Review Article

Breast cancer in the older population: a global challenge—an epidemiological perspective

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Abstract: Breast cancer is the most commonly diagnosed malignancy among women, with more than 30% of all patients being over 70 years at the time of diagnosis. The number of older women with breast cancer is expected to increase in the upcoming decades due to the ageing of the population worldwide. Incidence and mortality rates vary between and within continents because of variances in risk factors, health care quality and screening programmes. In older patients, breast cancer occurs to the background of ageing. Ageing increases the exposure to age-related diseases resulting in a heterogeneous population with large differences in multimorbidity. Multimorbidity is associated with mortality, functional impairment, poor quality of life, high health care utilization and costs, and it challenges traditional health care systems. It is therefore essential to get a grip on an individual's fitness and frailty status. Geriatric screening tools and assessments should be used to get a general idea about these aspects. In that way, biological age, rather than chronological age, in combination with an individual's life expectancy, patient preferences and potential side effects of a treatment can be the basis of individualized treatment strategies. Nowadays, this heterogeneous older population is underrepresented in clinical trials. Future research should focus on older patients with relevant endpoints, not only in developed countries, but also in less developed countries.

Keywords: Breast cancer; epidemiology; older patients; individualized treatment; geriatric assessment

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In 2020, the estimated worldwide incidence of cancer has risen to 19.3 million cases per year (1). Breast cancer is the most commonly diagnosed malignancy among women, with more than 30% of all patients being over 70 years of age at the time of diagnosis (2). Due to the increasing incidence of breast cancer and ageing of the population, it is expected that the global number of new cases of women aged 70 years and older with breast cancer will have increased with at least 70% in 2040 (3,4). Despite this growing older population diagnosed with breast cancer, knowledge about possible differences in the biology and clinical breast cancer outcomes in this age group is limited. Unfortunately, older patients are still underrepresented in clinical trials and those older patients included in trials are generally fitter (5). This article provides an overview on several epidemiological aspects of breast cancer in older adults worldwide.

Ageing of the world population

Populations around the world are rapidly ageing, with the proportion of adults aged 65 years or older growing from 6% in 1990 to 9% in 2019 (6). This percentage is expected

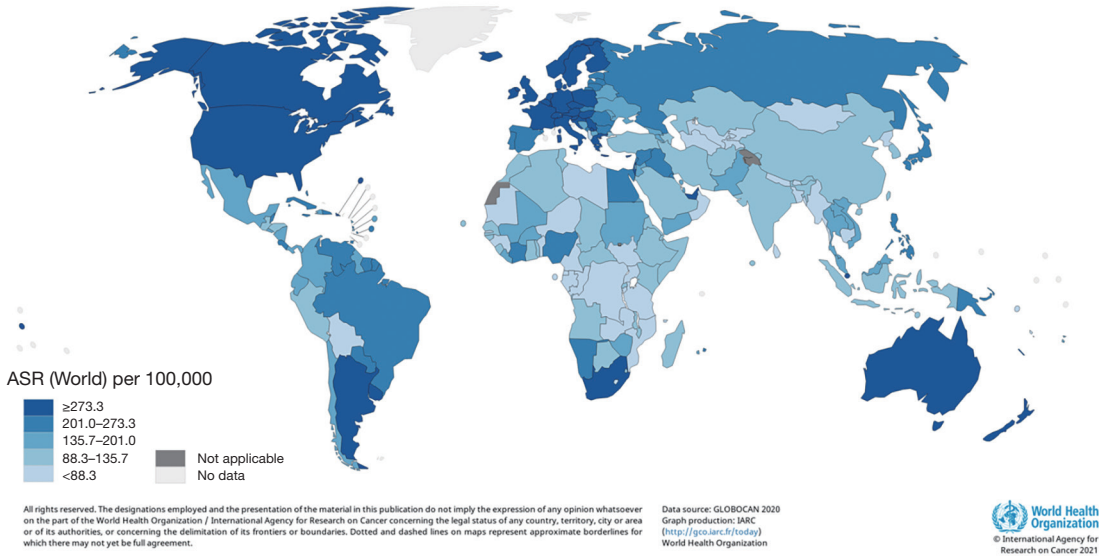

Figure 1 Estimated aged-standardized incidence rates (ASR) of breast cancer in women aged 70 and older.

to increase to 16% in 2050, with the largest increase in Eastern and South-Eastern Asia (6). Ageing increases the exposure to age-related diseases, one of which is cancer (7). Therefore, by the age of 65, more than half of the population has multiple chronic diseases, which increases to over 80% in those aged 80 years and older (8). Currently, cancer is the second leading cause of death worldwide behind cardiovascular disease (9). However, in high-income countries, the mortality burden of cancer has surpassed that of cardiovascular disease, and it is expected that cancer will become the leading cause of morbidity and mortality worldwide (9). Therefore, we can expect a substantial increase in the number of older patients diagnosed with cancer, that will pose serious challenges to our health care system and resources.

Variation in breast cancer incidence between continents

There is a global disparity in the incidence and mortality rate of breast cancer. Data from the Global Burden of Cancer study (GLOBOCAN) show that the incidence rates vary between and within continents. Northern America, Europe and Oceania generally have the highest estimated incidence rates, with age-standardized incidence rates of women of 70 years and older in 2020 of 394.6, 291.7, 372.3 per 100,000 persons, respectively (*Figure 1*) (4). Latin America with the Caribbean, Africa and Asia had age-standardized incidence rates of 215.4, 146.4 and 120.0 per 100,000 persons, respectively (*Figure 1*) (4). These high rates in the first three continents may be associated with intensive screening programmes and a higher prevalence of breast cancer risk factors, such as demographic, reproductive, hormonal and hereditary factors and lifestyle.

Breast cancer in older patients

Older women have more favourable biological tumour characteristics compared to younger patients with breast cancer. Tumours in the older population are more often hormone receptor-positive and HER2-negative (80% in patients aged ≥75 years and 65% in patients <50 years) and less often triple negative than tumours in younger patients (9% and 15% in patients aged ≥75 and <50 years, respectively) (10-12). Regarding the pathological type of malignancy, older women tend to have a higher rate of lobular carcinoma compared to younger patients (17% in patients aged ≥70 years and 2% among patients <40 years) (12,13). Older patients are also more likely to have less proliferating tumours (12). However, they are at higher risk to be diagnosed with more advanced tumours, and in a relatively large proportion of older women no proper staging is performed (10,14-16). The higher risk of advanced disease is thought to be due to delay in diagnosis at older age (17).

These late diagnoses may partly be caused by decreasing self-awareness and reduced screening in the oldest old (18).

Breast cancer in aging patients

Ageing is a heterogeneous process, that differs for individuals. This results in a very heterogeneous older population with large variation in fitness and frailty. In general, as individuals age, body compositions change: fat mass increases while muscle tissue, bone density and function of organs decrease. These changes might affect or coincide with deterioration of other domains, such as functional status, physical activity, and cognition. Patients with a decline in one or more of these characteristics are often referred to as 'frail', which is a state of decreased physiologic reserve caused by the accumulation of ageing processes across multiple organ systems, which affects the patient's resistance to stressors such as cancer or cancer therapy (19). A study investigating the prevalence of frailty among older patients with cancer classified 42% (range, 6–86%) as frail (20). Another study of women aged 65 years and older with breast cancer in the United States reported that more than 75% of patients were fit at time of diagnosis (21). Only 8% of older breast cancer patients in Australia were classified as frail in another study (22). Thus, it seems that the percentage of frailty is relatively small among older patients with breast cancer, but evidence remains scarce, and it might be due to under-reporting. Cancer and cognitive impairment are both age-related diseases, and therefore often coincide. Cognitive impairment may have significant consequences for older adults with breast cancer, impacting their level of independence, decision-making capacity, treatment compliance and quality of life. An American study showed that the prevalence of cognitive impairment in older patients with breast cancer was almost similar to age-matched controls without breast cancer (14% compared to 15%, respectively) (23). However, another study demonstrated that 41% of older patients with breast cancer had cognitive impairment at diagnosis, which is higher than what would have been expected in a comparable population without breast cancer (24,25). Moreover, a higher 10-year-cumulative-incidence of dementia was observed in older patients with breast cancer compared to their controls without breast cancer (hazard ratio 1.23; 95% confidence interval: 1.15–1.31; P value <0.001) (26). It is unclear whether this decline in cognition is due to cancer itself or to other factors, such as anticancer therapy (27). The effect of treatment on cognitive function has been excessively studied, but the results remain conflicting (28-31). Another aspect of older patients is the increase in functional dependence (32). Although multiple studies investigated functional status in patients with breast cancer, the variability among study populations, settings and questionnaires makes it difficult to interpret and compare these results with each other. One study showed that 51% of older patients had activity of daily living (ADL) impairment and 56% had instrumental ADL (IADL) impairment at the time of diagnosis (33). Another study of Hurria *et al.* investigated the effect of chemotherapy on physical function and demonstrated that 42% of older patients with breast cancer experienced a physical decline in the first month after initiation of chemotherapy. Interestingly, almost 50% of these patients recovered to approximately similar physical function scores at 12 months compared to baseline (34).

Screening programmes

Although many countries have implemented population-based screening programmes to detect early breast cancer among asymptomatic women, several countries do not have formal screening programmes. Most programmes focus on women aged 50–69 years old, while some programmes have no upper age limit, a limit of 75 years or are based on life expectancy (35-39). It is arguable whether screening in this older age group is appropriate since it might lead to overtreatment (40,41). However, it could be beneficial in situations with sufficient health care and when the individual decision, risks and benefits, life expectancy and physiological age are taken into account (40). Importantly, it is not feasible nor cost-effective for every country to implement screening programmes. Especially developing countries may lack the resources, appropriate follow-up and treatment facilities to establish screening programmes and it is therefore not recommended (42).

Treatment

The treatment of older patients is generally less aggressive than for their younger counterparts. This may partially explain the lack of improved relative survival of the former group (10). This difference in treatment strategies might be due to individual clinician preferences based on age, comorbidities or frailty (43). Due to frailty or comorbidity, intensive treatment such as chemotherapy, might not be feasible. In addition, older patients themselves might also have other treatment priorities, such as maintenance of

quality of life and cognition or the ability to carry out daily tasks instead of prolongation of life (44). In addition, most guidelines do not provide specific guidance for the treatment of older patients with breast cancer. The International Society of Geriatric Oncology (SIOG) and European Society of Breast Cancer Specialists (EUSOMA) did establish specific guidelines, which were recently revised (40,45). Some guidelines in other continents dedicate a small section to suggestions for treatment of older patients, but recommendations based on evidence-based medicine remain rare for this age group (46-48). Due to this lack of specific information, there is still a wide variation of treatment strategies within and between countries (49). The SIOG and EUSOMA state that the standard of care in surgical treatment for patients over 70 years with early-stage breast cancer should be similar to younger patients. Thus, either breast conserving surgery (BCS) combined with whole breast radiotherapy or mastectomy with or without postoperative radiotherapy (40,45). In general, older patients receive less surgical treatment, and less radiotherapy after BCS, compared to younger patients (10,50,51). The type of surgery and number of patients receiving radiation therapy also differ between countries and continents: BCS and radiotherapy is generally more common in Western Europe and the United States in comparison to Asian and African countries (13,49,52-57). There is also a large variety of patients receiving endocrine therapy and chemotherapy between different countries and age groups (10,52-54,58,59). These differences in patients receiving surgery, radiation therapy and (neo)adjuvant therapy are affected by many aspects, such as differences in socioeconomic status, cultural beliefs and accessibility and quality of health care (60-66). Although undertreatment is commonly reported among older women with breast cancer, it is difficult to discern how this impacts their prognosis and quality of life. Age alone should not dictate treatment decisions and it is therefore crucial to consider an individual's life expectancy, preferences and the expected efficacy and the potential adverse effects of a treatment. It is therefore important to involve older patients in shared decision making, and to use tailored prediction models where possible (67). There are some prediction models available for older patients to guide clinical decision-making regarding treatment strategies, such as the PREDICT tool (68,69). It is important to use prediction tools who are also validated for the older population (70,71).

Survival

The age-standardized breast cancer mortality rate for women aged 70 years and older is highest in Europe with 118.0 deaths per 100,000 persons, followed by Oceania with 105.3 deaths per 100,000 persons. Asia and Latin America, including the Caribbean, have the lowest age-standardized mortality rates with 70.8 and 86.6 deaths per 100,000 persons, respectively (4). The difference between these continents regarding the mortality rate may be associated, among others, with the higher incidence rates in Northern America, Europe and Oceania. Furthermore, it is important to consider the contribution of competing causes of death when interpreting mortality rates; in lower-middle-income countries, a relatively large proportion of people will die due to other causes than breast cancer, such as infectious diseases or cardiovascular diseases (72). Moreover, the risk for older patients of dying of other causes than cancer is higher than for younger patients, with more than 50% of patients older than 75 years dying of other causes (16,73,74). The impact of these competing risks might increase in the older generation due to aging of the population. Therefore, survival estimates that account for competing risk of mortality are especially important for this age group. One way to estimate survival is by using Fine and Gray survival models that take other causes of death into account. However, it is difficult to obtain reliable information about cause of death in the older generation, therefore, estimating breast cancer-specific survival might be challenging. Another way to estimate survival rates is by using the relative survival as it takes into account the risk of dying from other causes, by dividing observed and expected survival based on the matched general population. Relative survival has improved in many countries for younger patients, but studies reported none or only a slight improvement for older patients (3,10,75-77). This might be due to different treatment strategies and the lack of clinical trials which provide evidence-based medicine for older adults with poorer health. Generally, developed countries have higher relative survival rates than developing countries, possibly because of a poor quality of cancer care with limited accessibility in many developing countries. The stage-standardized 5-year relative survival for older patients in high-income countries in Australia, Northern America and Northern and Western Europe is estimated to be above 85% (75,78,79). In the Eastern Mediterranean region, the 5-year relative survival for patients aged 65 and older was 58% (80). Studies in Asia showed a 5-year relative survival for

this same age group of 66% in Singapore, while in a region in China this percentage was 41% for patients over 75 years of age (52,81). Korean women of 75 years and older had a 5-year relative survival of 65% (76). Africa showed similar varying rates with a 5-year relative survival of 41%, 67% and 87% for patients between 65–74 years of age in Zimbabwe, South Africa and Namibia, respectively (82). Nevertheless, it remains questionable whether cancer statistics of different countries or continents can be compared to each other, because of inconsistency in data collection and differences in the reliability of reported numbers.

Role of geriatric screening and assessment in treatment decisions and prognosis

Chronological age can differ from biological age and therefore is a poor indicator of the physiological and functional status of older adults. However, chronological age is often used in medical decision making, which can lead to both under- and overtreatment (43,83). Currently, the SIOG and EUSOMA advice a geriatric screening tool, such as the G8, for all patients aged 70 years and older to distinguish patients in either fit or potentially frail patients (40,84). If potentially frail, a comprehensive geriatric assessment should be performed to get a grip on an individual's fitness and frailty. A comprehensive geriatric assessment is a multidisciplinary evaluation that provides information about several domains, such as comorbidities, medication use, functional status, physical function, cognition, emotion, nutrition and psychosocial status. An important reason to perform a comprehensive geriatric assessment is to detect unidentified problems and risks to guide integrated geriatric and supportive care interventions (85,86). Another reason for performing a geriatric assessment is the ability to get a better impression about possible treatment outcomes, such as side effects (85,87). A comprehensive geriatric assessment also gives a better estimation of the expected life expectancy taking the competing risks into account (85). Despite the evidence of the beneficial effect of geriatric assessments regarding decision-making, treatment outcomes and treatment adherence, their current use in daily practise is still limited (88,89). This might be due to the inability to interpret a geriatric assessment (90). Moreover, a geriatric assessment is time consuming. There are also other interesting tools specifically designed to predict treatment outcomes, such as the chemotherapy toxicity tool developed by Hurria *et al.* on chemotoxicity in patients with cancer (87,91).

Performing research in an older population with breast cancer

Most clinical trials are based on younger patients and those older patients participating in trials often constitute a relatively healthy, homogeneous group (92-94). Conversely, as stated before, the general population of patients of 70 years and older is very heterogeneous regarding fitness, cognitive function and socioeconomic status. Consequently, this discrepancy between the general population and those included in clinical trial makes it challenging for clinicians to discern whether the study results can be extrapolated to clinical practice (95,96). Although several organizations encouraged researchers to design more trials for older patients, only 2% of all ongoing clinical trials on breast cancer treatment are specifically designed for older patients (94,97,98). As current clinical trials will not improve treatment strategies for older patients in the next decades, alternative research methods should be considered. An acceptable substitute could be the use of observational cohort studies when appropriate methodological methods to tackle confounding by indication, and outcomes are used (99). Currently, the most frequently reported outcomes are cancer-related endpoints, such as disease-free survival or overall survival (94). It remains questionable whether these endpoints are adequate and relevant to determine an appropriate risk-benefit ratio of therapy for older patients (44). Not only because older patients have a higher risk of competing mortality, but also because they may prefer maintenance of quality of life and functional status over prolongation of life (44). Future research should focus on older patients with relevant endpoints, not only in developed countries, but also in less developed countries.

Conclusions

Breast cancer is the most common cancer among women, affecting an increasing number of older adults around the world. Older patients with breast cancer comprise a very heterogeneous group, with differences in fitness and frailty. Chronological age alone should not be the basis of shared decision making, but rather an individual's life expectancy, preferences and the expected efficacy and the potential adverse effects of a treatment. It is therefore recommended to implement a screening tool for older patients to distinguish fit from frail patients and improve personalized medicine in the older population.

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Footnote

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