Original article

LONG-TERM SURVIVORS OF BREAST CANCER DIAGNOSIS: A DESCRIPTIVE STUDY ON RISK FACTORS, CHARACTERISTICS OF THE DISEASE AND ON LIFESTYLES OF A COHORT OF WOMEN ATTENDING A TERRITORIAL ONCOLOGICAL SERVICE.

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A R T I C L E   I N F O

A B S T R A C T

The role of a healthy lifestyle in improving the prognosis of many cancers is well known. The aim of this study is to describe the characteristics and lifestyles of a cohort of long-term breast cancer survivors in order to gain useful information to plan targeted educational interventions.

This retrospective study involved patients registered at the Oncology Service of the ASL. Napoli 1 who had survived at least 5 years post-diagnosis of breast cancer. The data were collected both from the medical records and through a telephone interview. Statistical analysis was performed with Stata 10.1. The study found that there is a high proportion of women diagnosed under the age of 40, and with second primary neoplasms, however with a fairly high average survival rate. The women interviewed displayed a good willingness to be healthy, but intervention is still required regarding obesity and being overweight.

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1. Introduction

In Italy, mammary carcinoma, excluding cutaneous carcinomas, is the most diagnosed neoplasia in women, in which about one malignant tumor every three (28.0%) is a breast tumor (1).

It is estimated that in 2017 about 50,000 new cases of female breast cancer were diagnosed in Italy. The incidence trend appears to be growing slightly while mortality continues to decline significantly (-2.2% per year). This decline in mortality is attributable both to the progressive increase of screening programs, and to the considerable improvements in cancer treatments that allow many people to live long lives even after a cancer diagnosis (1). Considering the frequency in various age groups, breast tumors are the most frequently diagnosed cancer among women in the 0-49 age group (41.0%), in the 50-69 age group (35.0 %), and in the older group ≥70 years (22.0%). The disease has a wide geographical variability; in Italy the differences between macro-areas observed in the period of 2008-2013 confirm a greater incidence in the North (162.2 cases/100,000 women) compared to the Center (143.2 cases/100,000 women) and to the South-Islands (124.5 cases/100,000 women) (1).

The 5-year survival rate of women with breast cancer in Italy is 87.0% (1), higher than the European (81.8%) and Northern European average rates (84.7%) (2). It does not present relevant heterogeneity among different age groups. In fact, it is equal to 91.0% in young women (15-44 years), 92.0% among women aged 45-54 years, 91.0% among women aged 55-64; however, it falls to 89.0% and 79.0% among women aged 65-74 and older (> 75) respectively (1). There is an unfavorable trend in the South-Island survival rates (85.0%) compared to North-West (87%), North-East (88.0%), and Center (87%) (1).

In long-term survivors, women have an increased risk of manifesting comorbidities, such as obesity, hypertension, hyperlipidemia and diabetes mellitus that certainly reduce the disease-free phase and ultimately affect overall survival. Many studies have already been conducted to understand risks associated with the occurrence of secondary complications of treatment protocols such as cardiovascular diseases, osteoporosis, development of lymphedema and the development of additional primary neoplasia (3-5).

The development of second tumors can be attributed to several factors: oncological treatments (radiotherapy, chemotherapy, hormone therapy), characteristics of the subject (genetic predisposition, alterations of the immune system), habits/lifestyle (smoking, alcohol, diet, weight management, physical activity). Indeed, several studies underline the role of proper nutrition and regular physical activity in improving health, prognosis and quality of life of long-term survivors (6-9). Also influenza and pneumococcal vaccination should play a key role in protecting long-term survivors from these fearsome infections (10-12).

Given that breast cancer, like other cancers, can gradually turn into a chronic condition, it is necessary for women affected by this pathology to be more closely monitored with dedicated programs.

At the Territorial Oncological Service of Naples ASL Naples 1 center, that already takes a comprehensive approach to women's health (which involves prevention, early diagnosis and support to ensure timeliness of care), various initiatives have been launched to promote a healthy lifestyle (6, 8, 10, 12). This study, therefore, aims to describe the cohort of long-term survivors with diagnosis of breast cancer who utilize the Service, analyzing, in particular, the socio-demographic characteristics, the presence of known risk factors, the evolution of the disease, and lifestyles of survivors in order to acquire useful information for the programming of targeted educational interventions, which are recommended by current scientific literature to improve prognosis and quality of life (13).

2. Methods

Participants

This retrospective study followed by a cross sectional survey, conducted from November 2015 to June 2017, involved all patients surviving to a breast cancer diagnosis, which was diagnosed within the period from 1998 to 2012, for at least 5 years. All patients came from the Service of Oncology in the sanitary district n° 26 of the ASL Naples 1, located in the western area of the city of Naples, servicing about 120,000 inhabitants.

Data Collection

The personal and clinical information was collected through consultation of the patients' medical records using a survey which collected:

- Personal data and medical history: age, residence, education, profession.
- Year of first access to the clinic.
- Data relating to the tumor pathology: date of diagnosis, histological type, degree and stage, site, hormone receptors, biological characteristics (Ki67), and treatments.
- Possible development of metastases, relapses and complications including second neoplasms.
- Eventual death.
- Presence of risk factors: familiarity, nulliparity, age at first pregnancy, age at menarche and menopause, lactation.

Death and causes of death were verified at the Register of the Causes of Death and the Cancer Registry of the Local Health Authority Naples 1 center.

Living patients were contacted through a structured telephone interview to investigate how patients discovered the diagnosis, the adherence to therapeutic treatment plans, and the presence of risk factors related to lifestyle: eating habits, voluntary (alcohol and smoking), physical activity and BMI.

Statistical Analysis

A descriptive analysis was carried out analyzing the dichotomous or ordinal variables through frequency distributions (absolute and relative), and using the synthesis and dispersion measures for the continuous variables.

Two univariate analysis was carried out. The first univariate analysis to identify prognostic factors associated to the death as the age, education, age at diagnosis, familiarity, severity of the disease, known complications, development of local relapses, second primary neoplasm and development of metastases.

Considering data was collected by a telephone interview with about 70.0% of response rate, to exclude a possible selection bias, a second univariate analysis was carried out to verify the difference between the two groups (respondents and non-respondents) based upon age, education and diagnosis stage. In both models the variables with a value of p <0.25 on the univariate analysis were introduced in the multiple logistic regression model to correct any confounders.

The Stata 10.1 statistical package for data analysis was used.

3. Results

596 long-term breast cancer survivors were enrolled. The socio-demographic and medical characteristics of the cohort are shown in Table 1. Between of enrolled women, 47.7% were over 70 years old, 57.6% had a low level of education, and 49.7% were housewives. The medical history of pregnancy showed that 81.3% had pregnancies, 15.4% were elderly first-time mothers (≥30 years), and 46.5% had 1 or 2 children. In 41.3% of cases, there were 1 or more abortions. 63.1% of the recruited women say they breastfed 89.0% and 49.7% respectively, reported a normal age for menarche and menopause between 46 and 55 years old. With respect to the onset and characteristics of the disease (Table 2), the majority of the patients enrolled were diagnosed with breast cancer between 2001 and 2010 (69.6%). The age at the time of diagnosis was over 50 years in just over half of women: 14.8% of women were diagnosed between 20 and 40 years and 52.8% post-menopausal (> 50 years). 23.5% had familiarity for breast cancer, 75.5% received a diagnosis of carcinoma classified as stage I or II, 92.1% practiced poly-therapies. 12.4% developed known complications, of these the most frequent were lymphedema (8.4%) and depression (2.2%). Relapses and second primary neoplasms occurred in 6.0% and 11.9% of cases, respectively. 13.3% of the enrolled women experienced metastases. 90 women died in the follow-up period (15.1%). For 41.1% of the deceased, the cause of death was breast carcinoma, in 15.6% it was a neoplasm different from breast cancer, for 11.1% a non-neoplastic cause intervened, while the cause of death it was unknown for the remaining women. The average survival rate in patients enrolled is 15.5 years, in patients deceased is 17.6 years.

		n°	%
Age	40-44 years	8	1.3
	45-54 years	76	12.7
	55-69 years	228	38.3
	>70 years	284	47.7
Education	Illiterate	5	0.8
	Elementary school	229	38.4
	Middle school	109	18.4
	High school	160	26.8
	Degree	48	8.1
	Not detectable	45	7.5
Occupation	Retired	92	15.4
	Housewife	296	49.7
	Technical or office	57	9.5
	Intellectual	38	6.4
	Worker/artisan	10	1.7
	Not detectable	103	17.3
Pregnancy	No	73	12.2
	Yes	484	81.3
	Not detectable	39	6.5
Age of first pregnancy	No pregnancy	73	12.3
	<18 years	11	1.9
	18-24 years	195	32.7
	25-29 years	186	31.2
	≥30 years	92	15.4
	Not detectable	39	6.5
Number of children	0	76	12.7
	1-2	277	46.5
	>2	217	36.4
	Not detectable	26	4.4
Number of abortions	0	323	54.2
	1	133	22.3
	>1	113	19.0
	Not detectable	27	4.5
Breastfeeding	No	100	16.8
	Yes	376	63.1
	No children	76	12.7
	Not detectable	44	7.4
Age at the menarche	<10 years	24	4.0
	10-16 years	530	89.0
	>16 years	8	1.3
	Not detectable	34	5.7
Age at menopause	<40 years	37	6.2
	40-45 years	111	18.6
	46-55 years	296	49.7
	>55 years	10	1.7
	Not in menopause	142	23.8

Table 1. Socio-demographic and medical characteristics of the survivors (n°596)

The multivariate analysis for finding potential prognostic factors that could be related to mortality confirms an increment of the mortality risk with the increase of the age and in presence of factors such as the severity of the disease, the presence of local relapses and of metastasis (Table 3).
Table 4 shows the lifestyle data of the 275 respondents to the interview. 80.4% of patients reported that they did not smoke cigarettes, 26.2% were former smokers, 21.1% suffered passive smoking. 92.0% drank coffee, 71.3% sweetened; 24.7% claimed to drink alcohol and 14.9% drank occasional spirits. With respect to eating habits, 54.2% did not consume industrial sweets, 72.0% ate little (once a week or less) or no red meat during the month, and grains were consumed by a high percentage of patients (93.8%). 85.8% and 89.5% of the interviewees reported consuming at least one portion of fish and legumes per week. 81.5% claimed to consume at least 5 portions of fruit/vegetables and/or vegetables a day. On the other hand, 47.3% did not practice physical activity. Overweight women and obese women were respectively 43.3% and 19.3%.

		n°	%
Follow-up start date	1998-2000	101	16.9
	2001-2010	415	69.6
	>2010	80	13.5
Age at diagnosis	20-40 years	88	14.8
	41-50 years	193	32.4
	>50 years	315	52.8
Survival to the diagnosis in years	5-10 years	165	27.7
	11-20 years	323	54.2
	>20 years	108	18.1
Familiarity	No	437	73.3
	Yes	140	23.5
	Not detectable	19	3.2
TNM Staging system	Stage 0	23	3.9
	Stage I	207	34.7
	Stage II (A e B)	243	40.8
	Stage III (A, B e C)	34	5.7
	Stage IV	6	1.0
	Not detectable	83	13.9
Known complications	No	522	87.6
	Lymphedema	50	8.4
	Depression	13	2.2
	Other	11	1.8
Therapy	Monotherapy	47	7.9
	Poly-therapy	549	92.1
Development of local relapses	No	560	94.0
	Yes	36	6.0
Second primary neoplasm	No	525	88.1
	Yes	71	11.9
Development of metastases	No	517	86.7
	Yes	79	13.3
Death	No	506	84.9
	Yes	90	15.1
Cause of death (n°90)	Breast cancer	37	41.1
	Other neoplasm	14	15.6
	Non-neoplastic cause	10	11.1
	Unknown cause	29	32.2

Table 2. Characteristics of the disease of survivors (n°596)

	Univariate OR (95% IC)	p-value	Multivariate OR (95% IC)	p-value
Mortality				
Chronological age (continuous variable)	1.05 (1.03-1.07)	<0.001	1.1 (1.04-1.11)	<0.001
Education (low vs high)*	0.7 (0.3-1.5)	0.367	n.e.**	
Age at diagnosis (<50 years vs ≥50 years)*	0.6 (0.4-1.0)	0.053	1.9 (0.8-4.4)	0.125
Familiarity (yes vs no)*	0.6 (0.3-1.1)	0.114	0.7 (0.3-1.6)	0.475
Severity of the disease (Stage II-IV vs Stage 0-I)*	3.5 (1.9-6.4)	<0.001	2.6 (2.3-5.0)	0.005
Known complications (yes vs no)	1.5 (0.8-2.8)	0.184	1.2 (0.5-2.9)	0.673
Development of local relapses (yes vs no)*	3.5 (1.7-7.3)	<0.001	6.6 (2.4-18.3)	<0.001
Second primary neoplasm (yes vs no)*	1.3 (0.7-2.5)	0.421	n.e.**	
Development of metastases (yes vs no)*	10.3 (5.8-18.4)	<0.001	8.9 (4.6-17.2)	<0.001

* referent   ** n.e.: not evaluable

Table 3. Relationship between mortality and risk factors of death in long survivors

The multivariate analysis between respondents and non-respondents to the telephone interview, to verify if there were significant differences between the two groups that could have influenced the adherence to the interview in particular with respect to age, education and stage at diagnosis showed that the group of non-respondents was only older (p = 0.040; OR 0.98, CI 0.96 - 0.99) while there were no significant differences for the other variables analyzed (data not shown in the table).

		n°	%
Smoker	Never smoked	149	54.2
	Former smoker	72	26.2
	Yes	54	19.6
Passive smoke	No	217	78.9
	Yes	58	21.1
Coffee consumption	No	22	8.0
	Yes, bitter	57	20.7
	Yes, sweetened	196	71.3
Alcohol consumption	No	207	75.3
	Yes	68	24.7
Superalcoholic consumption	No	234	85.1
	Occasionally	41	14.9
Industrial sweets consumption	No	149	54.2
	Yes	126	45.8
Red meat consumption	No	91	33.1
	Yes, 1/week	107	38.9
	Yes, >1/week	77	28.0
Grains, daily consumption	No	17	6.2
	Yes	258	93.8
Fish weekly consumption	No	39	14.2
	Yes, 1/week	118	42.9
	Yes, >1/week	118	42.9
Legume weekly consumption	No	29	10.5
	Yes	246	89.5
"Five a Day" adherence	No	51	18.5
	Yes	224	81.5
Physical activity	No	130	47.3
	Walk on foot	106	38.5
	Moderate/Intense	39	14.2
BMI	Normal weight	103	37.4
	Overweight	119	43.3
	Obesity	53	19.3

Table 4. Lifestyle of women interviewed (n°275)

4. Discussion

The cohort described consists of a selected series of cases related to an oncology unit located in a low-income area of the City of Naples. This explains the socio-demographic characteristics of the group of women, who were mainly of a low-medium cultural level. It is important to note, with respect to the characteristics of the disease, that the cohort has a frequency of familiarity for breast cancer that exceeds 20%, which is particularly high compared to the estimates of the Italian Association for Cancer Research (5.0-7.0%) (14). The percentage of women diagnosed under the age of 50 (47.2% of cases) was also particularly high, specifically those under 40 (14.8%) compared to the register of tumors in the province of Caserta (33.8% and 9.0% respectively) (15, 16). This could be explained both by an increased risk of developing neoplasia at a young age, but also by adherence to screening (with mammography and US according to the indications of the National Prevention Plan 2010-2012) which, due to the presence of the oncology unit, is particularly widespread and favored by the networks of friends and family who have a strong social role in this community (11). This territory has previously been defined as being at greater risk for cancer by the Ministry of Health and it is one of the areas of environmental and socio-economic degradation. As a result, this territory is currently the subject of specific monitoring and of an extraordinary program that implements the offer for free prevention services, especially for younger women (17). The percentage of women with a diagnosis of stage II or lower, who benefit from a better prognosis, is lower than that found in other studies (79.4% vs. 87.7%) (15).

The incidence of lymphedema related to breast cancer, which in our cohort is the most frequently occurring complication, is rather low (8.4%) compared to the frequencies reported in the literature that are quite variable (from 6.0% to 62.0%) (18). Diversely, in this cohort the frequency of women who developed a second primary neoplasm is higher than that reported in the literature (11.9% vs 5.0%-7.0%) (19-22). This could be explained by the increased frequency of women diagnosed at an early age (23).

Regarding lifestyle, comparing the data with those published by the Progressive Studies of Health Agencies in Italy (P.A.S.S.I) for Italy and Campania (24), it appears that in the group interviewed there is a higher percentage of women who adopt a healthy lifestyle compared to the population of Campania. In fact, there is a lower percentage of smokers (19.6% vs. 27.7% in Campania) and the percentage of former smokers is higher (26.2% vs. 13.2% in Campania). The interviewed women who drink alcohol are about half of the adults from Campania (males and females) who declare to consume alcoholic beverages (24.7% vs. 45.8%) (24).

Compared to the eating habits of the questioned patients, most of them follow a proper diet, in line with the indications of the European code against cancer and of the recent scientific literature that investigated the association between eating habits and tumors (25-30). In fact, women in this cohort declared low consumption of red meat and industrial sweets, high weekly consumption of legumes and fish, and adherence to the "five a day" rule (81.5%), much higher than the regional and national frequencies (respectively 7.6% and 10.0%) detected in both sexes (24).

With reference to physical activity, the percentage of sedentary women in our study is much higher than that reported for Italian women (35.4%), but it is in line with the regional figures (47.3% vs. 49.7%) (24).

The high sedentary lifestyle and the high frequency of women who consume pasta and/or grains daily can explain the percentages of overweight and obese women (43.3% and 19.3%) in our cohort, which are much higher than those of the Campanian population (37.4% and 14.1%) and of the Italian population recorded in women only (23.9% and 10.1%) (24).

The main limit of this work, based on an ambulatory case study of women spontaneously approaching to the oncological service, could be the bias of selection. Moreover, being a study on sick women, the aspects related to the risk of occurrence of the disease, such as the breast-feeding duration, were not covered. The eventual bias of information accounted in the phone interviews seems to be not relevant, considering that the multivariate analysis of the two groups (respondents and not to the interview) did not show significant differences in relation to the instruction level and to the severity of the disease.

In conclusion our study demonstrated that the interviewed cohort showed a good propensity to protect their own health, even if there are still possible areas of intervention to impact overweight and obese patients, which are known risk factors for various oncological and non-oncological diseases. Therefore, there is a need to strengthen the active offer of nutritional counseling services and services dedicated to the promotion of physical activity, accompanied by targeted information and awareness campaigns for women about the risk and protection factors for breast carcinoma..

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