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REVIEW

Breast cancer in elderly women and altered clinico-pathological characteristics: a systematic review

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Abstract
Purpose Breast cancer is the most common malignancy in women in terms of incidence and mortality. Age is undoubtedly the biggest breast cancer risk factor. In this study we examined clinical, histological, and biological characteristics and mortality of breast cancer in elderly women along with their changes with advancing age.
Methods We reviewed 63 original articles published between 2006 and 2016 concerning women over 70 years with breast cancer.
Results Compared to patients 70–79 years, patients aged 80 and over had larger tumor size with fewer T1 (42.9% vs 57.7%, $p < 0.01$) and more T2 lesions (43.5% vs 33.0%, $p < 0.01$). Lymph nodes and distant metastases were more frequent, with more N + (49.5% vs 44.0%, $p < 0.01$) and more M1 (8.0% vs 5.9%, $p < 0.01$). Infiltrating mucinous carcinomas were more frequent (4.3% vs 3.7%, $p < 0.01$). Tumors had lower grades, with more grade 1 (23.2% vs 19.8%, $p = 0.01$) and fewer grade 3 (21.5% vs 25.5%, $p < 0.01$), and were more hormone-sensitive: PR was more often expressed (72.6% vs 67.3%, $p < 0.01$). Lympho-vascular invasion was less frequent in the 80 years and over (22.9% vs 29.7%, $p = 0.01$). Breast cancer-specific mortality was higher both at 5 years (25.8% vs 17.2%, $p < 0.01$) and 10 years (32.7% vs 26.6%, $p < 0.01$).
Conclusion Clinico-pathological characteristics, increased incidence, and mortality associated with aging can be explained on one hand by biological changes of the breast such as increased estrogen sensitivity, epithelial cell alterations, immune senescence, and tumor microenvironment modifications. However, sociologic factors such as increased life expectancy, under-treatment, late diagnosis, and insufficient individual screening, are also involved.

Keywords Breast cancer · Elderly women · Clinical characteristics · Pathology · Aging

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Introduction

Breast cancer is the most common malignancy in women in terms of incidence and mortality, thus constituting a major public health problem. In 2012, breast cancer represented 28.1% of new cancers and 14.6% of cancer deaths in industrialized countries [1]. A number of modifiable and non-modifiable risk factors are involved in the occurrence of breast cancer including obesity [2], physical inactivity [3], hormonal treatments [4], and genetic or familial predisposition [5]. However, age is undoubtedly the predominant breast cancer risk factor. The number of women affected by breast cancer in France in 2008 was estimated at 1/430 and 1/19 for the ages below 45 years and over 75 years, respectively [6]. These data are comparable in the United States [7]. Although there is no general agreement on the age at which a person becomes old [8], in this paper we set the age threshold at 70 years, as proposed by the Breast International Group [9].

In the last fifteen years, breast cancer incidence and mortality have generally decreased. This improvement may be attributed to the progress of medical care, notably earlier screening and diagnosis, and more effective treatments, including targeted therapies. However there is evidence that this decrease in incidence and mortality has been less significant [10] or has even increased in elderly women. This was observed in the United States [7], Germany [11], Denmark [12], and France [13, 14] and it was estimated that in 2012, in developed countries, one out of two woman who died from breast cancer was over 70 [1].

Population aging is a major concern. It is estimated that between 2000 and 2050 the population of women aged over 80 will have more than tripled in developed countries [15]. Elderly women are rarely included in national breast cancer screening programs, the upper age limit varying from 65 years in Hungary [16] to 74 years in France, Italy, Sweden, Japan, Israel, and the Netherlands [16]. In the United States, recommendations are that breast cancer screening should be continued as long as life expectancy is at least 10 years, without age limit [17].

The common dogma is that cancer in the elderly spreads slowly and is less aggressive and that the leading cause of mortality in this population is related to co-morbidities. Epidemiology studies indicate that it is not true until the age of 85 [18].

Many authors have studied breast cancer treatment, but only a few studies have correlated this with the clinical and pathological characteristics in elderly women. We analyzed the literature between 2006 and 2016 and propose an updated overview on clinical, histological, and biological characteristics of breast cancer in elderly women along with changes due to aging. Incidence and mortality data have also been included.

Patients and methods

Bibliographic selection

An initial PubMed search, between 01/01/2006 and 01/04/2016, based on the following terms: "breast cancer" and "older, elder, eldest, elderly" gave 30,271 entries. A targeted search based on the following terms: "clinic/clinical," "biology/biological," "hormone/hormonal," "histology/histological," "pathology/pathological," "clinicopathology/clinicopathological," "histopathology/histopathological," "survival" reduced the number of results to 3524.

We then proceeded to a further screening by title, abstract, and/or full text. This step allowed us to select 50 original articles on clinico-pathological aspects in elderly women (discovery mode, TNM, histology, predictive, and prognostic factors) and mortality. Further research through the bibliographies of selected articles and certain review articles allowed us to single out 13 additional articles that were considered relevant for the study. Reviews, articles without abstracts, case reports, clinical trials, and articles including populations under the age of 70 years were excluded. Only articles in English, Spanish, and Chinese were included.

In total, our search yielded 63 original articles published between 2006 and 2016. The bibliographic approach is summarized in Fig. 1.

Data analysis

Of the 63 articles, 49 gave general characteristics of women aged over 70 (103,408 women): we analyzed clinical presentation (clinical or radiological), TNM stage, tumor grade (classified according to the Elston-Ellis modification of Scarff-Bloom-Richardson grading system), histological sub-types, tumor receptor status (Estrogen receptor (ER), Progesterone receptor (PR), Human Epidermal growth factor Receptor 2 (HER2)), and lymphovascular invasion.

Thirteen articles had more precise age sub-categories, allowing us to compare two age-related groups (94,070 women): those between 70–79 and those over 80 years.

Since the aim of our study was to analyze clinicopathological characteristics of breast cancer in women over 70 years, we included all populations, from primary operated breast cancer to primary metastatic endocrine therapy-only patients. We deliberately excluded treatment analysis because it was irrelevant to the purpose of our study.

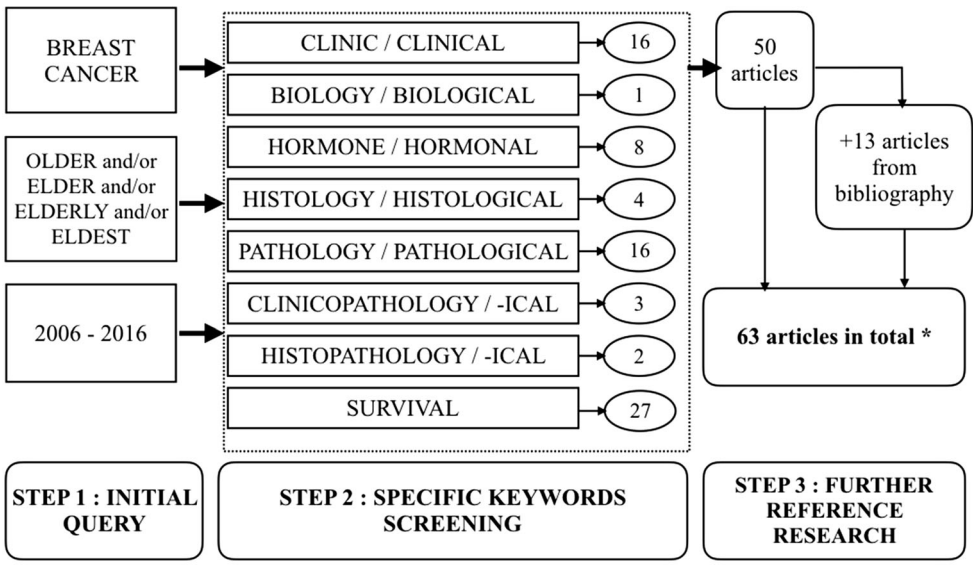

Fig. 1 Bibliographic selection

* : Total number (63) of articles is different form the sum of the step 2 (77) because some articles have more than one keyword (overlap)

Mortality analysis was made on 27 articles, on a population of 178,202 women.

Statistical analysis was performed with the GraphPad® 6 Prism software using a two-tailed $\chi 2$ test with a 95% confidence interval. The results are expressed as means with a range.

Incidence and mortality in general population and in elderly women

Epidemiological data were retrieved from Globocan 2012 online analysis (International Agency for Research on Cancer, World Health Organization) [1]. Incidence and mortality were calculated for women only, in 2012. Industrialized countries are defined as "Very High Human Development Index" according to the United Nations Organization.

Limitations of the study

In this report, the population studied is heterogeneous because it includes all the data in the literature on breast cancer diagnosed in women aged 70 years and over. The analysis includes primary operated breast tumors, and primary metastatic breast cancers, the latter lacking information on lymph node involvement. All the clinicopathological parameters taken into account in the review articles could not be studied in all the patients because some of them were not initially included in this literature database (most articles document the histological grade of the tumor but few reported on lympho-vascular invasion). In addition, it was not possible to make the distinction between elderly and very elderly patients in metastatic-free and loco-regional relapse-free survival because of insufficient data.

Results

Breast cancer incidence and mortality in general population and in elderly women

In 2012, breast cancer represented 747,203 (28.1%) out of 2,660,689 newly discovered cancers in women in industrialized countries [1]. Breast cancer was responsible for 161,131 (14.6%) out of 1157,394 cancer deaths in women in industrialized countries [1].

Table 1 shows breast cancer incidence and mortality with aging. Both incidence and mortality increase with age. Women aged 70 and over represent 225,080 (30.1%) out of 747,203 newly discovered breast cancers, and incidence increases between the different age sub-groups. Women

Table 1 Incidence and mortality in women in 2012, developed countries (very high human development index)

Age (years)	Incidence [*n* (%)]	Mortality [*n* (%)]
Under 40	45,913 (6.1)	3992 (2.4)
40–49	114,227 (15.3)	13,925 (8.2)
50–59	173,550 (23.2)	28,256 (16.7)
60–69	188,433 (25.2)	36,366 (21.5)
Over 69	225,080 (30.1)	86,592 (51.2)
Total	747,203 (100)	169,131 (100)

aged 70 and over represent 86,592 (51.2%) out of 169,131 breast cancer deaths and increases with age.

Tumor characteristics of breast cancer in women over 70 years

Forty-nine articles described the clinico-pathological features of breast cancer in women over 70 years without further age group distinction. A summary is given in Tables 2 and 3.

Breast cancer was detected clinically in 71.8% of cases on average (7597 women) [19–33]. Tumor size was less than 2 cm (T1) in 47.2% of cases, while T2 sized tumors (2–5 cm) were found in 42.9% of cases (13,981 women) [18–24, 28, 31, 32, 34–49]. Lymph node involvement (N) was evaluated in 21,164 women [18, 19, 22, 24, 28, 31, 34–56]. When axillary surgery was performed, metastatic extension to lymph nodes was detected by histology in 36.1% of cases. Extension was not detected in 56.1% of cases. The remaining 7.8% were considered unknown as it was not clear whether surgical sampling was performed.

At the time of diagnosis, distant metastasis was present in 6.3% of cases (87,601 women) [20, 22, 24, 27, 32, 35, 37, 41, 43–46, 50–52, 57–63].

Infiltrating ductal carcinoma represented 66.1% of cases (103,408 women) [19–21, 23, 25, 26, 29, 31–37, 39–45, 51, 56, 58, 59, 62, 64–67]. Histological tumor grade 1 represented 22.4% of cases (20,014 women) [18, 19, 21–23, 26, 28, 30, 32, 35, 37–40, 42, 43, 45, 47–52, 54–56, 58–62, 66]. ER and PR were expressed in 81.1% (19,627 women) and 59.3% (16,766 women) of tumors, respectively [18–23, 25, 26, 28, 30, 32, 33, 35–40, 42–45, 47–56, 58, 59, 62, 66]. HER2 over-expression or amplification was found in 13.4% of cases (8362 women) [19–21, 25, 28, 30–32, 35, 36, 38, 39, 42–45, 47–53, 56, 59, 61]. Lympho-vascular invasion was present in 24.4% of cases (9924 women) [19, 20, 28, 34, 35, 37, 41, 42, 44, 45, 55, 60, 62].

Differences between two age sub-groups over 70 years

Thirteen articles dealt with changes of clinico-pathological characteristics upon aging over 70 years (Tables 2 and 3) and made a distinction between two groups of age: from 70 to 79 and from 80 and over. In 4857 women, clinical detection was more frequent among the 80 and over group than for the 70-79 years sub-group (77.8% against 61.3%, $p < 0.01$), and detection by imaging was rarer (22.2% against 38.7%, $p < 0.01$).

In 4252 women, tumor size T1 (57.7%) was predominant for the 70 to 79-year age group, while tumor size T2

Table 2 Breast cancer clinical characteristics

	All patients aged 70 and over [patients (%)]	[70–79] [patients (%)]	≥80 [patients (%)]	Difference* (p)
Cancer detection				
Clinical	5457 (71.8)	2036 (61.3)	1193 (77.8)	<0.01
Radiological	2140 (28.2)	1288 (38.7)	340 (22.2)	<0.01
Total	7597	3324	1533	
Tumoral size				
T1	6603 (47.2)	1752 (57.7)	522 (42.9)	<0.01
T2	5998 (42.9)	1001 (33.0)	530 (43.5)	<0.01
T3	707 (5.1)	100 (3.3)	43 (3.5)	0.70
T4	583 (4.2)	134 (4.4)	88 (7.2)	0.17
Unknown	90 (0.6)	48 (1.6)	34 (2.8)	0.01
Total	13,981	3035	1217	
Lymph nodes involvement				
N0	11,868 (56.1)	2538 (53.7)	1014 (44.2)	N+ vs N0: <0.01
N1	7652 (36.1)	1998 (42.3)	992 (43.3)	N+ vs N0 + unknown: 0.44
Unknown	1644 (7.8)	187 (4.0)	286 (12.5)	
Total	21,164	4723	2292	
Metastatic disease at diagnosis				
M0	82,056 (93.7)	25,125 (94.1)	10,921 (92.0)	<0.01
M1	5545 (6.3)	1589 (5.9)	949 (8.0)	<0.01
Total	87,601	26,714	11,870	

* Statistical significative difference between 70–79 and 80 and over (p)

Table 3 Breast cancer pathological characteristics

	All patients aged 70 and over [patients (%)]	[70–79] [patients (%)]	≥80 [patients (%)]	Difference* (p)
Histological sub-type				
Ductal	68,305 (66.1)	39,958 (66.8)	21,062 (61.5)	<0.01
Lobular	9206 (8.9)	5981 (10.0)	2351 (6.9)	<0.01
Mucinous	3811 (3.6)	2196 (3.7)	1455 (4.3)	<0.01
Other	22,086 (21.4)	11,715 (19.6)	9352 (27.3)	<0.01
Total	103,408	59,850	34,220	
Tumoral grade				
I	4492 (22.4)	566 (19.8)	341 (23.2)	0.01
II	9261 (46.3)	1346 (47.1)	662 (45.0)	0.20
III	5268 (26.3)	729 (25.5)	316 (21.5)	<0.01
Unknown	993 (5.0)	217 (7.6)	153 (10.4)	<0.01
Total	20,014	2858	1472	
Hormonal receptors				
ER+	15,916 (81.1)	2366 (77.9)	1164 (77.0)	0.51
ER total	19,627	3037	1511	
PR+	9944 (59.3)	1297 (67.3)	568 (72.6)	0.01
PR total	16,766	1928	785	
HER2 receptor				
HER2 +++	1124 (13.4)	290 (12.6)	130 (13.1)	0.69
Total	8362	2304	994	
Lymphovascular invasion				
Yes	2423 (24.4)	309 (29.7)	56 (22.9)	0.03
No	7501 (75.6)	730 (70.3)	189 (77.1)	0.03
Total	9924	1039	245	

* Statistical significative difference between 70–79 and 80 and over (p)

(43.5%) was predominant in the 80 and over sub-group. Another significant difference between the two populations is that, in the 80 and over sub-group, T1 are less frequent (42.9% vs 57.7%, $p < 0.01$) and T2 are more frequent (43.5% vs 33.0%, $p < 0.01$). However, no statistically significant differences were found for T3 ($p = 0.70$) and T4 ($p = 0.17$) lesions.

Lymph node involvement (N) was studied in 7015 women from both sub-groups. Lymph nodes were less frequently assessed in the 80 and over sub-group; the unknown status (Nx) was significantly more frequent (12.5% vs 4.0%, $p < 0.01$). When axillary surgery was performed (i.e., Nx excluded), lymph node metastasis was observed more frequently in the 80 and over sub-group, with less N0 (56.0% vs 50.5%, $p < 0.01$) and more N + (44.0% vs 49.5%, $p < 0.01$).

The presence of distant metastasis at diagnosis, evaluated in 38,584 women, was more frequent in the 80 and over sub-group (8.0% vs 5.9%, $p < 0.01$).

The evaluation of histological type was described for 94,070 women. In the 80 and over sub-group: on one hand infiltrating ductal and lobular carcinomas were less frequently diagnosed (respectively 61.5% vs 66.8%, $p < 0.01$ and 6.9% vs 10.0%, $p < 0.01$); while mucinous (4.3% vs 3.7%, $p < 0.01$) and other histological type carcinomas (27.3% vs 19.6%, $p < 0.01$) were more frequent.

The histological tumor grade (classified according to the Elston-Ellis modification of Scarff-Bloom-Richardson grading system), assessed in 4330 women was lower in the 80 and over sub-group. Grade 1 was more frequent (23.2% vs 19.8%, $p = 0.01$) and grade 3 less frequent (21.5% vs 25.5%, $p < 0.01$), while no statistically significant difference was found in grade 2 (45.0% vs 47.1%, $p = 0.20$) tumors.

Hormone receptor expression was assessed for ER and PR in 4548 and 2713 women, respectively. For the 80 and over sub-group, more hormone-sensitive tumors were found; PR was more often expressed (72.6% vs 67.3%, $p = 0.01$), whereas no statistically significant change in ER (77.0% vs 77.9% $p = 0.51$) was observed. However, in 3298 women, the HER2 over-expression was not statistically different between the two sub-groups (13.1% vs 12.6%, $p = 0.69$).

Table 4 Breast cancer mortality

	All patients aged 70 and over (patients, %)	[70–79] (events/total, %)	≥80 (patients, %)	Difference* (p)
Overall survival				
5-years	53,976 (34.5)	1313/8133 (16.1)	6544/12,224 (53.5)	<0.01
10-years	2880 (59.4)	Insufficient data to compare		
Specific survival				
5-years	140,775 (17.0)	3843/22,285 (17.2)	3477/13,477 (25.8)	<0.01
10-years	37,427 (28.9)	5917/22,285 (26.6)	4410/13,477 (32.7)	<0.01
Loco-regional relapse-free survival				
5-years	5144 (9.7)	Insufficient data to compare		

* Statistically significative difference between 70–79 and 80 and over (*p*)

In 1284 women the presence of lympho-vascular invasion was less frequent in the 80 and over sub-group (22.9% vs 29.7%, $p = 0.03$).

Breast cancer mortality in women 70 years and over and differences between the two age sub-groups

In total, 27 articles dealt with breast cancer mortality in elderly women (Table 4). At 5 years from diagnosis, the overall mortality was 34.5% (53,976 women) [18, 21, 23–25, 27, 30, 33, 45, 47, 50, 51, 53, 60, 62, 67–71]. The breast cancer-specific mortality, was 17.0% (140,775 women) [11, 18, 21–23, 27, 45, 47, 57, 62, 67, 69, 71]. The loco-regional recurrence at 5 years was 9.7% (5144 women) [18, 21, 23, 27, 30, 50, 53]. At 10 years from diagnosis, the overall mortality was 59.4% (2880 women) and the breast cancer-specific mortality was 28.9% (37,427 women).

Nine publications focused on the variation in mortality upon aging after 70 years (Table 4). The overall mortality was higher in the 80 years and over sub-group (53.5% vs 16.1%, $p < 0.01$) along with the breast cancer-specific mortality, both at 5 years (25.8% vs 17.2%, $p < 0.01$) and 10 years (32.7% vs 26.6%, $p < 0.01$).

Discussion

The analysis of the international literature from the past 10 years on breast cancer shows that aging is remarkably associated with an increased risk of breast cancer. It is important to note that breast cancer in the elderly shows different clinico-pathological features than in the younger women [72]. Furthermore, by making the distinction between two age sub-groups, we observed that cancers in the very elderly (80 years and over) are different than those in elderly women (70–79). Indeed, in women, aging is accompanied by the frequent occurrence of breast tumors with favorable histology (low grade carcinomas, low lympho-vascular invasion, hormone-sensitivity, histological types with good prognosis, lack of expression, or amplification of HER2…), but with larger tumor size, lymph node involvement and more de novo stage IV metastatic disease. In the sub-group 80 years and older, an increase in breast cancer-specific mortality from breast cancer is observed both at 5 and at 10 years. These paradoxical observations can be explained by biological and society-related mechanisms.

Biological mechanisms

Estrogen hypersensitivity

Aging is accompanied by a considerable reduction of circulating estrogens, especially estradiol, resulting in reduced stimulation of the ER. Estrogen deprivation is actually at the basis of the treatment of hormone-dependent breast cancer by castration (be it medical, surgical or by irradiation), which significantly reduces the risk of breast cancer death, recurrence, and even contralateral cancer [73]. Similarly, the occurrence of early menopause is associated epidemiologically with a significant reduction in the risk of breast cancer [74]. In elderly women the level of circulating estrogens are extremely low, yet the risk of hormone-dependent cancer is significantly higher. This apparent contradiction can be explained by deep cellular and biological changes that occur in the mammary gland after menopause.

Indeed, aging is accompanied by increased expression of genes that regulate the activity of different enzymes such as aromatase, sulfatase, or 17β-hydroxy-steroid dehydrogenase-1 involved in the intramammary synthesis of estradiol, enabling breast epithelial cells to proliferate despite

low levels of circulating estrogens [75]. This adaptation is associated with greater breast sensitivity to estrogens. This was revealed by experimental data on the human cancer cell lines MCF-7 a model of luminal cancer cells [76].

Epidemiological studies confirm an age-related susceptibility to breast cancer. By exploiting four large clinical trials, Beral et al. [4] investigated the breast cancer incidence during a 5 years period, on more than 20,000 women having or not followed hormone substitution therapy. The number of cancers attributable to hormone substitution therapy was higher among women aged from 60 to 69 compared to those aged from 50 to 59. Similar findings were reported, in presence of endogenous obesity [2] and hyperthyroidism [77]. Altogether, endogenous and exogenous, hormonal stimulation associated with an increased risk of breast cancer in the elderly might be due to an increased susceptibility of epithelial breast cells to estrogens.

Mammary epithelial cell changes

Aging also changes the breast tissue with the presence of ducto-lobular tissue atrophy at the expense of connective and adipose stroma. Russo et al. [78] found that, after menopause, differentiated lobules regress to undifferentiated lobules similar to those observed before puberty. Thus puberty and elderly age are characterized by glandular immaturity. However, in contrast with puberty in older women, the atrophic ducto-lobular and immature tissue contains epithelial cells which have undergone modifications due to repeated exposure to carcinogens [79], or alterations of the double-stranded DNA repair system via a loss of the ATM protein (ataxia telangiectasia mutated) pathway repression [80], possibly increasing its transformation potential.

Tumor microenvironment (TME) (fibroblasts and adipocytes)

As mentioned above, in elderly women, ducto-lobular tissue atrophies at the expense of connective and adipose stroma. This tissue remodeling in the breasts of older women is characterized by global changes i.e., breasts becoming softer, ptosic, and of lower radiographic density. Consequently, older women's breasts are transparent to imaging [81], which facilitates cancer detection.

Biologically, tumor development capabilities (migration and cell proliferation, resistance to cell death, induction of angiogenesis, etc.) are modulated by the interaction of cancer cells with their microenvironment [82]. The elderly mammary gland becomes particularly rich in adipocytes and fibroblasts [83]. Aging entails the accumulation in the body of senescent cells, in particular fibroblasts. Cellular senescence involves different mechanisms such as shortening of telomeres, epigenetic de-repression of the INK4a locus/ARF, and DNA damage, leading to irreversible arrest of growth [84]. Cellular senescence was previously deemed as tumor-protective. However, more recent studies suggest that senescent cells contribute to the formation of an inflammatory and hence tumor-promoting environment [85]. Several experimental studies have shown that senescent fibroblasts promote in vivo and in vitro growth of cancer cells [86, 87]. For example, senescent fibroblasts induce in vitro migration of T47D breast cancer epithelial cells, originally non-mobile, via the RhoA/ROCK/myosin pathway [85] through inflammatory factors and pro-oncogenes, including among others interleukins 6 and 8 and the vascular endothelial growth factor (VEGF) [88]. The body of experimental data suggests that the accumulation of senescent fibroblasts and the resulting alterations in tissues can partly explain the marked carcinogenicity in aged breast tissue as well as the diffusion to lymph nodes and the more frequent presence of metastases at diagnosis.

The role of the TME in cancer represents a broad field of investigation, besides cancer associated fibroblasts, which is a well-known contributor of cancer progression [89], adipocytes and cancer associated adipocytes are recognized as emerging and major components of the TME [90–93]. Several mechanisms have incriminated the adipose tissue in cancer development, either indirectly due to the consequences of their dysfunction like obesity-related inflammation [92] or directly through the physical interaction between cancer cells and adipocytes during tumor progression [93–96]. Clinical studies have showed that local adipose tissue invasion by cancer cells was associated to a poor prognosis of ductal breast carcinoma [97, 98]. Several reports have documented profound modification of the adipocyte tissue morphology and function in cancer. Notably in breast cancer, adipocytes next to cancer cells called cancer associated adipocytes (CAA) have reduced size and progressively dedifferentiate to disappear at the expense of stromal cells [94–96]. Moreover, experimental studies provide evidence that CAA support cancer progression, by favoring cancer cell growth, migration, and metastases [92, 93, 96, 99]. To date, adipocytes by shaping the microenvironment are important contributors of the TME, therefore it is tempting to speculate that the hypertrophy of the breast adipose tissue in elderly women plays a central role in the rapid progression of the disease.

Immune senescence

With advancing age a decreased immune response, called immuno-senescence, is observed which lowers the defense against infection and the response to vaccination, and increases the incidence of cancer [79, 82]. This process

involves several factors. The first is the adipose involution of the bone marrow with alterations of the hematopoietic stem cells of B and T lymphocytes lineages. The second factor is abnormal migration, maturation and function of peripheral lymphocytes. A third factor is thymic involution, i.e., the reduction in mass and functionality of the thymus [100]. A global decrease of immune defenses can result in more rapid proliferation of cancer cells [101], and might explain that cancers found in elder women are larger in size and progress faster.

Our findings are consistent with recent data from the Surveillance, Epidemiology, and End Results (SEER) Program. In early stage breast cancer with high-risk 21-gene recurrence score assay, breast cancer-specific mortality is higher after 70 and increases with aging [102].

The biology of breast aging can only partially explain the high incidence and mortality rates of breast cancer in elderly women. This phenomenon is typical of developed countries, therefore other aspects i.e., related to societal characteristics need to be considered to get a bigger picture.

Society-related mechanisms

Life expectancy can be considered as a major factor explaining the increase incidence of breast cancer among elder women. Indeed, in developed countries, life expectancy has increased over the past two centuries, yielding an older population. However, since 2000, this phenomenon has grown exponentially [103]. This is one of the reasons for the increased incidence of breast cancer in elderly women.

National breast cancer screening programs do not involve women over 75 years of age. Moreover, since 2010 in France, participation is increasing among women aged 70–75, while it decreases among those 50–69 [104]. However, 70–75 participation rate is still significantly lower than among middle-aged women (50–70) [104]. The exclusion of the elderly from the screening can be mistakenly interpreted as a zero-risk situation by women. This may be the case also for health professionals. The net result is that breast clinical monitoring in elderly women is clearly insufficient. For example, only half of physicians perform a breast clinical examination routinely before prescribing mammography [105]. This omission may lead to late diagnosis with more advanced local lesions and more likely extension to lymph nodes or metastasis.

Common sense can also be misleading; it is not uncommon to hear that "the older the person, the slower cancer's progress" or "cancer in the elderly does not kill". Such die-hard lingering dogmas contribute to aggravate the problem because they lead to delays in the provision of necessary medical care. These assertions are ill conceived because it has been proven that the breast cancer-specific mortality from breast cancer increases with age [18]. In addition, up to 85 years, the leading cause of mortality in elderly women with breast cancer is the cancer itself and not co-morbidity [18]. It can be affirmed that in this respect the medical community, the patients and society in general are badly informed or not informed at all.

Moreover, co-morbidity in older women can render various therapies (chemotherapy, surgery, radiotherapy) contraindicated and thus lead to under-treatment. Proper onco-geriatric patient assessment should be made to analyze the appropriateness of a care project when therapeutic choices are difficult. In some situations, hormonotherapy is prescribed as the only therapy without considering that it is effective only on hormone-sensitive tumors. And sometimes caregivers disregard factors such as social isolation, insecurity [106], cognitive disorders, and disabilities, which are more common in the elderly. Such factors may render the therapy ineffective simply due to non-adherence.

It has been demonstrated that elderly women were less likely to receive medical and surgical treatment in concordance with guidelines [107]. Thus, different treatment patterns in the elderly may also explain the increased breast cancer-specific mortality [108].

However, unlike younger women, differences we found in clinico-pathological characteristics do not always have a clinical impact. Therapeutic impact of our findings is attenuated by co-morbidities. Nonetheless, those differences are more pertinent concerning cancer's prognosis and screening.

Conclusion

Epidemiological and societal information indicate that breast cancer in elderly women could be more properly diagnosed in "developed" countries. Its specific characteristics should be taken into account when dealing with an elderly woman. We suggest that information campaigns should be held and that training on breast clinical examination for physicians and caregivers in general should be strengthened. Efforts should also be made to educate health professionals on the importance of conducting an appropriate assessment of the health status of older patients with cancer, by using validated instruments such as geriatric assessment tools. Also, women over the upper age limit for screening programs should not be discouraged to undergo individual screening, both clinical and mammographic, if they wish so. In all cases, including in elderly women, early diagnosis implies a better prognosis. Finally, onco-geriatric assessment limits the risk of under-treatment or over-treatment, therefore if accessible, should be systematically considered.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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