Cancer Previvors in an Active Duty Service Women Population: An Opportunity for Prevention and Increased Force Readiness

Leann A. Lovejoy[*]; LTC Clesson E. Turner, MC, USA (Ret.)*[†,‡]; COL Craig D. Shriver, MC, USA (Ret.)*[‡,§]; Rachel E. Ellsworth*[‡,‖]

ABSTRACT

Background:

The majority of active duty service women (ADS) are young, have access to healthcare, and meet fitness standards set by the U.S. military, suggesting that ADS represent a healthy population at low risk of cancer. Breast cancer is, however, the most common cancer in ADS and may have a significant effect on troop readiness with lengthy absence during treatment and inability to return to duty after the treatment. The identification of unaffected ADS who carry germline mutations in cancer predisposition genes ("previvors") would provide the opportunity to prevent or detect cancer at an early stage, thus minimizing effects on troop readiness. In this study, we determined (1) how many high-risk ADS without cancer pursued genetic testing, (2) how many previvors employed risk-reducing strategies, and (3) the number of undiagnosed previvors within an ADS population.

Methods:

The Clinical Breast Care Project (protocol WRNMMC IRB #20704) database of the Murtha Cancer Center/Walter Reed National Military Medical Center was queried to identify all ADS with no current or previous history of cancer. Classification as high genetic risk was calculated using National Comprehensive Cancer Network 2019 guidelines for genetic testing for breast, ovary, colon, and gastric cancer. The history of clinical genetic testing and risk-reducing strategies was extracted from the database. Genomic DNA from ADS with blood specimens available for research purposes were subjected to next-generation sequencing technologies using a cancer predisposition gene panel.

Results:

Of the 336 cancer-free ADS enrolled in the Clinical Breast Care Project, 77 had a family history that met National Comprehensive Cancer Network criteria for genetic testing for *BRCA1/2* and 2 had a family history of colon cancer meeting the criteria for genetic testing for Lynch syndrome. Of the 28 (35%) high-risk women who underwent clinical genetic testing, 11 had pathogenic mutations in the breast cancer genes *BRCA1* ($n = 5$), *BRCA2* ($n = 5$), or *CHEK2* ($n = 1$). Five of the six ADS who had a relative with a known pathogenic mutation were carriers of the tested mutation. All of the women who had pathogenic mutations detected through clinical genetic testing underwent prophylactic double mastectomy, and three also had risk-reducing salpingo-oophorectomy. Two (6%) of the 33 high-risk ADS tested only in the research setting had a family history of breast/ovarian cancer and carried pathogenic mutations: one carried a *BRCA2* mutation, whereas the other carried a mutation in the colon cancer predisposition gene *PMS2*. No mutations were detected in the 177 low-risk women tested in the research setting.

Discussion:

Within this unaffected cohort of ADS, 23% were classified as high risk. Although all of the previvors engaged in risk-reduction strategies, only one-third of the high-risk women sought genetic testing. These data suggest that detailed family histories of cancer should be collected in ADS and genetic testing should be encouraged in those at high risk. The identification of previvors and concomitant use of risk-reduction strategies may improve health in the ADS and optimize military readiness by decreasing cancer incidence.

INTRODUCTION

In 2018, there were 215,834 female active duty service women (ADS), representing 16.5% of the U.S. military.[1]

[*]Clinical Breast Care Project, Chan Soon-Shiong Institute for Molecular Medicine at Windber, Windber, PA 15963, USA

[†]Department of Pediatrics, Uniformed Services University of the Health Sciences, Bethesda, MD 20814, USA

[‡]Murtha Cancer Center/Research Program, Uniformed Services University of the Health Sciences and Walter Reed National Military Medical Center, Bethesda, MD 20889, USA

[§]Department of Surgery, Uniformed Services University of the Health Sciences, Bethesda, MD 20814, USA

[‖]Clinical Breast Care Project, Henry M. Jackson Foundation for the Advancement of Military Medicine, Windber, PA 15963, USA

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Three facets of military service suggest that ADS may be healthier than women in the U.S. general population: 92% of ADS are ≤40 years of age,[1] all ADS are provided with equal-access healthcare through the DoD, and all ADS are required to meet physical fitness standards set by each branch of the U.S. military. Studies of overall cancer risk have detected lower overall cancer rates for both current and former military personnel compared with the U.S. general population.[2,3] A landmark study in 2009, however, found that the incidence of breast cancer is significantly higher in ADS than in the general population.[4] Over 1,000 ADS were diagnosed with breast cancer between 2000 and 2012,[5] and during that same period of time, breast cancer diagnoses were increasing within the veterans affairs healthcare system.[6] Breast cancer in ADS may be detrimental to force readiness because an affected service woman may be absent from her unit for an extended period of treatment and may not return to duty afterward. In addition, the financial cost to the DoD for treating breast cancer is significant, with an average per capita cost of $66,300.[7]

One approach to decreasing the effect of breast cancer on force readiness would be to identify ADS at high-risk before disease onset. The first genetic tests to detect germline mutations in *BRCA1* and *BRCA2* became available in 1996[8]; germline testing allowed for the identification of asymptomatic individuals at high risk of developing breast and/or ovarian cancer. Several strategies have been developed to reduce or prevent breast and ovarian cancer in mutation carriers or "previvors" including risk-reducing surgeries (RRS) such as risk-reducing salpingo-oophorectomy (RRSO), risk-reducing mastectomy (RRM), and chemoprevention.[9] In addition to *BRCA1* and *BRCA2*, a number of high- and moderate-penetrance genes associated with increased risk of breast and/or ovarian cancer have been identified, for which risk-reducing management guidelines such as mammography with tomosynthesis and MRI have been developed.[10]

Risk-reducing strategies have been associated with decreased risk of breast cancer in *BRCA1/2* carriers who underwent RRM and decreased risk of ovarian cancer, primary breast cancer, and breast and ovarian cancer-specific and all-cause mortality.[11] The use of multi-gene panel testing to detect carriers of non-BRCA mutations would lead to changes in clinical management beyond those based on personal or family history.[12] The effectiveness of these risk-reducing strategies in previvors depends, however, on patient willingness to undergo genetic testing and subsequent utilization of enhanced surveillance and RRS. A recent study from Kaiser Permanente found that 97% of women with a family history indicative of increased risk of hereditary breast and ovarian cancer did not pursue genetic testing despite having insurance and access to genetic testing services.[13] Evaluation of previvor adherence to risk-reducing strategies has been mixed: in a study of 1,499 previvors with *BRCA1/2* mutations, only 46% of women underwent RRM by age 70,[14] whereas 97% of previvors with mutations in *PALB2, ATM, CHEK2*, or *NBN* had or planned to have enhanced breast cancer surveillance through MRI.[15]

A recent study of 31,869 unaffected controls found a mutation frequency of 2.1% in 12 breast cancer predisposition genes[16]; however, the frequency of previvors in ADS is unknown. Furthermore, the willingness of ADS previvors to pursue risk-reduction strategies has not been evaluated. In this retrospective study, we evaluated genetic testing rates, germline status, and risk-reduction practices in a population of ADS enrolled in the Clinical Breast Care Project (CBCP) of the Murtha Cancer Center/Walter Reed National Military Medical Center (MCC/WRNMMC).

METHODS

Eligibility criteria included: (1) at least 18 years of age, (2) mentally competent and willing to sign informed consent documents, and (3) on active duty service with no current or past history of cancers that enrolled in the CBCP at MCC/WRNMMC, Bethesda, MD. All subjects voluntarily agreed to participate and gave written informed consent. Blood samples were collected with approval from the WRNMMC Human Use Committee and Institutional Review Board (protocol WRNMMC IRB #20704).

Active duty status and branch of service were self-reported. Patient ethnicity was self-described, and the age was recorded at the time of enrollment. Family cancer history through third-degree relatives was collected for each patient. ADS were classified as high or low genetic risk using the National Comprehensive Cancer Network (NCCN) Guidelines Version 1.2020 Hereditary Cancer Testing criteria, NCCN Guidelines Version 3.2019 High-Risk Colorectal Cancer Syndromes criteria, or NCCN Guidelines Version 2.2020 Gastric Cancer Principles of Genetic Risk Assessment for Gastric Cancer.[17-19] Genetic test results and data for RRS were extracted for all patients who underwent clinical testing.

Genomic DNA was isolated from 210 ADS who had blood samples available for research purposes using the Gentra Clotspin and Puregene DNA purification kits (Qiagen, Valencia, CA) and quantitated by fluorometry. Sequencing libraries were created using the TruSight Rapid Capture kit and TruSight Cancer panel and sequenced on a MiSeq (Illumina, Inc., San Diego, CA) according to the manufacturer's protocols. Data were analyzed using Variant Interpreter (Illumina, Inc., San Diego, CA) and filtered to include only missense or frameshift mutations, stop codon gains or losses, initiator codons, in-frame insertions or deletions, and splice site alterations with a minor allele frequency of ≥0.25. The predicted effect of variants (pathogenic, likely pathogenic, variant of uncertain significance, likely benign, or benign) was evaluated using ClinVar (http://www.clinvar.com/).

RESULTS

Three hundred thirty-six cancer-free ADS enrolled in the CBCP between 2001 and 2019. The majority of ADS (86.9%)

TABLE I. Demographic Characteristics of 336 Cancer-Free ADS Enrolled in the CBCP

Characteristics	Number	Percentage
Treatment at MCC/WRNMMC		
Biopsy for benign condition	292	86.9%
Family risk assessment	32	9.5%
Screening mammogram	8	2.4%
Reductive mammoplasty	4	1.2%
Ethnicity		
African American	110	32.7%
Asian	12	3.6%
Hispanic	21	6.2%
European American	170	50.6%
Other[a]	10	3.0%
Unknown	13	3.9%
Family history[b]		
0	172	51.2%
1	99	29.5%
2	44	13.1%
≥3	21	6.2%
Military branch		
Air force	76	22.6%
Army	198	58.9%
Coast Guard	6	1.8%
Marine corps	8	2.4%
Navy	48	14.3%

Abbreviations: ADS, active duty service women; MCC/WRNMCC, Murtha Cancer Center/Walter Reed National Military Medical Center.
[a]Other includes American Indian/Native American, Caribbean, and Native Hawaiian/Pacific Islander.
[b]Family history includes breast, ovarian, or pancreas in first- or second-degree relatives.

enrolled in the CBCP after undergoing biopsies for benign conditions such as fibroadenoma or fibrocystic changes. Average age at enrollment was 35.8 years (range: 19.0-61.5 years). Most ADS were self-described European American (50.6%) or African American (32.7%), did not have a strong family history of cancer, and were serving in the Army (58.9%, Table I). Average length of follow-up was 7.62 years and included one woman who subsequently developed ductal carcinoma *in situ*, five women who developed invasive breast cancer, and one woman who was diagnosed with and died of lung cancer.

Seventy-nine (23.5%) ADS were eligible for clinical genetic testing under NCCN guidelines, including 77 who met NCCN criteria for hereditary breast/ovarian cancer and 2 who had a significant family history of colon cancer (Fig. 1). Although neither of the ADS with a family history of colon cancer had genetic testing, 28 of the ADS at risk of breast/ovarian cancer underwent clinical genetic testing, including 6 who had a family member with a known pathogenic mutation (Fig. 2). Eleven of the 28 ADS with clinical test results harbored pathogenic mutations in *BRCA1, BRCA2*, or *CHEK2,* including 5 of 6 women who had a family member with a known pathogenic mutation (Table II). Each

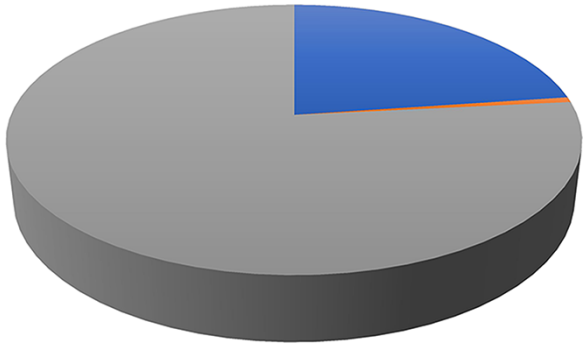

FIGURE 1. Eligibility for genetic testing in 336 cancer-free active duty military service women. Gray = low risk, blue = high risk of breast/ovarian cancer, orange = high risk of colon cancer. No patients were at high risk of hereditary diffuse gastric cancer.

of the 11 previvors underwent RRM and 3 also underwent RRSO.

DNA from 33 high-risk ADS who did not undergo clinical genetic testing was sequenced in the laboratory. Two patients harbored pathogenic mutations in cancer predisposition genes. One patient with a *BRCA2* mutation [NM_000059.4(BRCA2):c.1800T>G (p.Tyr600Ter)] was a 20-year-old African American woman with a significant family history of breast and ovarian cancer who was diagnosed with fibroadenoma in 2018. The other patient with a *PMS2* mutation [NM_000535.7(PMS2):c.248T>G (p.Leu83Ter)] was a 23-year-old African American with a family history of breast and ovarian (but not colon) cancer who was diagnosed with fibroadenoma in 2009.

DNA from 177 low-risk women was sequenced in the research setting. None of the low-risk ADS harbored detectable pathogenic mutations in cancer predisposing genes.

DISCUSSION

The identification of previvors provides the opportunity to prevent or detect cancers at an earlier stage; however, successful previvor management is dependent upon identification of women who would benefit from testing, uptake of genetic testing, and pursuit of risk-reducing strategies. Similar to the ~20% of women in the general population with a family history of breast cancer, 23.5% of this ADS cohort met NCCN testing criteria based on the family history. In this study, uptake of genetic testing in test-eligible women and RRM were higher in ADS (35% and 100%) compared with women in the general population (20% and 49%).[20,21] Together, these data suggest that ADS are receptive to testing and risk-reduction strategies and that MCC/WRNMMC is proficient in delivering these services.

Demographics of ADS portend less favorable tumor characteristics than those in the general population. For example, the average age of ADS nationwide is 28.5 years of age;

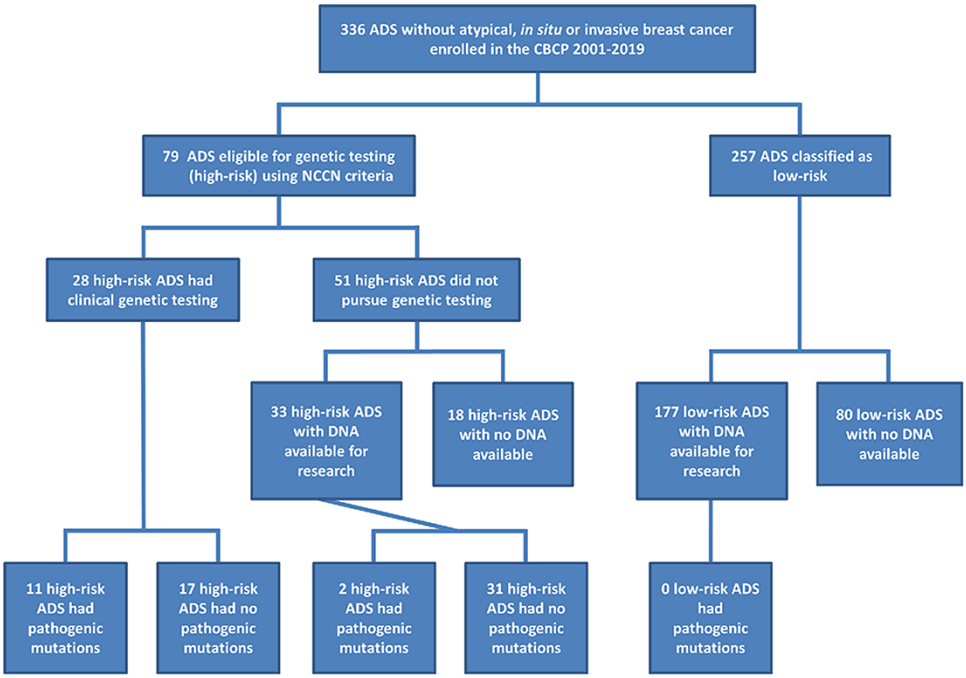

FIGURE 2. Flow chart detailing patient risk, test uptake, and detection of pathogenic mutations.

TABLE II. Characteristics of ADS Previvors

Patient	Mutation	Age	Ethnicity	Military branch	RRS[a]
94[b]	NM_000059.3(BRCA2):c.2808_2811del (p.Ala938Profs)	28	EA	Army	RRM
146	NM_007294.4(BRCA1):c.5277 + 1G > A	37	EA	Army	RRSO/RRM
169	NM_000059.3(BRCA2):c.7977-1G > C	29	EA	Army	RRM
179[c]	NM_000535.7(PMS2):c.248T > G (p.Leu83Ter)	23	AA	Army	Biopsy only
180	NM_000059.3(BRCA2):c.6644_6647delACTC (p.Tyr2215Serfs)	38	EA	Army	RRM
205	NM_000059.3(BRCA2):c.956dupA (p.Asn319Lysfs)	35	EA	Marine Corps	RRSO/RRM
225	NM_007294.4(BRCA1):c.5165C > T (p.Ser1722Phe)	40	EA	Navy	RRM
257[b]	NM_007299.4(BRCA1):c.213-11T > G	38	EA	Air force	RRM
309[b]	NM_000059.3(BRCA2):c.2808_2811del (p.Ala938Profs)	38	AA	Air force	RRSO/RRM
313	NM_000059.4(BRCA2):c.1800T > G (p.Tyr600Ter)]	20	AA	Navy	Biopsy only
324	NM_007294.4(BRCA1):c.379del (p.Ser127fs)	29	EA	Army	RRM
325[b]	NM_007194.3(CHEK2):c.1100delC (p.Thr367Metfs)	26	EA	Air Force	RRM
334[b]	NM_007294.3(BRCA1):c.815_824dup (p.Thr276fs)	40	HS	Army	RRM

Abbreviations: AA, African American; ADS, active duty service women; EA, European American; HS, Hispanic; RRM, risk-reducing mastectomy; RRS, risk-reducing surgeries; RRSO, risk-reducing salpingo-oophorectomy.
[a]RRS include RRSO and RRM.
[b]ADS with family members harboring known pathogenic mutations.
[c]Patients 179 and 313 had mutations detected only in the research setting.

tumors diagnosed in women <40 years of age have more aggressive tumor characteristics and higher overall mortality than in older patients.[22,23] In conjunction, >30% of ADS are African American, and African American women have increased risk of triple-negative breast cancer, an aggressive breast cancer subtype, associated with poor prognosis.[24] The identification of previvors and engagement in risk-reduction approaches would, therefore, not only preserve force readiness but may prevent or detect tumors at earlier stages, improving what otherwise may be poor outcomes within ADS.

As in the U.S. general population, the majority of ADS in this cohort (77.2%) did not have a significant family history and did not qualify for genetic testing under current NCCN criteria. Importantly, none of the low-risk ADS harbored pathogenic mutations in any of the known cancer predisposition genes, arguing against the need for population screening within the U.S. military.[25] Importantly, because most ADS

are <40 years of age and thus unlikely to be seen within a breast clinical center such as CBCP/MCC/WRNMMC, it is critical that a complete family history of cancer[26,27] should be taken at enlistment and periodically updated by the primary care physician or obstetrician/gynecologist. Likewise, any high-risk ADS should be offered the opportunity for clinical genetic testing.

The cost of providing genetic testing ($300 for testing for a known mutation to potentially as high as $5000 for multi-gene tests) to all high-risk ADS must be considered (https://www.breastcancer.org/symptoms/testing/genetic/facility_cost). If 22.8% of the current ADS population were to undergo testing, the cost to the DoD would be >$10,000,000, which does not include the costs of pre- and posttest genetic counseling or costs for RRS. Evaluation of cost savings for testing unaffected women with a significant family history found that genetic testing with RRS is cost-effective compared with no intervention.[28] More recently, an evaluation of testing and RRS compared with the cost of no intervention and treatment when cancer developed found an incremental cost-effectiveness ratio of $10,555 per quality-adjusted life-year, with fewer cases of breast and ovarian cancer and lower all-cause mortality.[29] These data suggest that genetic testing and RRS in ADS would result in cost savings to the DoD and would prevent cancer development in previvors, thus protecting force readiness.

Although these data suggest that ADS with a significant family history of breast and/or ovarian cancer are willing to undergo genetic testing and pursue risk-reduction strategies, there are limitations to this study. This patient cohort is composed of ADS who enrolled in the CBCP through the breast cancer center of the MCC/WRNMMC, rather than recruited from the general ADS population. This cohort may represent patients with a greater knowledge of breast health or willingness to pursue genetic testing and RRS than the entire ADS population. Therefore, genetic testing and RRS uptake maybe lower in the ADS as a whole than levels reported here. Second, this was a retrospective study and data were not available for pre- or posttest genetic and clinical counseling, thus, data regarding the number of patients who were offered genetic testing or RRS were not available. Thus, this study could not determine whether the 65% of high-risk ADS who did not pursue genetic testing declined testing or were not provided with the options. Finally, all patients were enrolled through the MCC/WRNMMC where a licensed medical geneticist and a staff of genetic counselors were available. This service may not be available at all military treatment facilities; thus, alternate approaches such as telemedicine or provision of increased education regarding collecting family histories of cancer and genetic testing to nongenetic healthcare providers may be needed.

CONCLUSIONS

In a cohort of ADS without cancer, 23% were classified as high-risk and eligible for clinical genetic testing. Although only one-third of the test-eligible ADS pursued genetic testing, all clinically detected previvors engaged in risk-reduction strategies. These data suggest that a detailed family history of cancer should be collected in every ADS and genetic testing encouraged in all test-eligible women. The identification of previvors and concomitant use of risk-reducing strategies may improve the health of ADS population and optimize readiness of the U.S. military by decreasing future cancer burden.

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CONFLICT OF INTEREST STATEMENT

None declared.

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