Breast carcinoma in elderly women. Our experience

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SUMMARY: *Breast carcinoma in elderly women. Our experience.*

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Purpose. *To analyze the biological features of breast cancer in women aged more than 70 years and to evaluate the utility of complete breast examination in elderly patients.*

Patients and methods. *In the period between January 2000 and March 2009, 147.189 women aged more than 39 years underwent breast examination. In 1.527 diagnosis of breast carcinoma was made. Patients affected by breast carcinoma were subdivided into two groups basing on age (< 70 and ≥ 70 years). The two groups were compared for tumor size on imaging studies, histology, pT stage, grading and the presence of estrogen and progesterone receptors.*

Results. *In comparison with younger women, breast carcinoma in elderly presented as invasive ductal form in most of cases (p 0.004), T1 and T2 stages (p 0.0001), G1 grade (p 0.0001) and positive for the presence of estrogen and progesterone receptors (p <0.0001).*

Conclusions. *Basing on the incidence rate and the biological features of breast cancer in elderly women without co-morbility, breast cancer prevention in women is considered useful until the age of 74 years.*

RIASSUNTO: *Il carcinoma della mammella nelle donne anziane. Nostra esperienza.*

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Obiettivo. *Analizzare le caratteristiche biologiche dei tumori della mammella e valutare l'utilità del controllo senologico completo in donne di età ≥70 anni.*

Pazienti e metodi. *Nel periodo gennaio 2000 - marzo 2009, sono stati effettuati 147.189 controlli senologici in donne di età >39 anni. In 1527 casi è stato diagnosticato un carcinoma della mammella. Le pazienti affette da carcinoma mammario sono state suddivise in due classi di età (< 70 e ≥ 70 anni). Per le due classi sono state analizzati e confrontati le dimensioni del tumore all'imaging, l'istotipo, il pT, il grading, la presenza di recettori per estrogeni e progesterone.*

Risultati. *Rispetto a soggetti più giovani, il carcinoma della mammella nella paziente anziana si presenta prevalentemente come carcinoma duttale infiltrante (p 0.004), compreso tra T1 e T2 (p 0.0001), con basso grading (G1 - p 0.0001) e positività dei recettori per estrogeni e progesterone (p<0.0001).*

Conclusioni. *In relazione all'incidenza e alle caratteristiche biologiche del tumore della mammella nella donna anziana, si ritiene opportuno in assenza di comorbilità il prosieguo dei programmi di prevenzione senologica fino a 74 anni.*

KEY WORDS: Breast cancer - Elderly women.
Carcinoma mammario - Donne anziane.

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Introduction

Breast cancer represents the most common tumor in women. Recent data show an incidence of 122.9/100.000 (1), with a mean age of 61 years at the time of diagnosis. Women aged > 65 years with breast cancer are about 40.9% and incidence rates (SEER 9) increased from 0.32% in 1975 to 0.42% in 2002 (1). The increase in the incidence rate of breast cancer in older women is related to two factors: the aging of general population and the increased use of screening programs. The over sixty, which in 1980 were 11.3%, in 2030 will represent 20% of the general population (2, 3).

Numerous studies show that the incidence rate of breast cancer increases with age (4 - 7). About 50% of breast carcinomas, in fact, are diagnosed in women > 65 years (3.8 to 10), while the percentage of cancer diagnosed in women > 70 years ranges from between 30 and 47% (10,11) and it is expected that in 2035 this percentage could reach 70% (12). The survival rate of women with breast cancer over sixty rose from 76.9% in 1975 to 91.7% in 2002 (SEER9) (1) and, to date, it is similar to that of the general population (13, 14).

Screening programs for the age group from between 50 and 69 years have shown a reduction in mortality in women up to 69 years (4), but no reported data demonstrate the usefulness of further controls in women ≥ 70 years, except for the experience of Tabar (15) which includes women up to 74 years. However, the increased life expectancy and the increased incidence of breast cancer in the general population require careful evaluation of breast cancer in older women, not only for the proper treatment planning, but also for the reassessment of the age group to be included in screening programs.

Therefore, our study aims to analyze the biological characteristics of breast cancer in women aged ≥ 70 years and to assess the cost-benefit ratio of the complete breast control in this group of women.

Patients and methods

In the period from January 2000 and March 2009, 147.189 women aged > 39 years were evaluated at the Breast Unit of Bari,"San Paolo" Hospital. All women underwent clinical breast examination, mammography and ultrasound as outpatients, except for women with mammographic fibro-fatty structure, in which complete ultrasound examination was indicated only in selected cases. Clinical breast examination, mammography and ultrasonography were performed by a breast "dedicated" radiologist.

The mammography equipments used in the course of time were: analogic GE Alpha RT, Diamond GE and digital Senograf 2000 (GE Healthcare, Waukesha, Wisconsin, USA). Two projections (craniocaudal and oblique) were performed. If necessary, additional screenings were performed in targeted compression and / or direct radiographic magnification. Ultrasonography was performed by AU5, My Lab 50, 70 X Vision (Esaote, Genoa, Italy) devices, with a multi-frequency linear array probe (7-14 MHz).

In selected cases, patients underwent MRI and fine-needle aspiration for cytology and/or histological examination. MRI was performed with a 1.5-T unit (Magnetom Symphony Maestro Class, Siemens, Forcheim, Germany) using a dedicated breast coil, with the patient in the prone position. The study protocol included a transverse T1 localization sequence, a sagittal T2 fat-sat sequence and a T1 Gre 3D-Flash sequence in order to study the dynamics of the enhancement, acquiring five series of images on an axial plane in quick succession, after the intravenous injection of gadobutrol (Gadovist, Bayer) at a dose of 0.1 mmol / kg body weight.

The fine needle aspiration for cytology was performed under ultrasound guidance using 21G needle. For the percutaneous microbiopsy a digital stereotactic prone table associated with Fischer Mammotome® system (Ethicon Endo-Surgery, Breast Care, Norstedlt, Germany) was used. This device allowed the sampling of the lesion with a 360° mechanical aspiration (23-25 mmHg) . For the sampling, 11G needles have been used. From between 8 to 18 samples have been performed, with a mean value of 11. The cores removed were subsequently checked by direct magnification X-ray technique. In the site of biopsy, a non-magnetic clip was positioned in all cases in order to identify the exact site of sampling.

Among the 147.189 controls, 145.662 were negative, while 1527 resulted positive for malignancy.

In our series, we analyzed: tumor size (<1 cm, 1-1.9 cm, 2-4.9 cm, ≥ 5 cm), histology (ductal carcinoma, lobular, mucinous, tubular, medullary, other), T (pT0, pT1, pT2, pT3, pT4), grading (G1, G2, G3), receptors for estrogen and progesterone (ER +, PgR +, E / PgR +) and the presence of co-morbidities (hypertension, cardiovascular disease, diabetes).

Patients were divided into two age groups (<70 and ≥ 70 years) and the main characteristics of cancer were analyzed in women aged ≥ 70 years as compared with those of age <70 years.

Statistical analysis

The chi-square test was used for comparison (StatXact-7 Cytel Studio Version 7.0.0 - Oct 21, 2005). A p-value <0.005 was considered statistically significant.

Results

Among the 147.189 patients aged > 39 years who underwent breast full control at our facility, breast cancer was diagnosed in 1527 (1.04%). Of these, 1.346 (88.2%) were aged < 70 years, 181 (11.8%) ≥ 70 years. The group of women aged < 70 years included patients with a wide age range (from 39 to 69 years) and this may represent a limitation of our study, because it is likely that biological characteristics of tumor affecting a 65-69 year-old woman are closer to those of a tumor affecting a woman ≥ 70 years rather than between 40 and 50 years.

Table 1 summarizes tumor characteristics in both groups. The tumor size detected in the different imaging methods is slightly higher in women over 70; in fact, 45% of tumors (vs. 39% in women aged <70 years) has a maximum transverse diameter of between 2 and 4.9 cm, on the contrary , millimetric injuries are more common in women under 70 (14% vs 7% in older women). Similar data have been obtained on the size of tumors between 1 and 1.9 cm (38% in women under 70 vs 39% in older women) and a diameter ≥ 5 cm (9% vs 9%). However, these data are not statistically significant (p 0.0728).

With regard to the histological features of tumors, in both groups, ductal carcinoma (Fig. 1) represents the most frequent histological type (84% in women aged <70 years vs 83% in women aged ≥ 70 years). However, the percentage of in situ cancers diagnosed in women under 70 is higher (44%) as compared with older women (23%). The statistically significant difference (p 0.0004) is also evident in the percentage of invasive carcinoma, which

TABLE 1 - DIMENSIONAL, HISTOLOGICAL AND BIOLOGICAL CHARACTERISTICS OF BREAST CANCER AND CO-MORBIDITY IN WOMEN AGED <70 AND ≥ 70 YEARS TESTED POSITIVE FOR BREAST CONTROL IN THE PERIOD BETWEEN JANUARY 2000 AND MARCH 2009.

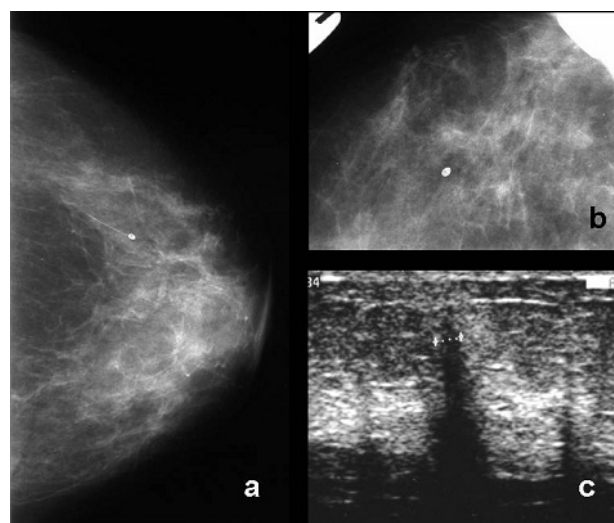| Parameter	<70 years (%)	≥70 years (%)	p
Tumor size			
<1	188 (14)	13 (7)	0.0728
1-1.9	512 (38)	71(39)	
2-4.9	525 (39)	81 (45)	
>5	121 (9)	16 (9)	
Histology			
Ductal	1.130 (84)	150 (83)	0.0004*
Ductal in situ	592 (44)	41 (23)	
Invasive ductal	538 (40)	109 (60)	
Lobular	108 (8)	16 (9)	
Mucinous	14 (1)	4 (2)	
Tubular	13 (1)	2 (1)	
Medullar	27 (2)	2 (1)	
Other	54 (4)	7 (4)	
T			
T0	27 (2)	2 (1)	0.0001*
T1	842 (62.5)	81 (44.7)	
T2	390 (29)	76 (42.1)	
T3	47 (3.5)	9 (5.2)	
T4	40 (3)	13 (7)	
G			
G1	269 (20)	77 (42.5)	0.0001*
G2	599 (44.5)	54 (30)	
G3	478 (35.5)	50 (27.5)	
Receptors			
Pg	538 (40)	140 (77.34)	<0.0001*
E+	1009 (75)	147 (81)	
P+	713 (53)	116 (64)	
Comorbidity			
Hypertension	161 (12)	42 (23)	0.001*
CV diseases	54 (4)	38 (21)	
Diabetes	13 (1)	3 (16)	
≥2 diseases	141 (10.5)	40 (22)	
Total patients 1.527	**1.346 (100)**	**181(100)**	

statistically significant

Fig. 1 - Mammography in 71-year old woman. a) Left cranio-caudal mammography with targeted compression (b), absolutely non specific and performed in the site of US finding (c), which shows millimetric hypoechoic gap with posterior acoustic barrier (C5 US guided cytology). Histological diagnosis: invasive ductal carcinoma (T1a, N1a, Mx; G1).
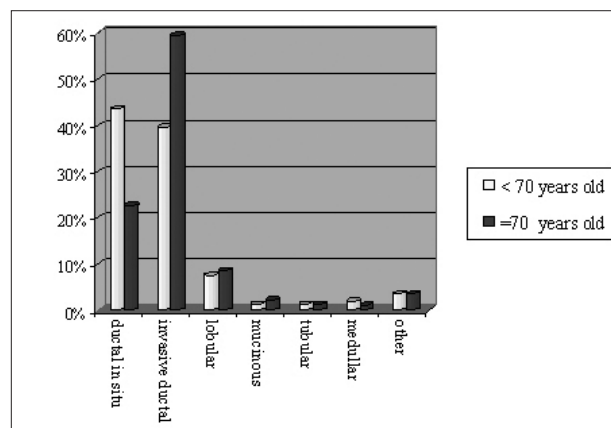

Fig. 2 - Distribution of histological types of breast cancer in women aged < 70 and ≥70 years (total number of patients: 1.527).

derly women (2% vs 1% in women aged <70 years) and medullary carcinoma in women under 70 (2% vs 1% in the ≥ 70 years).

The analysis of T parameter showed a lower percentage of T0 and T1 in women aged ≥ 70 years than those aged <70 years (a total of T0 + T1 of 45.7% vs 64.5%) and a higher percentage of T2, T3 and T4 in women older than 70 as compared with women < 70 (a total of T2 + T3 + T4 of 54.3% vs 35.5%) (Fig. 4). In particular, in women under 70 a greater number of T0 (2% vs 1% in the ≥ 70 years) and T1 (62.5% vs 44.7%) was shown, whereas in older women T2 (42.1% vs 29% in women aged <70 years), T3 (5.2% vs 3.5%) and T4 (7% vs 3%) were predominant, with statistically significant differences (p 0.0001).
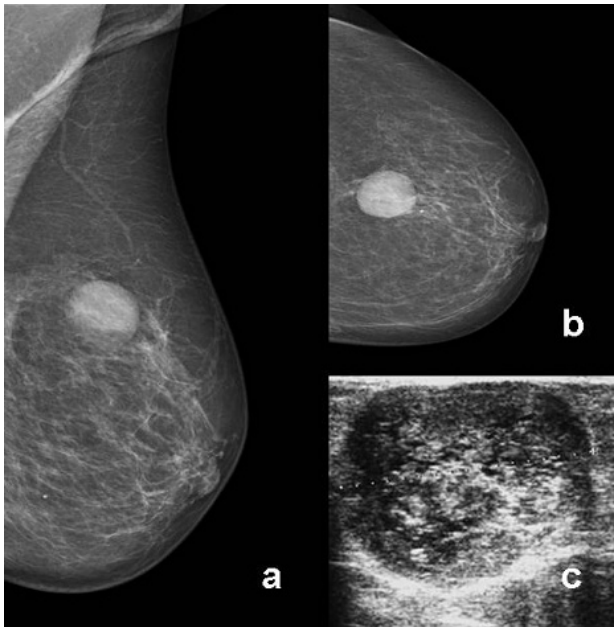
has a higher value in older women (60% vs 40% in women aged ≥ 70 years) (Fig. 2). The distribution of other histological types (lobular, mucinous, tubular, medullary carcinoma) is almost similar in both groups, with a slight predominance of mucinous carcinoma (Fig. 3) in el

Fig. 3 - **Breast imaging in 76-year old woman. a) e b) Left mammographic cranio-caudal and oblique projections showing massive opacity with partially undefined caudal margins and homogeneous density. c) Corresponding ultrasound: inhomogeneous hypoechoic nodule with regular and defined margins. Histological diagnosis: mucinous carcinoma (T1c, N0, M0).**
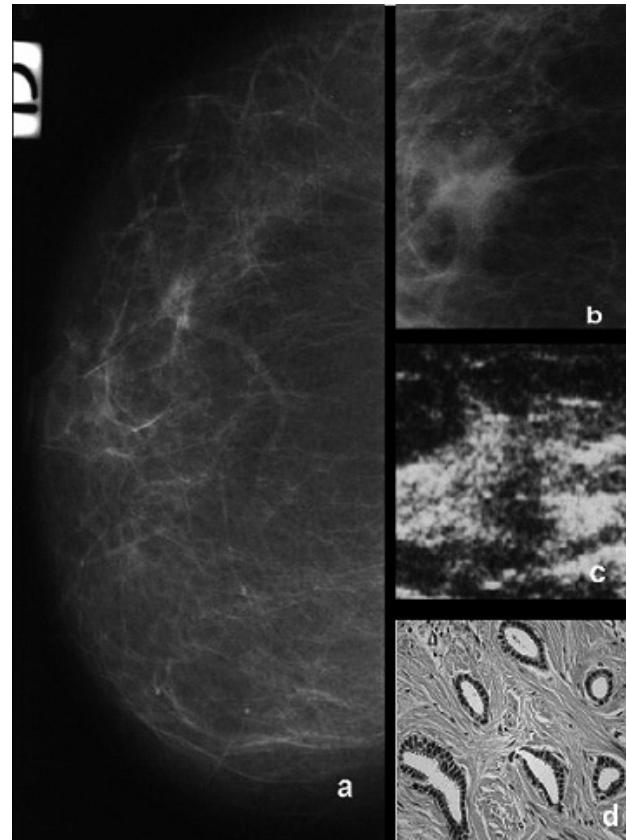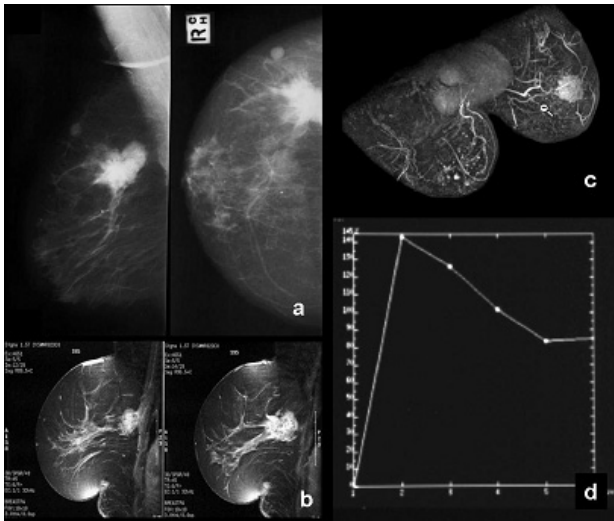

Fig. 4 - **Breast imaging in 75-year old woman. a) Right cranio-caudal and oblique mammographic projections showing a massive opacity with irregular and spiculated margins in fibro-fatty breast. b, c) MRI confirms malignant massive nodular area of inhomogeneous enhancement. d) Corresponding Intensity/time curve characterized by type III pattern according to Fischer classification. Histological diagnosis: invasive ductal carcinoma (T3, N2, Mx, G3).**

Fig. 5 - **Breast imaging and histology in 70-year old woman. a) Right cranio-caudal mammographic projection showing millimetric undefined opacity; the targeted compression (b) confirms irregular and inhomogeneous margins. c) Corresponding ultrasound: inhomogeneous hypoechoic irregular gap in most vertical axis (US guided cytology C4). Histological diagnosis: invasive ductal carcinoma (T2, N1, Mx, G1). d) Histological section of breast carcinoma with well-differentiated tubular architecture, mild nuclear pleomorphism and glandular elements contained in a stromal elastosic matrix. EE staining; 200x magnification.**

The analysis of grading allowed to identify statistically significant differences between the two groups (p 0.0001). In fact, a lower biological aggressiveness of breast cancer in older women (G1 42.5% vs 20% in women aged <70 years) (Fig. 5) and a prevalence of G2 and G3 cancers in women under 70 (G2: 44.5% vs 30 % in ≥ 70 years; G3: 35.5% vs 27.5%) were found.

The positivity of receptors for estrogen and progesterone is higher in women aged ≥ 70 years. Data were statistically significant (p <0.0001) and showed not only a positivity for estrogen and progesterone receptors in elderly women (77.34% vs 40%), but also a positivity for individual receptors, respectively, for estrogen (81% vs 75%) and for progesterone (64% vs 53%).

Any co-morbidity of patients, in particular the presence of hypertension, cardiovascular disease and diabetes, was finally analyzed. These diseases were more frequent in women aged ≥ 70 years than in women aged <70 years (a total of 80% vs 27.5%, p 0.001).

Discussion

Basing on a review of the literature and the results of our study, a statistically significant lower biological ag-

gressiveness of breast cancer in older women is reported (3, 7, 13, 16, 17). According to Singh (p 0.86) (16), our results do not show a significant difference of tumor size between women under 70 and elderly women (p 0.728); besides, regardless of the lesion size, the biological characteristics of the tumor are most favorable in older women, as compared with those of cancer in post-menopausal under 70 women (17).

As reported in literature, the invasive ductal carcinoma represents the most common cancer in older women (3), medullary and inflammatory carcinomas are less common than in women under 70 (16), while the papillary and mucinous carcinomas occur with increased frequency in older women (7). In our study, we found a prevalence of invasive ductal carcinomas in older women (60% vs 40% in women aged < 70 years) and a slight difference in the frequency of mucinous carcinoma (2% vs 1% in women aged <70 year - p 0004).

The grading of breast cancer in women over seventy is lower as compared with women aged <70 years (p 0.0001, in agreement with other series) (18) and the positivity rate of estrogen and progesterone receptors is clearly higher (p <0.0001), as shown by Holmes, Diab, Gajdos (p <0.0001, p 0.007), and Owusu Bultitude (3,13,18-20).

A prevalence of well-differentiated cancers in older women (p <0.001) was already reported in literature (18).

However, despite the favorable biological characteristics of breast cancer in women aged ≥ 70 years, the mortality rate is high (10). The possible underlying causes of this data can be related to the presence of co-morbidity (3, 7, 8, 14, 19), to patient under-treatment (8, 10, 18 - 21), or to the poor sensitivity to the prevention in women over seventy (5, 7, 8).

Surgical and adjuvant therapies in the treatment of carcinoma in older women are effective and well tolerated (7) and burdened with minimal toxicity (6), with a 30-day mortality after surgery of less than 1% (7). The effectiveness of the treatment varies with age (22) and therapy can increase the disease-free interval and reduce the symptoms of the disease in advanced stage (11,23,24). However, in many cases, elderly women with breast cancer do not receive adequate treatment, probably because of the coexistence of other pathologies that could affect the result. Data are not easily confirmed, due to the non-recruitment of older patients in clinical trials (22).

It has been shown that prevention of breast cancer reduces mortality in women aged between 39 and 69 years (4), but at the moment data on the effectiveness of the prevention of breast cancer in women over seventy are rather controversial (4, 6, 25, 26). In fact, while Nystrom in 1993 (25) stated that the reduction of mortality in women aged between 70 and 74 years who underwent periodic breast controls was not significant, Morrow in 1994 (7) showed that the prevention of breast cancer can re-

duce mortality even in the presence of co-morbidities. In particular, Morrow reported that in women aged between 65 and 69 years, prevention allowed to prolong the survival of 617 days in healthy patients and 311 days in patients with heart failure, whereas, in women aged more than 85, respectively of 178 and 126 days (7). Diab (13) believes that the role of prevention of breast cancer is limited because the causes of death among women over seventy affected by breast cancer are independent of the tumor; on the contrary, McCarthy (26) reports that prevention reduces the mortality even in women > 85 years. In a paper reported in 2001, Caplan (6) proposed to continue to check the breast care period in the older women, despite the unfavorable opinion of the USPSTF (United States Preventive Service Task Force). Jonnson in 2003 (27) stated that the reduction of mortality in women aged between 70 and 74 years who underwent periodic controls was not significant. Besides, Galit in 2007 (28) stressed that prevention programs allow early diagnosis and reduce mortality of patients and Bagdwell in 2008 (29) reported that prevention programs reduce mortality, but do not alter survival in women aged ≥ 80 years, especially in the absence of significant co-morbidity. In 2009, Nelson (4) confirms that data on the benefits of breast cancer prevention in women aged > 70 years are to date insufficient. Unlike Nelson (4), Diab (13), Nystrom (25) and Jonnson (27), who consider inefficient to prevent breast cancer in older women, many other authors (7,26,28 , 29) believe that screening for breast cancer in older women can reduce mortality. In fact, the participation of older women to prevention programs is rather low (56.7% women > 70 years vs 71.1% women aged < 70 years) and diagnosis of breast cancer is late in this group of patients (12).

We believe that by encouraging the participation of women over seventy to programs of prevention, it is possible to increase the survival rate, as shown by Morrow (7), especially in the absence of co-morbid factors. It has been shown that a woman of 70 years has a life expectancy of 15.5 years (11) and, according to Holmes and Kimmick (3, 9), a woman with a life expectancy of more than 5 years should continue to conduct examinations for early diagnosis of breast cancer. Thus, theoretically, a woman should continue to check until the age of 80 years. However, McPherson (14) shows that in case of severe co-morbidity, the efficacy of screening program is reduced and the mortality from breast cancer is reduced in the large elderly (> 85 years) as compared with elderly patients (75-84 years) (30).

Conclusions

Despite the small percentage of in situ tumors, as compared with invasive forms, low T (staging) and G (grading) stages and the increased breast cancer positivity for

estrogen and progesterone receptors in older women as compared with younger patients represent statistically significant data (p <0.005). These data allow to affirm that in women over seventy, as compared with women aged < 70 years, breast cancer is biologically less aggressive.

For these reasons, given the life expectancy in the absence of co-morbidity, we propose the prevention of breast cancer even in the range of over 70 years and the extension of breast screening every two years to 70 – 74 year old women, with any subsequent clinical-instrumental monitoring every 2 - 3 years in the absence of co-morbidity.

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