were eliminated from our analyses, was 545, equal to 10.5% of the cases. Therefore, the study was carried out on 5186 cases.

Patients were divided into three age groups: <50, 50–69 (because of mammography screening) and 70+.

Results

The distribution of cases by single CR, stage, and age is reported in Table 1. The three northern CRs contributed 46% of the data, CRs of the center (Tuscany) contributed 29.3%, and the four CRs of the south contributed 24.7% of the cases. Adherence to organized screening shows a certain variability in terms of compliance (almost 90% in the north, 80% in the center and 60% in the south) but also in terms of time period, because in the north the screening started in the late 1980s, while in the south it began in more recent years.

2612 cases were diagnosed in stage I (50.4%), 1682 in stage II (32.4%), 559 in stage III (10.8%) and 333 in stage IV (6.4%). The highest number of patients were in the screening range (46.2%), 21.8% were under the age of 50, and 32% were over 70.

The distribution by geographical area (Table 2) shows that metastatic tumors do not have the same distribution in Italy: 5.1% in the north, 7.4% in the center, and 7.8% in the south. Regarding age, Table 3 shows that of the 333 cases of MBC, 5.6% concern both age groups <50 and 50–69 years, while in older women the percentage rises to 8.1%.

34.9% of cases have multiple metastases, 27.1% developed a metastasis to the bone, 12.4% to the liver, 8.6% to the lung and 2.6% to the brain (Figure 1).

Table 4 shows the incident cases in Italy divided by single region with percentages of metastatic cancer, where it results that although breast cancer is more frequent in the north than in the south, the number of MBCs offers a different picture. The largest number of cases is estimated in Lombardy (520 new cases per year), followed by a region in the center (Lazio with 350 cases per year) and in the South (Campania with 330 cases per year). Prevalence also follows the same north to south trend: Lombardy 8150 patients, followed by Lazio (5200) and Campania (4300).

Discussion

Globally, in 2020, there were 2.3 million women diagnosed with breast cancer and 685,000 deaths. Fortunately, breast cancer mortality changed a little from the 1930s through to the 1970s, related to early detection programs combined with different modes of treatment to eradicate invasive disease.¹⁶

In Italy, due to the availability of screening programs and greater awareness among women and general practitioners, in Italy most breast malignancies are diagnosed at an early stage of disease. This means that the 5-year survival rate is very high (87%, one of the highest recorded in Europe),¹⁷ but survival falls dramatically for metastatic forms to 34.2%⁸ or 30%.¹⁸

The aim of this work is to provide population data on the presence of BC metastases in Italy and an estimate of the expected cases (incident and prevalent) for each region. This will make it possible to inform stakeholders and patient

Table I Distribution of Number of Cases by Cancer Registry, Stage and Age

Cancer Registry (years)	Breast Cancer		Resident Population	Screening Coverage*
	n.	%	n.	%
<i>North</i>				
Bolzano (2016–2017)	722	13.9	110,000	89
Parma (2016–2018)	728	14.0	210,000	87
Reggio Emilia (2016–2019)	938	18.1	170,000	87
<i>Center</i>				
Tuscany (2013)	1517	29.3	3,800,000	79
<i>South</i>				
Taranto (2018)	389		200,000	66
Siracusa (2014–2015)	468	9.0	120,000	59
Ragusa (2016–2017)	234	4.5	72,000	59
Caltanissetta (2016–2017)	190	3.7	60,000	59
<i>Total</i>	<i>5186</i>	<i>100.0</i>	<i>4,742,000</i>	
<i>Stage</i>				
I	2612	50.4		
II	1682	32.4		
III	559	10.8		
IV	333	6.4		
<i>Total</i>	<i>5186</i>	<i>100</i>		
<i>Age</i>				
<50	1132	21.8		
50–69	2395	46.2		
70+	1659	32.0		
<i>Total</i>	<i>5186</i>	<i>100</i>		

Notes: *AIOM-AIRTUM-PASSI-PASSI D'ARGENTO-SIAPEC IAP. I numeri del cancro in Italia, 2019. Intermedia Editor. October 2019. (p71). It only includes adherence to programmed screening.

associations about the extent of the problem of metastatic breast cancer in order to confront and manage it with increased awareness.

Our analysis shows 6.4% of metastatic cancers at diagnosis, comparable with the rate reported in Western countries in general and in the US in particular,⁴ as well as in Italy.⁹

As regards the different areas, there is a certain variability between the regions of northern, central and southern Italy, which partly reflects the different ways the healthcare system is organized. The extension of mammography screening invitations is 98%, 96% and 59% in the regions of northern, central and southern Italy, respectively. Adherence to the invitation is also affected by a significant lack of homogeneity: 62%, 56% and 47%, respectively, in the regions of northern, central and southern Italy. This difference is reflected in the presence of a high number of early forms in the

Table 2 Distribution of Number of Cases by Stage and Area

Stage	North		Center		South		Italy	
	n.	%	n.	%	n.	%	n.	%
I	1231	51.5	721	47.5	660	51.5	2612	50.4
II	785	32.9	518	34.1	379	29.6	1682	32.4
III	251	10.5	166	10.9	142	11.1	559	10.8
IV	121	5.1	112	7.4	100	7.8	333	6.4
Total	2388	100	1517	100	1281	100	5186	100

Table 3 Distribution of Number of Cases by Stage and Age

Stage	<50		50–69		70+		Italy	
	n.	%	n.	%	n.	%	n.	%
I	568	50.2	1357	56.7	687	41.4	2612	50.4
II	380	33.6	697	29.1	605	36.5	1682	32.4
III	121	10.7	206	8.6	232	14.0	559	10.8
IV	63	5.6	135	5.6	135	8.1	333	6.4
Total	1132	100	2395	100	1659	100	5186	100

northern regions and in the fact that the advanced forms are more frequent in the southern regions. Central Italy, represented here only by Tuscany, presents an intermediate situation: the metastatic forms (7.4%) refer to the entire region, while for the province of Florence alone (which has a long tradition of mammography screening), this value drops to 5.4%.¹⁹

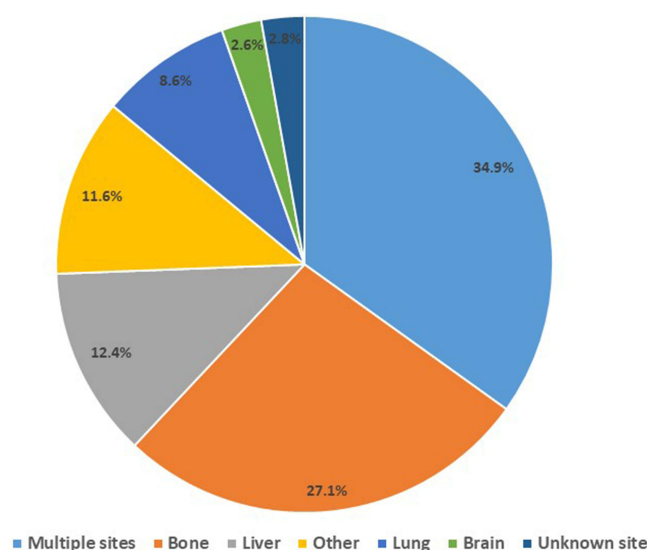
**Figure 1** Proportion of 333 breast cancer patients with single and multiple sites of metastasis.

Table 4 Estimate of Metastatic Breast Cancer for Each Region: Incident and Prevalent Cases

		Breast Cancer	MBC-Incident Cases		MBC-Prevalent Cases	
		n.	%	n.	%	n.
North	Emilia Romagna	4500	5.1	230	5.1	3900
	Friuli Venezia G	1459	5.1	80	5.1	1100
	Liguria	1650	5.1	90	5.1	1600
	Lombardy	10,000	5.1	520	5.1	8150
	Piedmont	4400	5.1	240	5.1	3930
	Trentino Alto A.	1000	5.1	60	5.1	760
	Valle D'Aosta	150	5.1	10	5.1	140
	Veneto	4900	5.1	250	5.1	4100
Center	Lazio	4600	7.4	350	7.4	5200
	Marche	1300	7.4	110	7.4	1500
	Tuscany	3500	7.4	270	7.4	3700
	Umbria	800	7.4	70	7.4	900
South	Abruzzo	1000	7.8	80	7.8	1250
	Basilicata	380	7.8	30	7.8	650
	Calabria	1300	7.8	110	7.8	1700
	Campania	4050	7.8	330	7.8	4300
	Molise	250	7.8	20	7.8	390
	Puglia	3200	7.8	250	7.8	3350
	Sardinia	1300	7.8	110	7.8	1480
	Sicily	3800	7.8	310	7.8	4200
Italy		55,000	6.4	3520	6.4	52,300

Due to the presence of screening, the number of MBC diagnoses is lower in the screened group (50–69 years) and in younger women, while it is higher in older women not screened. In most cases, the metastases are to the bone, followed by liver, lung and brain, which is in line with what has been reported in other studies.^{9,20}

Overall, our data are in line with what is reported in the literature. And the additional effort provides estimated data for each region with the aim of quantifying the burden of metastatic disease and providing useful data to clinicians, health planning, and patients associations often involved in the management of these patients.

In fact, where it is not always possible to cure the disease, the goal is to treat the disease and arrive at a large number of “metavivorships”, which must be accomplished through biopsychosocial screening efforts, monitoring of patient-reported outcomes, education and communication interventions, interdisciplinary symptom management, advanced care planning, and behavioral interventions to cultivate psychological resilience.²¹

The future goal should be to identify the number of women who could benefit from innovative treatments: surgery is now contemplated in some types of MBC;²² the treatment of oligometastatic cancer with surgery and/or hypofractionated radiotherapy, which improves outcomes and may be curative.²³

Personalized treatments based on biology have shown to improve outcomes and quality of life (combination of endocrine therapy with cyclin dependent kinase inhibitors 4–6 for patients with metastatic and receptor positive cancer).²⁴ Inhibition of PI3K and m-TOR is another promising strategy that could surpass endocrine therapy resistance. Triple-negative BC remains the most aggressive subtype because many patients develop resistance to available agents.²⁴

The strengths of this study include the reliable data of good quality referring to population cancer registries and not to individual hospitals.

Unfortunately, there is no information on the appearance of metastasis after diagnosis or on biological variables, which are very important today in the evaluation of neoplasia. In particular, there is a lack of relevant information on receptor status and HER2, which could strongly influence the prognosis of metastatic disease, especially in recent years.

Conclusion

The results of our study confirm what has been reported in the literature but specify for the first time the extent of metastatic breast tumors in Italy with estimates for individual regions. Information by age, site of metastasis, and patient residence should allow for better management of these patients by oncologists and policy makers.

Disclosure

Professor Antonino Musolino reports grants and/or personal fees from Lilly, Novartis, Seagen, Eisai, and Daiichi-Sankyo, outside the submitted work. The authors report no other conflicts of interest in this work.

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