Clinical characteristics and outcomes in elderly women with *BRCA1* and *BRCA2* mutations

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HIGHLIGHTS

- Elderly BRCA carriers were more likely to opt for ongoing breast surveillance rather than RRM.
- A large proportion of elderly women elected RRSO after BRCA testing and very few opted for ovarian cancer surveillance.
- Pancreatic cancer was the most common new cancer diagnosed in older *BRCA* carriers.

ARTICLE INFO

ABSTRACT

Objective. Describe clinical characteristics and risk reducing strategies utilized among women with a *BRCA* mutation who lived to age 75 and above.

Methods. A retrospective study of women with *BRCA* mutations identified from 1995 to 2015 in a California health care system. From a database of 1189 women, 69 participants were identified who lived to age 75 or older. Demographic and clinical characteristics were recorded, as well as cancer history and risk-reducing strategies utilized. Descriptive and bivariate analyses were used to analyze the cohort.

Results. The median age of the cohort at study entry was 78 (IQR: 76–84) and the median age at time of genetic testing was 73 (IQR 68–79). Fifty (72%) women had a prior history of breast cancer and 27 (39%) had a history of ovarian cancer. Three of 19 (16%) women with no history of breast cancer elected to undergo a risk-reducing mastectomy (RRM) after their positive genetic test. Among 30 women with ovaries still in place, 14 (47%) underwent a risk-reducing salpingo-oophorectomy (RRSO); six were age 70 or older at the time of surgery. Four (6%) women in the cohort developed *BRCA*-related cancer after testing, one developed breast cancer and three developed pancreatic cancer.

Conclusions. Most women with *BRCA* mutations surviving beyond age 75 received their genetic test result at an older age and had a history of *BRCA*-related cancer. Women continued surveillance and risk reducing surgeries at an older age. Pancreatic cancer was the most common new cancer diagnosed in older *BRCA* mutation carriers.

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1. Introduction

Nearly half of all women diagnosed with breast or ovarian cancer are age 65 and above, and the healthcare needs of these women is a growing concern as the number of these cancers is increasing due to longer life expectancy [1]. Women with *BRCA* mutations are reported to have an approximate 65% lifetime risk of breast cancer and up to 40% risk of ovarian cancer [2–5]. However, most studies stop risk estimates at age 70, with only a few extending to age 80 [3–7]. In one prospective study which reported cancer up to age 80, *BRCA* carriers were at highest risk for breast cancer at age 41–50, but women age 71–80 still had an elevated breast cancer incidence of 16.5 per 1000 person-years for *BRCA1* and 21.9 for *BRCA2*. Similarly, for ovarian cancer, women were at highest risk at age 61–70, but still had an

elevated ovarian cancer risk at age 71–80 with an incidence of 5.7 per 1000 person-years for *BRCA1* and 2.3 for *BRCA2* [7]. This suggests that the risk of breast and ovarian cancer does decrease with age, but women with *BRCA* mutations can still develop new malignancies beyond age 70.

Currently, the National Comprehensive Cancer Network (NCCN) recommends that all patients, regardless of age, who meet personal and family history criteria should receive counseling to discuss *BRCA* testing [8]. After a positive test, the NCCN and United States Preventive Services Task Force (USPSTF) recommend that these women have regular surveillance testing, starting at age 30 or ten years before the age of the first cancer in the family, and are offered risk-reducing surgery with risk-reducing mastectomy (RRM) and risk-reducing salpingo-oophorectomy (RRSO) [8,9]. Women can consider RRM at any age, but RRSO is recommended by age 35 to 40 in *BRCA1* carriers and age 40 to 45 in *BRCA2* carriers [8–10]. However, these guidelines do not specify at what age surveillance should be modified or discontinued, or preventive surgery should no longer be recommended. This is likely because the elderly population with *BRCA* mutations has not been extensively studied.

In medical literature 'elderly' is usually defined as age 65 and above, but many international geriatric societies have proposed that this definition be extended to age 75 and above given that adults are living longer and are active well into their seventies [11–13]. Thus, the current study focused on *BRCA* carriers aged 75 and above, to capture the oldest women within the elderly population, which have largely been excluded in previous research. With a better understanding of cancer risk and outcomes within this population, we hope to gain insight into how best to counsel elderly women regarding the role of surveillance testing and risk-reducing surgery.

2. Methods

This is a retrospective cohort study of women who were age 75 or older and carriers of pathogenic or likely pathogenic *BRCA1* or *BRCA2* mutations within Kaiser Permanente Northern California (KPNC), an integrated health care system serving 4.3 million members. The primary objective was to describe clinical characteristics and risk-reducing strategies utilized by these elderly women (age 75 years and beyond) with *BRCA1* or *BRCA2* mutations. This case series was IRB approved by KPNC with informed consent waived. We identified all women at KPNC who were diagnosed with a *BRCA1* or *BRCA2* mutation between January 1995 and August 2015 and lived to age 75 or older from a cumulative database of 1189 *BRCA* mutation carriers. Retrospective chart review was conducted using August 1, 2015 as the date of data collection to evaluate patient characteristics among these elderly *BRCA* mutation carriers. The variables evaluated included age at time of data collection, age at time of gene test, reason for genetic testing, race/ethnicity, personal cancer history, surgical history, surveillance testing, and utilization of risk-reducing surgery with either RRM or RRSO. All *BRCA*-related cancer diagnoses both before and after their positive gene test were recorded, as well as age at time of cancer diagnosis.

All information was obtained from the KPNC electronic medical record. Descriptive statistics were used to analyze the cohort and sub-analyses were performed in women who did not develop cancer and women who lived to age 90 and older during the study period. Bivariate analyses were performed to compare *BRCA1* to *BRCA2* mutation carriers and women who had genetic testing before and after age 70. Comparisons involving categorical variables were performed using the chi-square or Fisher's exact tests, and normally distributed continuous variables were compared using Student's *t*-tests or ANOVAs. Comparisons of non-normally distributed continuous variables were conducted using the Wilcoxon rank-sum or Kruskal-Wallis tests.

3. Results

3.1. Demographics and genetic testing

Out of a database of 1189 woman with pathogenic or likely pathogenic *BRCA1* or *BRCA2* mutations, there were 69 women who lived to age 75 or older within the study period. The median follow-up time from *BRCA* diagnosis at the time of our chart review was 83 months. Demographic and clinical characteristics of the study cohort are shown in Table 1. During the study period, between January 1995 and August 2015, the median age of the cohort was 78 (interquartile range: 76–84). Most women were white (81%) and 14% were Ashkenazi Jewish.

Most of the 69 women in the cohort had a history of a *BRCA*-related cancer; 49% had a history of breast cancer only, 16% had a history of ovarian cancer only, 23% had a history of both breast and ovarian cancer, 3% had other BRCA-related cancer, and 9% had no cancer history. Non-*BRCA* related cancers were less common and only occurred in 14% of the cohort, but all of these women had also had a previous *BRCA*-related cancer as well. All 50 women with breast cancer underwent surgery; 39% of the women in the cohort had a lumpectomy and 33% had a mastectomy. Prior to genetic testing, 55% of the cohort had a history of bilateral salpingo-oophorectomy (BSO), including 39% at the time of ovarian cancer diagnosis and 17% for benign indications. At the time of data collection in 2015, 20 women had died and the most common cause of death was ovarian cancer (9%). The median survival time from *BRCA* diagnosis to death was 43 months.

Outcomes of genetic testing are shown in Table 2. The median age at time of genetic testing was 73 (interquartile range: 68–79), more women tested positive for *BRCA2* (61%) than *BRCA1* (39%), and most women had a newly identified mutation (67%) rather than a known familial mutation (33%).

Table 1
Demographic and clinical characteristics of elderly BRCA mutation carriers.

	n = 69
Demographic characteristics	
Current age or age of death, median (IQR)	78 (76–84)
Current age or age of death, n (%)	
75–79 y	42 (61%)
80–84 y	13 (19%)
85–89 y	8 (11%)
90+ y	6 (9%)
Race, n (%)	
White	56 (81%)
Non-white	13 (19%)
Ancestry, n (%)	
Ashkenazi Jewish	10 (14%)
Non-Ashkenazi Jewish	59 (86%)
Cause of death, (%)	
Ovarian cancer	6 (9%)
Breast cancer	4 (6%)
Other cancer	5 (7%)
Non-cancer	5 (7%)
Clinical characteristics	
Personal cancer history, n (%)	
Breast cancer only	34 (49%)
Ovarian cancer only	11 (16%)
Breast and ovarian cancer	16 (23%)
Other *BRCA*-related cancer	2 (3%)
No cancer history	6 (9%)
History of breast surgery prior to genetic test, n (%)	
Lumpectomy	27 (39%)
Mastectomy	23 (33%)
No breast surgery	19 (28%)
History of BSO prior to genetic test, n (%)	
Ovarian cancer	27 (39%)
Benign indications	12 (17%)
No surgery, ovaries intact	30 (44%)

Table 2
Outcomes of genetic testing.

Age at time of genetic test, median (IQR)	73 (68–79)
Age at time of genetic test, n (%)	
<70	22 (32%)
≥70	47 (68%)
Gene, n (%)	
BRCA1	22 (32%)
BRCA2	47 (68%)
Mutation type, n (%)	
Newly identified	46 (67%)
Familial	23 (33%)

3.2. Surveillance and risk-reducing surgery

After a positive genetic test, many of the elderly women opted to undergo surveillance testing and/or risk-reducing surgery (Table 3). There were 28 women who were age 75 or older and still had at least one breast; 19 of these 28 women had no prior history of breast cancer and 9 of them had breast cancer in the past but had either a lumpectomy or unilateral mastectomy. For breast surveillance, 57% of these 28 women opted to have mammograms one to two times per year, 14% had alternating annual mammograms and MRIs, 21% had some other schedule for screening, and only 7% opted for no screening at all. One of the women who was having alternating mammograms/MRIs was age 87 at the time of data collection; she had been diagnosed with breast cancer twice at ages 50 and 77 and was still opting for ongoing surveillance. Three (11%) women elected RRM after learning of their BRCA positive status, and all three had their surgery before age 70. Two of these women had previously been diagnosed with ovarian cancer.

There were 30 women in the cohort with no history of ovarian cancer who had intact ovaries at the time of genetic testing. Only four (13%) of the 30 women opted for ovarian cancer surveillance testing with CA-125 and pelvic ultrasounds. Fourteen (47%) elected to have RRSO, and six were above age 70 at the time of their surgery including one woman who was 81 years old. Most women who elected RRSO had a prior history of breast cancer (86%). The 16 women who elected to keep their ovaries did not develop a new ovarian or peritoneal cancer during the study period and were all living at time of data collection; median follow-up time after BRCA diagnosis in this group was 55 months.

3.3. Detection of new cancers

There were four women (6%) in the cohort who developed a new cancer diagnosis after BRCA testing, all of whom had BRCA2 mutations. Three women developed pancreatic cancer at ages 76, 76, and 86. One woman with pancreatic cancer had a prior diagnosis of breast cancer at age 64 and a second had a prior non-BRCA related cervical cancer at age 31. The fourth patient developed breast cancer after genetic testing at age 67. She had undergone BRCA testing after receiving ovarian cancer diagnosis at age 57 and was age 75 at the time of data collection. None of the women in cohort developed a new ovarian or peritoneal cancer diagnosis after BRCA testing during the study period.

3.4. Cohort sub-analyses: women with no history of BRCA-related cancer and women who lived to age 90 and above

There were only six (9%) women who did not have a BRCA-related cancer diagnosis during the study period. Their age at the time of data collection or the age of death ranged from 75 to above 90 years, with a median age of 80 years. Similar to the cohort as a whole, the median age at time of BRCA diagnosis in this subgroup was 74; three of them were BRCA1 carriers and three were BRCA2 carriers. After learning of their BRCA status, 5 of these women opted for breast surveillance with imaging studies but none of them had ovarian cancer screening with pelvic ultrasounds or CA-125. Three of these women elected to have risk-reducing surgery: one woman had a RRM at age 58 and two women underwent RRSO at ages 68 and 69.

There were six (9%) women in the cohort who lived to age 90 and above, and all had their positive genetic test after age 75. Two of these women did not develop cancer in their lifetime and are also included in the subgroup described above. Three of these women who lived to age 90 and above had a prior history of breast cancer; one was diagnosed twice at ages 45 and 57, and the other two women were diagnosed at ages 34 and 82. Two of the six women were diagnosed with ovarian cancer at ages 42 and 77. The woman who developed ovarian cancer at age 77 also had a history of bladder cancer (age 61) and uterine cancer (age 77). None of these nonagenarians elected to have risk-reducing surgery after their BRCA positive result.

3.5. Bivariate analysis

Bivariate analyses were performed to compare BRCA1 and BRCA2 mutation carriers and women who had genetic testing before and after age 70 (Table 4). There were no significant differences between BRCA1 and BRCA2 mutation carriers in terms of demographic or clinical characteristics. The study did identify differences between women who had testing before and after age 70; age 70 was selected as it has been used as a clinical cut off for risk assessment and was near the median age at time of genetic testing (73 years) for the cohort. The 47 women who had their genetic testing at age 70 and above lived to older ages and chose more conservative breast cancer surgeries compared to the 22 women who had genetic testing before age 70. Thirty percent of women who had testing at age 70 or older were either currently above age 85 at the time of data collection or died after this age, whereas none of the women who had testing before age 70 lived beyond age 85 (p = 0.003). Women who had testing at age ≥70, were more likely to opt for lumpectomy (49%) over mastectomy (28%) for breast cancer surgery, whereas women who had testing prior to age 70 were more likely to have a history of mastectomy (45%) rather than lumpectomy (18%, p = 0.045). There were no other demographic or clinical variations according to age at time of genetic testing.

4. Discussion

This study examined clinical characteristics, cancer history, utilization of risk-reducing surgery and the incidence of new BRCA-related cancers among BRCA1 and BRCA2 mutation carriers who survived to age 75 and beyond. Our study confirms a high lifetime incidence of

Table 3
Surveillance and risk reducing surgery, n (%).

At least one breast at time of data collection	N = 28	Ovaries intact	N = 30
Breast cancer surveillance, n (%)		Ovarian cancer surveillance, n (%)	
Mammogram q 1-2y	16 (57%)	CA-125 and pelvic ultrasounds	4 (13%)
Alternating mammogram/MRI	4 (14%)	No screening	12 (40%)
Other screening	6 (21%)		
No screening	2 (7%)		
No prior breast cancer, n (%)	19 (68%)	Risk-reducing salpingo-oophorectomy, n (%)	14 (47%)
Risk-reducing mastectomy	3 (11%)		

Table 4
Comparison of BRCA mutations carriers according to mutation type and age at time of genetic test.

	BRCA carriers (n = 69)	Mutation type			Age (time of genetic test)		
		BRCA 1 (n = 27)	BRCA 2 (n = 42)	p-Value*	<70 (n = 22)	≥70 (n = 47)	p-Value*
Mutation type				–			–
BRCA1	39%	–	–		–	–	
BRCA2	61%	–	–		–	–	
Demographic characteristics							
Age at time of genetic test, median (IQR)	73 (68–79)	70 (66–78)	75 (70–81)	0.186	–	–	–
Age at time of genetic test, n (%)				0.073			–
<70	32%	44%	24%		–	–	
≥70	68%	56%	76%		–	–	
Current age or age at death, n (%)				0.749			0.003
75–84	80%	78%	81%		100%	70%	
≥85	20%	22%	19%		0%	30%	
Race, n (%)				0.547			0.528
White	81%	15%	21%		86%	79%	
Non-white	19%	85%	79%		14%	21%	
Ancestry, n (%)				1.000			0.152
Ashkenazi Jewish	14%	15%	14%		5%	19%	
Non-Ashkenazi Jewish	86%	85%	86%		95%	81%	
Clinical characteristics							
Personal cancer history							
Had breast cancer	72%	70%	74%	0.755	64%	77%	0.261
Had ovarian cancer	39%	41%	38%	0.826	41%	38%	0.836
Developed BRCA-related cancer	91%	89%	93%	0.672	86%	94%	0.375
Underwent BSO prior to genetic test	55%	63%	50%	0.291	55%	55%	0.952
Underwent breast surgery prior to genetic test				0.158			0.045
Yes, lumpectomy	39%	26%	48%		18%	49%	
Yes, mastectomy	33%	44%	26%		45%	28%	

breast and ovarian cancers in *BRCA* mutation carriers. We found that most of the elderly women in our cohort had their *BRCA* testing after age 70, and most women without breast cancer opted for breast surveillance rather than RRM. Ovarian cancer surveillance was less commonly utilized with most women having had their ovaries removed prior to genetic testing but of those who had intact ovaries, 44% chose to have their ovaries removed after genetic testing.

Interestingly, of the four cancers which occurred following genetic testing, three were pancreatic cancers, all in *BRCA2* mutation carriers and diagnosed after age 75. Previous studies have shown a 2.5-fold increase in the incidence of pancreatic cancer in *BRCA* mutation carriers, and this incidence increases with age [14,15]. The majority of the women in our cohort received surveillance and/or treatment for breast and ovarian cancer, and many had opted for risk-reducing surgery. However, as there are no known effective screening tests and limited treatment options for pancreatic cancer, this could predominate as a common cause of cancer related morbidity in elderly *BRCA* mutation carriers [16]. None of the women in our study developed a new ovarian or peritoneal cancer, including the 16 women who elected to keep their ovaries. This finding could be confounded by the follow-up time, as the median follow-up time for these 16 women was 55 months compared to 83 months in the cohort overall. The same is true for the 20 women who died during the study period, as they had a median follow-up time of only 43 months which also gave them less time to develop new malignancies.

Another interesting finding in our study is that the majority of elderly women were *BRCA2* carriers. Given that women with *BRCA1* mutations have earlier cancer occurrences, it is possible that less women with BRCA1 survived to age 75 for inclusion in our study [2–5]. However, when we compared *BRCA1* and −2 carriers, there were no significant difference in their age at time of genetic test or cancer history. We cannot conclude from this study whether there were less elderly women with *BRCA1* because they died at a younger age, but this would be an interesting avenue for future research.

Currently, there are no clear guidelines to aid clinicians counseling older women with *BRCA* mutations. Providers must make recommendations for screening and risk-reducing surgery based on individual cancer risk, performance status, personal preferences, and guidelines that are intended for younger women. Often clinicians question the value of preventive surgery in elderly women as the morbidity of surgery is higher in this age group. However, breast and ovarian cancers diagnosed in elderly women are correlated with worse outcomes, as cancers in this population are often of a more aggressive subtype and may be more inherently resistant to chemotherapy [17–19]. Thus, it may be of benefit to consider risk-reducing surgery in elderly women with an adequate performance status who are healthy enough to undergo surgery [17,20].

This study was limited by a small size and the descriptive design, therefore we cannot make evidence-based management recommendations. However, we show that older women with *BRCA* mutations are making medical decisions based on gene status and are utilizing surveillance and preventive strategies. This overlooked population could benefit from age specific management guidelines to direct and standardize their care.

Author contribution

C.B.P. designed the study, analyzed data, and prepared the manuscript. C.S. collected and analyzed data and prepared the manuscript. C.K. collected and analyzed data and assisted with preparing the manuscript. A.B. assisted with designing the study and collected and analyzed data. M.R.W. analyzed data and assisted in interpreting study findings and preparing the manuscript.

Declaration of Competing Interest

The authors have no potential conflicts of interest.

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