Influence of Genetic Factors on the Development of Breast Cancer in the Older Woman

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Abstract: Although the major part of the burden of disease for female breast cancer occurs at older age, less is known about the development and progression in this age group than in women under 60 years of age. As the world population continues to age, the percentage of elderly is increasing in all communities and the incidence of breast cancer will rise accordingly. Improving detection and diagnosis, and a better understanding of the mechanisms that play a role in this age group, will not only improve quality of life in older sufferers but could also contribute to the management of this disease in the adult population as well.

Development of breast cancer in the older woman is influenced by many variables that may differ from the risk factors that are involved in younger women. In addition to well-described variables at younger ages such as family history, hormonal exposure, lifestyle factors and pre-existing benign breast disease, in older women age-related changes in breast tissue, biochemistry, inflammatory responses and the immune system, as well as accumulation of DNA damage and spontaneous mutations are suspected to contribute to the complex relationship between ageing and breast cancer. We review the available data on the role of age-related changes and genetic mutations in the development of breast cancer in older women as well as their effects on estrogen metabolism and free oxygen radical inactivation.

Keywords: Aging, Breast, Cancer, Elderly, Epidemiology, Genetics

INTRODUCTION

Over 30% of new onset breast cancer occurs in women over the age of 70 [1], over 50% of breast cancer deaths in those over 65 and it is well known that both incidence and mortality rates increase with age [2]. Currently worldwide there are an estimated 3,426 billion women at risk of developing this disease, of whom about 200 million are over 70 years of age. With increasing life expectancy this figure is estimated to increase to almost 300 million in 2030 [3], causing an estimated doubling of incident breast cancer cases.

Breast cancer in women over 70 years old seems to have a better prognostic profile due to the ageing process of the mammary gland, with low tumour grade, higher estrogen receptor (ER) positivity, low HER2 positivity and low proliferative index [4]; in spite of this profile, mortality is 6-11 times higher than in the <70 year age group [2]. A variety of factors could contribute to the high frequencies, including the process of ageing itself, low screening uptake with late presentation, co-morbidities, ageism and sub-optimal treatment; and genetic alterations that promote increased susceptibility or malfunctioning defence systems and might have been latent during adult life [2,5-8]. As is the case for many of the diseases that affect individuals at a later age, there is a lifelong interaction between genetic predisposition, hormones and lifestyle factors [8]. This makes breast cancer a heterogeneous disease, as expressed in molecular markers, histology, gene-expression profiles and patterns of genomic instability.

Cellular mechanisms exist that could link ageing and cancer, as reduction of cellular proliferation will protect against cancer but promote ageing and vice versa [9]. Many cellular mechanisms are genetically determined, including the enzyme systems that regulate oestrogen, progesterone and androgen metabolism, free-radical production and scavenging, anti-oxidant metabolism, and mechanisms for genomic stability (e.g. telomere length), tumour suppression, DNA repair, senescence and apoptosis. However, the role these mechanisms play in the initiation, development and spreading of cancer is largely unknown as is their contribution in the older individual with cancer [5]. This article will focus on the influence of genetically determined risk factors on development of breast cancer in women over 70 years of age.

EPIDEMIOLOGY

Incidence

Worldwide, in women under 70 years of age, the incidence of breast cancer has increased with 2-3% per year
since the 1960's, the main increase occurring in the age group of 50-69 years [10]. Widespread introduction of screening mammography in the 1980's resulted in a steady incline in the number of diagnoses in many developed countries [10]. In the over-70 group however, slight decreases were found in the early 2000's in some countries in North Western Europe and the United States (compared with 1990) [11]. What causes these decreases is unknown; speculations as to the influence of changes in reproductive patterns, use of hormonal replacement therapy (HRT) and the effects of screening in younger age groups or the lack of it in the elderly have not yet been substantiated [10]. Taking geographical differences into account, incidences in older individuals were consistently 2 to 3 times higher than in the younger women (1997-2004) [2].

In an earlier report on the SEER database (USA), the incidence in women over 65 years was 0.322%, increasing to 0.375% in those over 85, compared to 0.060% in the under 65 [12]. The overall age-specific breast cancer incidence curve is bimodal and reflects the superimposition of two rate curves: the early-onset cancers with a mean age of diagnosis at about 50 years and the late-onset ones with a mean age of diagnosis at around 70 [13]. This bimodal curve shows the deflection point to occur at the time of menopause [13]. It has been estimated that by 2030, almost two-thirds of patients with breast cancer will be over 65 [14]. Yet this age group is consistently under-represented in both research and clinical trials.

Mortality

Worldwide, breast cancer is the leading cause of cancer-related death in women and again, mortality rates are known to increase at older age [11]. In contrast with rising incidences, mortality has been stable or even decreased in most countries since the 1970's [10]. This has been attributed to widespread implementation of screening, better early detection (of small tumours) and improved treatment [10]. After the year 2000 in a number of countries mortality declined with 2-3% per year in the younger age groups but increased in the elderly [15,16]. Between 2001 and 2004 the mortality in the 70+ age group in North Western Europe and North America was 6-11 times higher than in the 35-49 year olds [2]. Various factors have been implicated to contribute to this mortality trend, including ageing per se, delayed presentation and reduced (mammographic) screening, decreased immunological defences in older individuals and differences in tumour biology and hormone-receptor status with increasing age.

Firstly, ageing and development of cancer seem closely linked. Older populations are also known to have a generally poorer prognosis when diagnosed with a malignancy; the causes of both the higher incidence and mortality are likely to be varied and manifold, such as wear-and-tear of cellular machinery, accumulation of damaged DNA or mutations causing genomic instability [5]. Secondly, the definition of "older" has undergone a paradigm shift in the last century from one with chronological age as the central criterion, to a definition incorporating the physiological age, functional independence and co-morbidities of the individual. Co-morbid conditions and functional independence are inde-
crease of the subcutaneous and perimammary fat [21]. There is general agreement that the lobular involution and stromal senescence are determining the decline in proliferative activity after menopause [7] and that this regression results in lower tissue density on mammography making detection of lesions easier in some older women [22]. Predisposition to develop breast cancer may be linked to incomplete involution of normal mammary tissue with ageing [8], increased intrammary adipose tissue and senescence of the stroma [21]. With regards to tumour biology, older studies did not find an age-related variation in tumour histology, with infiltrating ductal carcinoma the most frequent tumour type [12]. More recent studies also found infiltrating ductal carcinoma the most prevalent but concluded that with ageing there is an increase in the percentage of tumours that are oestrogen receptor (ER) positive, with a low S-phase, a low tumour grade and human epidermal growth factor receptor (HER) 2 negative [23]. This lower proliferative index however, has not resulted in better survival in this age group.

As ovarian oestrogen production decreases, ER expression will increase due to up-regulation, whereas Progesterone Receptor (PR) density does not seem to undergo age-related changes. Between the third and the sixth decade, ER expression increases >3-fold (normal ageing of the breast), levelling off after around 60 years of age [13]. In certain individuals, postmenopausal oestrogen in the mammary gland approach the premenopausal ones as androstenedione and testosterone are converted to oestrone and oestradiol by the enzyme aromatase in mammary adipose tissue and stromal cells. Intramammary production of aromatase (encoded by CYP19A1) shows a marked age-related increase although there is individual variation in its expression [24]. Stromal senescence is thought to alter the extracellular matrix in such a way that neighboring premalignant epithelial cells are attracted and stimulated, promoting tumorigenesis [25]. In conclusion, normal ageing of the mammary gland will generally lead to variable levels of epithelial involution, high ER expression, variable levels of oestrogen production within the gland’s adipose tissue and an altered extracellular matrix, predisposing the individual to development of breast cancer. Currently at least 5 breast cancer phenotypes are known each having specific genomic changes, expressed in their transcriptional profile, histology, biology and behavioural pattern [26]. This classification associates well with clinical parameters, clinical diagnostic criteria and even some mutations. In older women the predominant type is the "Luminal A", low grade with a low proliferative index, positive for ER and PR and mostly with wild type p53. "Luminal B" has few or no PR’s, mostly also the wild type p53, and a higher rate of local recurrence than "Luminal A". Basal tumours and BRCA1-related ones occur mostly in young, premenopausal women and contain specific mutations that determine biology and behaviour [27]. Gene associations therefore need to take tumour heterogeneity into account.

Breast tissue is known to contain a limited number of stem cells - pluri-potent cells that can produce groups of differentiated malignant cells that form a tumour. Numbers of these stem cells decline with advancing age and the cells themselves change - a phenomenon found also in certain tumours in the elderly [28]. Ageing of the stem cell itself might thus predispose the older breast to malignant transformation.

**Changing Biochemistry**

The complex processes of ageing are suspected to play a central role in the development and progression of cancer, mediated by activation of oncogenes and suppression of the function of suppressor genes [5]. This "final common pathway" could be reached via different mechanisms including genomic instability caused by accumulation of damaged DNA (reactive oxygen species, repair defects) or centrosome amplification; inefficient autophagy - where damaged organelles and cells might be partly responsible for cancer development; a decline in mitochondrial function causing lack of ATP, ineffective removal of free oxygen radicals and damage of mitochondrial DNA; and situations where chronic inflammation is present - in which a variety of inflammatory substances are produced that lead to DNA damage (causing changes in gene-expression), post-translational protein modification and microRNA expression all promoting tumorigenesis [5,29].

**Age-induced Compromise of the Immune System**

Reduction in immunological defences with ageing has been well described [30]; studies found age per se to be a determinant of the way breast cancer behaves. Up to 70 years of age, increasing age decreased the prevalence of metastasis with 13% for every decade, but in the over 70, the chances of lymph node involvement doubled per decade for tumours smaller than 15 mm; however, if the tumour size was over 42 mm, the risk of lymph node invasion decreased [31]. These facts support the hypothesis that there might be two kinds of tumours in older women: those that grow slowly and do not metastasize irrespective of their size, and those ones that invade lymph nodes in an early stage. This invasion then cannot be prevented due to the reduction in immunological function [31].

Elderly were found to have higher production of several pro-inflammatory cytokines and chemokines but lower activity and efficiency of other parts of the immune system [30]. This causes dysregulation of the inflammatory process, leading to a state of chronic inflammation. Within this inflammatory environment, the pro-inflammatory molecules are suspected to promote development of mutations, a pro-tumorigenic response [5]. Various polymorphisms of cytokines have been found to confer an increased risk on inflammatory disease [32], and cancer. On the other hand, oncoproteins have been found to induce an inflammatory milieu; the ras- and myc- oncogenes for example, were found to play a causal role in a.o. tumor angiogenesis [33] via secretion of certain cytokines (e.g. IL-6). Human breast cancer cells were found to express chemokine receptors and their ligands detected in organs where metastatic potential was high [34]. In summary, dysregulation of the immune system coincides with ageing, and promotes a carcinogenic response via a chronic inflammatory state.
HORMONE-RELATED RISK FACTORS

Endogenous and Exogenous Hormonal Exposure

Initiating events for cancerogenesis have to occur relatively early in life as breast tissue seems most sensitive to adverse exposure before the age of 36 years [35,36]; the well-known association of birthweight and height (surrogate marker of growth factor exposure in utero) are an example of initiators in early life [37]. There occur a variety of changes in gene-expression in mammary epithelial cells following pregnancy and lactation, and immediately post weaning inflammation takes place, followed by apoptosis. Tissue-resident adult stem- or progenitor cells repopulate the gland at the time of the next pregnancy [38]. Progesterone might be involved in activating these mammary stem cells [39]. These hormone-sensitive and replication-competent subpopulations within undifferentiated terminal duct lobular units are the most sensitive to malignant transformation and numbers decline with ageing and parity [40], explaining the influence of parity on breast cancer incidence.

One study [41] found ER expression to be abnormally increased in breast cancer tissue: the increase in ER content of normal ageing breast tissue was found to be 10-fold less than the increase in ER content of breast cancer tissue up to age 60; this difference rose steeply with further ageing, reaching a 25-fold difference at about 80 years of age [13,41]. This is in sharp contrast to all other biomarkers (used as surrogate indicators of cancer growth and genomic instability) which decreased markedly after age 40 [41]. This on the one hand helps to clarify the increase of breast cancer incidence in women with long-term estrogen exposure [9], and on the other hand suggests that the biology of breast cancer is age-dependent with late-onset breast cancer found to be slower growing, genomically more stable and with higher ER content than the early-onset variety.

Increased BMI and Insulin Resistance

Overweight and obesity induce varying degrees of insulin resistance, resulting in hyperinsulinaemia. Hyperinsulinaemia decreases the concentration of sex-hormone binding globulin, thus increasing the amount of free estrogen in the body. In postmenopausal women, high insulin levels are associated with an increased risk for breast cancer [42], and in the WHI study-arm on HRT with low estrogen dosage, this increased risk was seen to be modified in obese subjects. Three prospective cohort studies with over 6500 breast cancer patients all concluded that increased physical activity was associated with a decline in risk [43]. Physical activity is known to decrease insulin resistance. Peripheral insulin resistance is the underlying mechanism of hyperinsulinaemia and non-insulin dependent diabetes mellitus in the elderly and is known to increase with ageing. However, whether this peripheral resistance contributes to development of late-onset breast cancer is yet unknown.

Benign Breast Disease

The relative age-specific incidence of clinically detectable benign breast disorders declines dramatically after the menopause [44]; although in an autopsy series the incidence of histologically benign lesions did increase with age [45]. Precursors for breast cancer are likely to exist in benign breast disease [46], and age at diagnosis might modify the cancer risk related to the histology of the lesion [47]. The switch from benign to metastatic disease is likely to be largely determined by the extracellular matrix. Many cell types produce soluble factors that signal to the tumour cells, including adipocytes, endothelium, fibroblasts, blood-derived cells and the mammary epithelium [48], and senescent stroma is also thought to change the extracellular matrix, promoting cancer development [49].

EXTERNAL EXPOSURES

Lifestyle Factors

A review of recent studies on the association of alcohol, diet and physical activity confirmed the importance of a healthy lifestyle to reduce the risk of breast cancer [43].

Early-life Exposures

As mentioned before, studies performed on groups of women who underwent accidental irradiation (e.g. Hiroshima) found, that the initiating event for the development of breast cancer had to take place before 36 years of age [36]; studies of occupational exposure are rare, but reached the identical conclusion [35]. The "LEARn" model [50] offers an interesting explanation of the mechanism by which environmental influences can modulate gene-expression – the secondary structure of the gene undergoes permanent changes on contact with the offending agent, despite an unchanged primary DNA sequence.

GENETIC MUTATIONS AS RISK FACTORS

Many diseases in later life are the result of interactions between genes, their expressions, and environmental factors. This is perhaps the main reason why diseases in old age are more heterogenous than at any other stage in life. There are several mechanisms in which genes can exert influences in the aged individual, including germ-line mutations in genes with a delayed age of onset (late-onset diabetes mellitus, Huntington's Disease), in genes that have a survival advantage at childbearing age but become detrimental later- the principle of antagonistic pleiotropic gene action- (e.g. hereditary haemochromatosis, obesity), in tumour-suppressor- and proto-oncogenes, and in genes that confer longevity (those involved in stress responses, anti-oxidant defense, apoptosis, cellcycle regulation and genes involved in genome-stability pathways –like DNA mismatch repair genes, including BRCA1 and 2) [48]. Somatic mutations and genomic instability accumulate with ageing and may be the cause of cancer per sé. In aged cells, several cancer-related genes were found to be transcribed in a different way than in younger cells as were certain genes that control epigenetic changes [51]. BRCA1 and 2 are involved in repairing breaks in double-stranded DNA; both are tumour suppressor genes and certain mutations confer a life-time risk of breast cancer of >90%. However, other mutations in this gene are found less frequently in breast cancer patients than in controls and so are thought to confer protection against breast cancer [52].
However, less than 5% of breast cancer cases can be explained by hereditary high penetrance mutations; the other 95% is sporadic, meaning that there is no identifiable mutation in one of the known breast cancer susceptibility genes and involvement of moderate- and low-penetrance genetic variants is strongly suspected [53]. However, in older age groups there has not yet been much research done into the frequencies, combinations and effects of these polymorphisms.

Inherited Mutations with High Penetrance and Low Frequency

High penetrance genes occur in familial breast cancer syndromes where germline mutations in single genes are found that confer a high risk, e.g. BRCA1 and 2 [54]. However, these genetic risk factors are predominantly found in premenopausal women, and the possibility of detecting a mutation in the BRCA genes decreases markedly with age [55]. BRCA1 and 2 are tumour suppressor genes, located on 17q21 and 13q12-13 respectively and specific hereditary mutations are described to increase breast cancer risk to 65% and 45% at age 70 respectively [56]. In contrast to the rare, specific familial mutations alluded to, no other common SNP’s that confer a measurably increased risk have been found, neither on an individual basis or with a combination of tag SNP’s [51]. In this study of familial breast cancer, only 4% of the studied subjects was >70 years old. However, BRCA genes are large with mutations spread over the whole gene, and different mutations have been associated with different risks on developing breast cancer [53,58]. Mutations in tumour-suppressor genes often result in a loss or a “reduction to homozygosity” of the second allele, so the wild-type allele is lost [59] and the function of the BRCA locus eliminated. Certain studies have suggested that an intact wild type allele could be protective against development of breast cancer [60], and that it’s absence would confer an increase in risk. Risk estimates also show marked variation with age at diagnosis, the localisation of the mutation in the gene and site and histology of the cancer [61], and the influence of lifestyle factors has been discussed earlier.

Very few studies have focused on the presence and effects of mutations in these genes in older individuals (70 years and older), but with the human genome project completed techniques are now available to detect gene variants and their potentially associated risks in aged individuals. One study has looked at BRCA1 polymorphisms in centenarians - as breast cancer is exceedingly rare in this age group it was hypothesised that sequence variants with optimal effect could contribute to the absence of this malignancy in this age group. In this study, 2 groups of centenarians from different backgrounds were tested against breast cancer probands and controls and no significant differences in BRCA1 allele frequencies were found [48]. All these facts together makes it unlikely that high penetrance tumor suppressor genes are a major role player in breast cancer development in women over 70 years of age.

A second group of high penetrance alleles are the germ-line mutations that occur in familial cancer syndromes like TP53 mutations in Li-Fraumeni cancer syndrome, PTEN mutations in Cowden syndrome and STK11/LKB1 mutations in the Peutz-Jegher syndrome [62]. Mutations in these genes typically occur in only one allele that then acts as the dominant one; cancers can develop in any tissue in contrast to mutations in tumor suppressor genes that tend to be limited to a specific tissue [59]. As these allele frequencies are rare in the general population, carriers are not likely to survive into their 7th decade and no specific relationship to breast cancer exists, they will not be discussed further.

Somatic mutations of TP53 however, can arise in many different tissues and then are only present in the tumor cells: BRCA1/2-related breast cancers are found to have somatic mutations of TP53 in 29-84%, indicating that the DNA damage caused by the loss of BRCA function can not be suppressed by the p53 protein. TP53 is a proto-oncogene, part of one of the evolutionary conserved pathways which respond to stress and play a regulatory role in ageing and age-related diseases like cancer. In mice, the efficiency of the TP53 response to stress decreases with ageing, creating an increased chance on malignant transformation [60]. Certain mutations of TP53 confer an increased survival to their carriers, but at a cost of an increased risk of cancer [62]. A recent report [63] has described a novel enzyme (Pin 1) which helps to keep certain proteins (a.o. p53) in a functional state- promoting longevity and preventing cancer. Pin 1 seems to be ubiquitous, is involved in telomere biology as well as in the cell cycle, and influences secondary protein structure- thus conveying a means of cellular signalling. Over-expression (possibly by the ageing process) influences oncogenesis via signalling pathways and by its involvement in cellular division.

Inherited Mutations with Low Penetrance and Low Frequency

Some genetic variants that have been associated with breast cancer risk are rare polymorphisms with a small effect, all involved in DNA damage detection- and repair mechanisms. This group includes CHEK2, PALB2, BRIP1, NBS1 and ATM; characteristically there is a limited number of variants that increase risk of breast cancer and estimation of contribution to familial risk was less than 3% [53], but other variants might exist - whose frequencies in the general population are likely to be even lower [64]. At present testing is recommended when there is increased familial risk [65] and very few if any women over 70 have been included in these studies.

Inherited Variants with Low Penetrance and High Frequency

The Population Attributable Risk (PAR) caused by the mentioned inherited high- and low penetrance genes is low - as these genes are rare. For the general population, there is a 7% risk on breast cancer by age 70 [53]. Other genes that may increase susceptibility to breast cancer are the so-called low-penetrance, high-frequency genes, conferring a small or moderate contribution to the risk on breast cancer, but expected to be found in high frequency in the general population [67]. Genome-wide association studies (GWASs) have identified variants of genes in this group that can contribute to familial risk as well as to sporadic cancers and might be mediating the effect of environmental factors [66]. The Mil-
lion Women Study however, did not find any variation in breast cancer risk for 12 SNP's and 10 known environmental risk factors [67]. Candidate genes are found in diverse molecular systems, including metabolic-, oestrogen- and progestosterone-, and immunomodulator pathways, as proto-oncogenes, in epigenetic- and in apoptotic mechanisms [53,66]. Most of the variation in these genes exists as single nucleotide polymorphisms (SNP’s). Summaries of known genes, their allele frequencies, odds ratios and other statistics have been published by various groups [53,66,68], but there are major flaws in many studies causing multiple contradictions and poorly reproducible results [27]. The fact that many studies’ population size is too small to provide statistical significance, that there is failure to stratify populations into groups that correlate with the 5 different types of breast cancer, that cases are compared to controls which are not biologically or genetically equivalent and that SNP’s in certain genes have different expressions in malignant tissues lead to false positives as well as false negatives. GWASs studies have delivered some better reproducible genes that can be linked to the development of breast cancer (FGFR2, LSP1, MAPK3K1, TGFB1, TOX3, TNRC9, CASP8, 2q35 and 8q) but very few studies have included women over 70 years of age. The study by van Heemst et al. [62] in a group of patients 85 years and over, clearly showed that a certain SNP may have effects at older ages only as it protects the individual from accumulation of DNA damage, uncovering a phenotype that cannot be measured in younger age groups. Another study, investigating the association of SNP’s in steroid hormone pathways with breast cancer in different age groups, found 4 SNP’s with a markedly different effect at different ages [69]. A limited overview of the classification of breast cancer related genes is presented in Table 2.

### Table 2. Classification of Genes Implicated in Breast Cancer

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<tr>
<th>Inherited mutations with high penetrance and low frequency</th>
<th>Inherited mutations with low penetrance and low frequency</th>
<th>Inherited variants with low penetrance and high frequency</th>
<th>Somatic mutations</th>
<th>Gene-amplification</th>
<th>Gene-deletions</th>
<th>Population genetic background</th>
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<tr>
<td>Germ-line mutations conferring high risk: BRCA1, BRCA2</td>
<td>Germ-line mutations in familial cancer syndromes: TP53, PTEN, STK11/LKB1</td>
<td>Germ-line polymorphisms conferring a small individual risk: FGFR2, LSP1, MAPK3K1, TGFB1, TOX3, CASP8, TNRC9, 2q35 and 8q (risk increased in presence of BRCA1 or 2)</td>
<td>Somatic mutations</td>
<td>Gene-amplification: HER-2/Neu, Cyclin D, WIP1, GASC1</td>
<td>Gene-deletions: PTEN, TP53, CHECK2</td>
<td>SNP’s (Single Nucleotide Polymorphisms), CNV’s (Copy Number Variations) (MDM2, 4)</td>
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<tr>
<td>Inherited mutations with low penetrance and low frequency</td>
<td>Germ-line mutations with moderate risk: CHEK2, PALB2, BRIP1, NBS1, MRE 11 and ATM</td>
<td>Germ-line polymorphisms conferring a small individual risk: FGFR2, LSP1, MAPK3K1, TGFB1, TOX3, CASP8, TNRC9, 2q35 and 8q (risk increased in presence of BRCA1 or 2)</td>
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<td>Inherited variants with low penetrance and high frequency</td>
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### CONCLUSIONS

In recent years, much has been discovered with regards to individual variations in genetic expression that confer an increased risk of breast cancer. Most of this research was done on patients with familial breast cancer and younger, premenopausal women; however, as over 90% of breast cancer cases are sporadic and elderly patients (unlikely to possess the genes found in the group with familial cancers) make up roughly one-third of incident cases, this group could provide us with new insights in the mechanisms of development of this cancer. The few studies that have been published delivered unexpected results and with the worldwide increase of breast cancer in the older population, research in this field could contribute to the well-being and quality of life of this age group. Moreover, if certain polymorphisms would be found in higher frequencies in this age group, screening in the offspring could help with stratification of risk groups among this offspring, with the intention of optimalising investigations and detection in the different risk groups.

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### CONFLICT OF INTEREST

None declared.


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