Review Article

Does genetic testing have any role for elderly breast cancer patients? A narrative review

Yuk-Kwan Chang, Ava Kwong

Department of Surgery, The University of Hong Kong, Hong Kong Hereditary Breast Cancer Family Registry, Hong Kong, China

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Correspondence to: Professor Ava Kwong, MBBS, BSc, PhD, FRCS, FRCS (Edin), FCSHK, FHKAM (Surgery). Division of Breast Surgery, Department of Surgery, Queen Mary Hospital, No. 102, Pokfulam Road, Hong Kong, China. Email: akwong@asiabreastregistry.com.

Background and Objective: Hereditary breast cancer is associated with young age of onset. However, a recent study showed that the prevalence of genetic mutations in postmenopausal breast cancer patients was 3.5%, which was significantly higher when compared to 1.3% in cancer-free women. This posed the question of whether genetic testing should be extended to older patients. This literature review aimed to highlight the controversies of genetic testing for older breast cancer patients, and their subsequent management after a positive genetic test.

Methods: Literature search was performed targeting published papers in English from year 2000 onwards in PubMed.

Key Content and Findings: In BRCA mutation carriers, breast cancer incidence rapidly increases from early adulthood until 50 years old, then it reduced with age. Nonetheless, older BRCA mutation carriers have a higher breast cancer incidence when compared to non-carriers. The implementation of genetic testing in elderly breast cancer patients should take into account the chance of underdiagnoses, the benefits of identifying a genetic mutation and balancing it with increased medical cost and patient anxiety. Recent data suggested that BRCA1/2 mutation detection rate in postmenopausal breast cancer patients until 65 years old could be higher than what was traditionally expected, at 2%, while breast cancer patients who were 65 or above had a detection rate of about 1%. Benefits of risk-reducing contralateral mastectomy for primary breast cancer could be less in older patients due to competing causes of mortality, and a lower risk of contralateral breast cancer when compared to their younger counterparts.

Conclusions: Current management guidelines for BRCA mutation carriers were based on evidence targeting younger population; there were no specific guidelines or studies targeting older mutation carriers. Individual factors such as comorbidity, competing causes of mortality, cancer risks and personal preference should all be considered when managing elderly mutation carriers.

Keywords: BRCA mutation; breast cancer; elderly; postmenopausal; genetic testing

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Introduction

Identifying breast cancer patients with hereditary genetic mutations, particularly in *BRCA1* and *BRCA2* genes which are renowned to impose substantial life-time risks for cancers, has significant impact not only in the proband patients, affecting their cancer management and prevention, but also in cancer-free family members through family testing. Conventionally, genetic testing is offered to breast cancer patients who had hereditary risk factors including young age of disease onset, personal cancer history such

Table 1 The search strategy summary

Items	Specification
Date of search	July–November 2021
Databases and other sources searched	PubMed
Search terms used	BRCA mutations", "genetic mutations", "hereditary breast and ovarian cancer syndrome", "elderly", "post-menopausal", "genetic testing", "cancer incidence", "cancer detection rate", "contralateral breast cancer", "risk-reducing mastectomy", "prophylactic mastectomy", "chemoprevention", "tamoxifen", "bilateral salpingo-oophorectomy"
Timeframe	Year 2000 onwards
Inclusion criteria	Language: English
Selection process	Single author performed search and selection of literature independently

as bilateral and multiple cancers, and strong family cancer history particularly those involving first-degree relatives and multiple generations. However, the prevalence of genetic mutations in relatively older breast cancer patients might have been underestimated over the years. Given that nearly half of the women diagnosed with breast cancer are age 65 and above, and the breast cancer incidence is increasing (1), the role of genetic testing and management of hereditary breast cancer in older women warrant attention. Therefore, this literature review aimed to highlight the controversies of genetic testing for elderly breast cancer patients, the breast cancer incidence of elderly BRCA mutation carriers, and to summarize the management considerations. We present the following article in accordance with the Narrative Review reporting checklist (available at https://abs.amegroups.com/article/view/10.21037/abs-21-122/rc).

Methods

Literature search was performed targeting published English literature from year 2000 onwards in PubMed. Search terms included "BRCA mutations", "genetic mutations", "hereditary breast and ovarian cancer syndrome", "elderly", "post-menopausal", "genetic testing", "cancer incidence", "cancer detection rate", "contralateral breast cancer", "risk-reducing mastectomy", "prophylactic mastectomy", "chemoprevention", "tamoxifen", "bilateral salpingo-oophorectomy". The search strategy is summarized in *Table 1*.

Prevalence of genetic mutations in elderly breast cancer patients

The prevalence of *BRCA1/2* mutation-associated breast cancer among all breast cancer has been reported to be 5–15% (2). It is well-known that breast cancer patients with *BRCA1/2* mutation have a young age of disease onset, with more than half being diagnosed at an age of less than or equal to 40 (3,4). However, the prevalence of pathogenic variants in older breast cancer patients is not well studied. Until recently, Kurian *et al.* reported a study with data from a Women's Health Initiative which compared 2,195 female breast cancer patients who were diagnosed at a median age of 73 years old to 2,322 breast-cancer free women. The prevalence of mutations in 10 hereditary breast cancer associated genes, including *BRCA1* and *BRCA2*, were 3.5% (95% CI: 2.82–4.42) of the unselected postmenopausal breast cancer patients, compared with 1.3% (95% CI: 0.87–1.84) of cancer-free women. In particular, 1.2% (95% CI: 0.78–1.73) were detected to have *BRCA1/2* mutation; the percentage was even higher at 2.2% in postmenopausal women who were diagnosed before age 65. While for those aged 65 or above, 1.0–1.3% were found to have *BRCA1/2* mutations and 1.3–3.2% had mutations in other breast-cancer associated genes. These percentages were higher when compared to only 0.22% *BRCA1/2* mutation positive rate in control group (5). Thus, the mutation detection rate was lower in older breast cancer women when compared to their younger counterparts, but was higher when compared to cancer-free women.

One point to note was that in this study, this group of postmenopausal primary breast cancer patients were unselected. When considering their hereditary risks such as family history, personal cancer history, biology of cancer etc, 30.8% (8 out of 26) of the *BRCA1/2* mutation positive and 32.1% (25 out of 78) of any other breast-cancer associated genes mutation positive breast cancer patients were fulfilling

the conventional genetic testing guidelines (5). In other words, without genetic testing of all breast cancer patients, 0.8% (18 out of 2,195 patients) of *BRCA* mutations and 2.4% (53 out of 2,195 patients) of any other breast-cancer associated genes mutations in postmenopausal breast cancer patients would be underdiagnosed. These underdiagnosis rates may not seem to be over alarming. Nevertheless, this study by Kurian *et al.* has demonstrated that the prevalence of pathogenic variants in postmenopausal breast cancer patients was similar to that of Ashkenazi Jewish population, whose prevalence of *BRCA* mutation was 2.3% due to three founder mutations, and the percentage was higher in women and younger patients (6). Therefore, the U.S. Preventive Service suggested genetic counselling and testing in all patients with Ashkenazi Jewish ancestry (7). Similarly, could the prevalence of mutations in older breast cancer patients be high enough to justify universal genetic testing?

Controversy of extending genetic mutation testing

Genetic testing extending to all breast cancer patients regardless of clinical hereditary risk factors is controversial. It has been argued that the proportion of mutation carriers who didn't fulfil conventional testing criteria was not negligible, due to small pedigrees and incomplete penetrance. In an earlier study in 2007, it was shown that more than 60% of the mutation carriers didn't fulfil clinical criteria for genetic testing (8). This high percentage could be due to more stringent genetic testing criteria in the past. In a more recent cohort of 1,371 breast patients including 42 (3.1%) *BRCA* mutation carriers, using young onset age of below 40 years old or triple-negative breast cancer as criteria detected 32–34% of carriers; using positive family history identified 37%; while using age less than 60 years old identified 90% (9). The potentially undiagnosed mutation carriers could be missed from preventive measures and enhanced surveillance. Recently, the American Society of Breast Surgeons Consensus Guideline in 2019 stated that all breast cancer patients (newly diagnosed or with a personal history) should be offered with genetic testing (10), and explained genetic testing criteria was initially set high due to cost in the past. In the era of next generation sequencing, the cost of testing has dropped dramatically.

On the other hand, given the high prevalence of breast cancer and good survival, offering all breast cancer patients genetic counselling and testing could still pose a significant challenge in terms of cost. A systematic review of *BRCA* genetic testing programmes evaluation showed that family history-based screening was potentially very cost-effective, while there was currently no evidence for screening of all newly diagnosed breast or ovarian cancers (11). The National Comprehensive Cancer Network recommended testing for *BRCA1* and *BRCA2* only in women with a high risk of hereditary breast cancer syndrome based on conventional genetic test criteria, with the latest inclusion of breast cancer of particular biological subtypes for therapeutic use of polyadenosine diphosphate-ribose polymerase (PARP) inhibitors, such as HER2 negative metastatic breast cancer (12,13). US Preventive Services Task Force also recommended against routine genetic testing for breast cancer patients without personal or family history/ancestry which suggested a potentially harmful *BRCA1/BRCA2* gene mutation (7). Particularly for elderly patients, it is important to know if there would be any benefits or changes in management if genetic mutation is identified.

Breast, ovarian and pancreatic cancer risk of elderly patients with *BRCA* mutations

Limited data was available for elderly *BRCA* mutation carriers in the literature. Lifetime risks of breast cancer were 45–80% for *BRCA1* and 30–60% for *BRCA2*, while ovarian cancer risks were 20–55% for *BRCA1* and 5–20% for *BRCA2* mutation carriers (14-16). However, studies usually stopped risk estimates at age 70 with only a few extended to age 80 (17). In a prospective study by Kuchenbaecker *et al*, the cumulative breast cancer risk to age 80 years was 72% for *BRCA1* and 69% for *BRCA2* mutation carriers. The age with the highest risk of breast cancer was 41–50 years old for *BRCA1* and 51–60 years old for *BRCA2* mutation carriers, while older women at age 71–80 also had an elevated incidence of breast cancer: 16.5 and 21.9 per 1,000 person-years for *BRCA1* and *BRCA2* mutation respectively. This showed that breast cancer incidences in *BRCA* mutation carriers increased sharply in early adulthood until 50 years old, then the incidence reduced to be at a rate of 16–22 per 1,000 person-years until age 80 years (*Table 2*) (17). Similarly, for ovarian cancer, mutation carriers were at highest risk from age 61–70 with an incidence of 10–29 per 1,000 person-years, while older women at age 71–80 had an incidence of ovarian cancer at 5.7 and 2.3 per 1,000 person-years respectively for *BRCA1* and *BRCA2*

Table 2 Breast cancer and ovarian cancer incidence in *BRCA1/2* mutation carriers above 50 years old

	Age (years)	Breast cancer			Ovarian cancer		
		Incidence per 1,000 person-years	Cumulative risk, %	Standardized incidence rate	Incidence per 1,000 person-years	Cumulative risk, %	Standardized incidence rate
BRCA1	51–60	25.7	56	9.7	13.8	20	53
	61–70	25	66	7	29.4	41	69
	71–80	16.5	72	4.8	5.7	44	12
BRCA2	51–60	30.6	53	11.4	6.5	7	24.5
	61–70	22.9	61	6.4	10.3	15	21.5
	71–80	21.9	69	6.6	2.3	17	4.4

Data from Kuchenbaecker *et al.* (17).

mutation (*Table 2*) (17). This suggests that the risk increase of breast and ovarian cancer does decrease with age, but older mutation carriers still have a higher cancer risk than normal individuals and can still develop new malignancies beyond age 70.

Besides breast and ovarian cancer risk, risk of pancreatic cancer is of particular concern for elderly mutation carriers, especially for those who had family history of pancreatic cancer (18). The pancreatic cancer risk was approximately doubled in both female *BRCA1* and *BRCA2* mutation (19). In a retrospective study of 69 female *BRCA* mutation carriers who lived to age 75 or above, 72% had a prior history of breast cancer and 39% had a history of ovarian cancer. Three out of four new cancers developed after genetic testing in the cohort were pancreatic cancers; all diagnosed in *BRCA2* mutation carriers (20). Inherited pancreatic cancer was reported to have a younger age of onset (58–68 years old) than sporadic pancreatic cancer (61–74 years old) (21), but the common age of onset was still older than *BRCA*-associated breast and ovarian cancer. However, as there were no known effective screening options for pancreatic cancer (22), this could be a major cause of cancer-related morbidity/mortality in elderly *BRCA* mutation carriers whose breast cancer or ovarian cancer were either being treated or prevented by risk-reducing operations.

Contralateral breast cancer risks of elderly *BRCA* mutation carriers

While substantially higher risk of contralateral breast cancer has been reported in *BRCA* mutation carriers who had young age of onset of first breast primary cancer, it is of a lesser extent for older mutation carriers who had a later onset of first breast malignancy. *Table 3* summarized the reported risks for contralateral breast cancer in *BRCA1/2* mutation carriers. A retrospective, multicentre cohort study comprising 2,020 women with unilateral breast cancer showed that after 25 years, the contralateral breast cancer rate was 62.9% for *BRCA1* mutation patients who were diagnosed with first breast cancer at an age younger than 40 years old, compared to only 19.6% for those who were diagnosed after 50 years old. Similar trend was also seen in patients with *BRCA2* mutation; however, the difference is not statistically significant (23).

The above results were confirmed with prospective studies. A prospective, multicentre cohort with 6,036 *BRCA1* and 3,820 *BRCA2* female carriers showed that the cumulative risk of contralateral breast cancer 20 years after the first breast cancer diagnosis was 40% for *BRCA1* and 26% for *BRCA2*. The hazard ratio (HR) declined with increasing age at the first breast cancer diagnosis: for women with first breast cancer at age 40–50 years, HR was 0.81; compared to 0.71 in women with first breast cancer at age <40 years (17). One possible confounding factor of age difference for contralateral breast cancer risk would be the use of hormonal therapy after first breast cancer. Breast cancer patients who are post-menopausal are indicated for aromatase inhibitor which was known to have better secondary breast cancer risk reduction than tamoxifen, while younger and premenopausal patients have a higher percentage of oestrogen receptor (ER) negative cancers; and for those ER positive ones, tamoxifen would be used. A prospective study to look for predictors of contralateral breast cancer by Metcalfe *et al.* following 810 women with *BRCA* mutations showed that the 15-year actuarial risk of contralateral breast cancer was 36.1% and 28.5% for women with *BRCA1* and *BRCA2* mutations

Table 3 Risk of contralateral breast cancer in *BRCA1/2* mutation carriers

	Age of primary breast cancer diagnosed (years)	Contralateral breast cancer cumulative risk, (%) at years after primary cancer				
		5 years[1,2]	10 years[1,2]	15 years[1,2]	20 years[1]	25 years[2]
BRCA1	<40	14.2–15	27–30.7	36–42.6	43	62.9
	40–50	7.3–10	10.6–21	17.7–30	39	43.7
	>50	7.9–14	7.9–20	13.4–24	38	19.6
BRCA2	<40	3.8–9	17–20.7	20.7–23	31	63
	40–50	6– 7.9	12.8–14	18.9–20	23	48.8
	>50	3.1–9	9.2–17	16.7–20	20	16.7

[1], data from Kuchenbaecker *et al.* (17); [2], data from Graeser *et al.* (23).

respectively. Again, women older than 50 years old at the time of first breast cancer diagnosis had significantly lower risk to develop a contralateral breast cancer at 15 years, compared to those younger than 50 years (16.8% *vs.* 37.6% P=0.003). Use of tamoxifen was not found to be an independent predictor for contralateral breast cancer in multivariate analysis, in view high percentage of *BRCA* mutation carriers in the cohort (60%) had received oophorectomy; and oophorectomy could significantly reduce risk of contralateral breast cancer (24).

Impact of genetic mutation on management for elderly patients

Identifying patients with mutations in cancer-associated genes can affect patient management regarding high-risk surveillance, risk-reduction strategies and therapeutic options related to surgery, systemic therapies and radiation (25-27). For instance, *BRCA* mutation carriers with breast cancer fulfilling certain criteria are indicated for PARP inhibitors, and patients may consider risk-reducing operations. Additionally, cancer-free mutation carriers could be identified through genetic counselling and testing for proband family members; and this could potentially prevent cancer occurrence or detect cancer early. The difference between elderly and younger *BRCA* mutation carriers may warrant specific recommendations due to the difference in cancer risk, comorbidities and survival.

Risk-reducing operations

After a positive test, most international guidelines such as the National Comprehensive Cancer Network would recommend starting regular imaging surveillance from age 25–30 or 10 years before the age of the first cancer in the family, and would discuss risk-reducing surgery such as risk-reducing mastectomy (RRM) and risk-reducing salpingo-oophorectomy (RRSO) (7,13). Women might consider RRM at any age. For RRSO, it was usually recommended to mutation carriers at 35–40 years old for *BRCA1* and age 40–45 for *BRCA2* (7,13,28), taking into account the median onset age of ovarian cancer and adverse effects from surgical menopause. However, all the guidelines do not specify how the surveillance programme should be catered to patients with increasing age, or risk-reducing surgery should no longer be advised.

Benefits of risk-reducing mastectomy for primary breast cancer could be smaller in older patients due to competing causes of mortality. In a simulation model, the actuarial risk of developing breast cancer until age 80 years was estimated to be 70.8%. The actual risk after incorporating competing risks including ovarian cancer was 64.0%. The probability of being alive at age 80 increased from 42.7% to 51.3% by having bilateral risk-reducing mastectomy at age 25 years. However, if the risk-reducing mastectomy was performed at 50 years old, the survival gain was only 2.8%, from 42.7% to 45.5%. This showed that the survival benefit of risk-reducing mastectomy declined with increasing age at mastectomy (29).

Similarly, a long period was required to demonstrate a reduction in mortality for contralateral mastectomy. In another simulation model, among women who retained the contralateral breast, 0.4% of women were expected to die of a contralateral breast cancer within 5 years; the percentage increased to 6.8% at 20 years after diagnosis (30). In addition, as discussed above, patients with a later age of onset of first breast cancer had a comparatively lower

risk of contralateral breast cancer. In other words, elderly breast cancer patients with *BRCA* mutations might not have apparent benefits even if they opt for a preventive contralateral mastectomy.

On the other hand, risk-reducing salpingo-oophorectomy (RRSO) was consistently shown to have protective effect on ovarian cancer, primary and secondary breast cancer. In a cohort of 551 *BRCA* mutation female carriers, 259 had RRSO and 292 did not. RRSO reduced the risk of ovarian cancer by 95% in *BRCA1/2* mutation carriers. In addition, in a subgroup analysis of 241 women without history of breast cancer, RRSO also decreased the risk of primary breast cancer with a risk ratio of 0.47 (95% CI: 0.29–0.77) (31-33). Particularly for women younger than age 35, RRSO had a 61% decrease in the risk of breast cancer. For women older or equal to 50 years old, the risk reduction was 48% (31). However, most of the studies did not include subgroup analysis for patients who were older in age. Nonetheless, there was no data to completely exclude elderly genetic mutation carriers from preventive RRSO. Given that diagnosis of ovarian cancer in elderly women were correlated with worse outcomes, it might still be beneficial to consider RRSO in patients with a good performance status (34-36). Since there are no definite guidelines to aid clinicians to counsel older genetic mutation carriers, recommendation for screening and preventive surgery should be considered individually based on cancer risk, comorbidities and personal preferences.

Chemoprevention

Studies have addressed the protective effect of endocrine manipulation in *BRCA* mutation carriers. Special attention is required before these could apply to relatively older patients, especially for the implications of ER status and age of breast cancer onset.

It has been reported that 70–80% of *BRCA1*-associated breast cancers are ER negative (37), compared to 30% of sporadic tumours (38) and *BRCA2*-associated tumours (39). However, in a small study comparing 31 *BRCA1* mutation positive to 81 age-matched unselected breast cancer patients, women over age 50 were equally likely to be ER positive, which means older *BRCA1* mutation carriers have a higher proportion to be ER positive than younger carriers (40). For prevention of disease-recurrence or contralateral breast cancer, after primary breast cancer, these patients would likely be benefited from adjuvant aromatase inhibitors, which was consistently shown to be more superior than tamoxifen in reducing recurrences and breast cancer risks by multiple trials. A meta-analysis showed that aromatase inhibitors when compared to adjuvant tamoxifen in 5-year treatment could reduce recurrence rate by 30% while treatment differs, and reduce 10-year breast cancer mortality rate by 15% (41). For those patients whose primary breast cancers are ER negative, or breast cancer-free patients, opinion for tamoxifen as chemoprevention rather than adjuvant treatment for high-risk patients was inconclusive. It was generally assumed that women with *BRCA1* mutations, since majority are ER negative breast cancer, are not impacted by hormonal therapy. However, studies suggested otherwise. In a recent meta-analysis including mainly retrospective analysis with *BRCA1/2* carriers, tamoxifen started after treatment of the first breast cancer resulted in a significant breast cancer risk reduction for both *BRCA1/2* mutation carriers: in *BRCA1* mutation carriers, summary risk ratio was 0.47(95% CI: 0.37–0.60) and in *BRCA2* mutation carriers, summary risk ratio was 0.39 (95% CI: 0.28–0.54) (42). There were not any primary prevention trials of tamoxifen or raloxifene conducted with *BRCA* mutation carriers specifically; only a subgroup analysis of the NSABP trial showed a potential breast cancer risk reduction in *BRCA2* (risk ratio =0.38; 95% CI: 0.06–1.56) but not in *BRCA1* (risk ratio =1.67; 95% CI: 0.32–10.7) mutation carriers (43). Results of this trial should be interpreted with caution since the numbers of patients in each group were very small: 8 patients with *BRCA1* mutations (5 with tamoxifen, 3 did not) and 11 patients with *BRCA2* mutations (3 received tamoxifen, 8 did not). Therefore, it may not have the statistical power to confirm a genuine benefit. To conclude, elderly breast cancer patients who are ER positive should utilize aromatase inhibitor as adjuvant hormonal therapy for risk reduction, while those who are breast-cancer free, prospective data supporting the use of tamoxifen for primary prevention was lacking but retrospective data suggested a potential benefit.

Conclusions

Hereditary breast cancer is usually associated with young age of onset. Nevertheless, recent studies have shown that the prevalence of breast cancer-associated mutations could have been underestimated in older women with breast cancer: *BRCA1/2* mutation detection rates were 2% in postmenopausal patients to age 64, and 1% in those who were 65 years or older. Whether we should extend the genetic testing criteria to include older breast cancer patients who do not have any other particular hereditary risk factors such as family history is controversial. This will

need to take into account the balance between the under-diagnosis of pathogenic variants and increased medical cost. Before considering genetic testing for all breast cancer patients regardless of age, broadening the genetic testing criteria such as identifying additional risk factors and testing patients until an older age such as 60–65 years old besides the conventional ones could serve as a middle ground to increase detection of mutations while avoiding over testing in extreme elderly patients who has a lower prevalence of mutations. Genetic test should only be offered to older patients if a positive test would potentially alter management which benefits the patients. Current management guidelines for *BRCA* mutations are designed based on evidence targeting the younger population. Given a comparatively lower risk of breast cancer and contralateral breast cancer than younger mutation carriers, and less benefit of risk-reducing mastectomy at an older age, individual factors such as comorbidity, competing causes of mortality, cancer risks, personal preference and beliefs should all be taken into account when formulating management plans for elderly breast cancer patients with genetic mutation.

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Footnote

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