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SHORT COMMUNICATION

BRCA1 and *BRCA2* pathogenic variants increase the risk of four less common cancer types

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Background: Previous family-based and case-control studies have expanded the cancer risk profile associated with pathogenic variants in *BRCA1* and *BRCA2*, providing the potential for expanding personalized medicine. Less common cancer types may benefit greatly from such expansion of genetic evidence because of their limited treatments and poor prognoses.

Methods: We conducted a case-control analysis of 3489 patients with nine less common cancer types (bladder, bone, brain, head and neck, sarcoma, skin, testis, thyroid, or ureteral cancer) and 38 842 controls without cancer to estimate the risk associated with *BRCA1* and *BRCA2* pathogenic variants of nine less common cancer types.

Results: We identified 105 pathogenic variants among 994 germline variants. We observed four significant associations: *BRCA1* with thyroid cancer [odds ratio (OR) 5.25, 95% confidence interval (CI) 2.06-13.38]; *BRCA2* with bladder (OR 4.67, 95% CI 2.57-8.47), head and neck (OR 3.89, 95% CI 2.01-7.53), and skin cancers (OR 6.13, 95% CI 2.47-15.24). For bladder cancer, the impact of *BRCA2* pathogenic variants was greater in females than in males ($P_{heterogeneity} = 2.15 \times 10^{-4}$; $I^2 = 92.70\%$).

Conclusions: These results provide evidence to inform more precise personalized medical options for individuals with *BRCA1* or *BRCA2* pathogenic variants.

Key words: less common cancer type, *BRCA1/2*, germline pathogenic variant, case-control study, sex difference, personalized medicine

INTRODUCTION

Pathogenic variants in *BRCA1* and *BRCA2* (*BRCA1/2*) are widely recognized for increasing the risk of breast, ovarian, pancreatic, and prostate cancers.[1-3] Personalized medicine based on *BRCA1/2* pathogenic variants has become standard in clinical practice. Family-based genetic studies demonstrated that the risk profile of *BRCA1/2* pathogenic variant carriers extends to less common cancer types, such as gastrointestinal and skin cancers, beyond those previously assumed.[1,4,5] Our previous study based on Japanese populations revealed that *BRCA1/2* pathogenic variants increase the risk of biliary tract, gastric, and esophageal cancers.[2] Moreover, the importance of considering nongenetic factors alongside genetic factors has also been increasingly clarified. Pathogenic variants and *Helicobacter pylori* infection interacted with each other for the risk of gastric cancer, suggesting that the impact of pathogenic variants might be affected by environmental factors.[6] The importance of such integrated risk assessments has also been shown in studies on breast and colorectal cancers.[7,8]

Expanding genetic evidence to additional cancer types could significantly advance personalized medicine for pathogenic variant carriers. Less common cancer types may benefit greatly from such expansion of genetic evidence, as many of these cancer types have limited treatment options

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and poor prognoses.[9] Although genetic information on less common cancer types has been limited, some of these cancer types, such as bladder and head and neck cancers, have been reported to respond to poly [ADP (adenosine diphosphate)-ribose] polymerase (PARP) inhibitors.[10,11] Identifying further associations with *BRCA1/2* pathogenic variants could strengthen the rationale for clinical trials and the use of such treatment options for more cancer types, leading to advances in personalized medicine.

Therefore, to provide further evidence to support trials in and use of treatment options for less common cancer types associated with *BRCA1/2* pathogenic variants, we evaluated the association between *BRCA1/2* pathogenic variants and nine less common cancer types in a Japanese population.

MATERIAL AND METHODS

Study participants

Our study obtained samples from BioBank Japan, a multi-institutional, hospital-based registry that collected clinical information and blood samples from all over Japan between 2003 and 2018.[12,13] We included 3489 patients with a self-reported medical history of nine less common cancer types for which >40 patients had been reported (bladder, bone, brain, head and neck, sarcoma, skin, testis, thyroid, or ureteral cancer) and 38 842 controls without cancer. Details of the hospital location, cases, and controls are described in the Supplementary Methods, available at https://doi.org/10.1016/j.esmoop.2026.106900. All participants provided written informed consent. The study received approval from the ethical committees of the Institute of Medical Sciences, the University of Tokyo, and the RIKEN Center for Integrative Medical Sciences. The authors vouch for the accuracy and completeness of the data in this study.

Sequencing and bioinformatics

Following the methods of our previous studies, we analyzed all coding regions and two base pairs flanking intronic sequences of *BRCA1/2* (16 111 base pairs) using a multiplex PCR-based targeted sequencing method.[2] For quality control, we included only individuals for whom >98% of the targeted region was covered by ≥20 sequencing reads. We assigned clinical significance to all genetic variants using *BRCA1/2* variant classification criteria developed by members of the Evidence-based Network for the Interpretation of Germline Mutant Alleles (ENIGMA) Consortium.[14] Pathogenic and likely pathogenic variants were collectively designated as pathogenic variants. Details are provided in the Supplementary Methods, available at https://doi.org/10.1016/j.esmoop.2026.106900.

Statistical analysis

To assess the association between *BRCA1* and *BRCA2* pathogenic variants and the nine cancer types, we used a logistic regression model adjusted for age at entry, sex, and hospital location. In each analysis, noncarriers were defined as individuals without pathogenic variants in the respective gene. Given that sex differences in incidence rates and response to treatment in some cancer types are recognized,[15] we also carried out further analyses stratified by sex for bladder, head and neck, and thyroid cancers with known sex differences in incidence rate among cancer types identified as associated with *BRCA1/2* pathogenic variants.[15,16] The cumulative risk and their 95% confidence interval (CI) up to 85 years of age were calculated for both carriers and noncarriers of pathogenic variants, as in our previous studies.[2,6] Details are provided in Supplementary Methods, available at https://doi.org/10.1016/j.esmoop.2026.106900.

All statistical tests were two-sided, and statistical significance was set at $P < 0.05$. The Bonferroni correction was applied for multiple comparisons. All statistical analyses were carried out using R version 4.2.3 (R Foundation for Statistical Computing). We used the R package, such as 'stats (ver. 4.2.3)', 'dplyr (ver. 1.1.1)', and 'metafor (ver. 4.6.0)'.

RESULTS

Characteristics of study participants

The characteristics of the 3489 patients with cancer (3584 cases; 95 patients had two cancer types) and 38 842 controls are shown in Table 1. The median age at entry (interquartile range) was 71 years (64-77 years) for patients and 68 years (60-75 years) for controls. The proportion of males was 68.3% among all patients and 56.2% among controls. The proportions of patients with smoking history and alcohol drinking history were 62.4% and 57.1%, respectively, compared with 51.4% and 50.4% among controls.

Association analysis between BRCA1/2 pathogenic variants and each cancer type

After applying quality control measures, we included 3454 patients (3549 cases) and 38 288 controls in our analysis, with >99.9% of the targeted region covered by ≥20 sequencing reads. The average coverage rate (the proportion of the target region covered by ≥20 sequencing reads) was 99.9% in the cases and 99.8% in the controls. The average depth and coverage rate for each individual were shown in Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2026.106900. Regarding individuals excluded due to insufficient coverage, there were 35 cases (1.00%) and 554 controls (1.43%). We identified 105 pathogenic variants among 994 germline variants based on the classification criteria from ENIGMA Consortium.

Association analyses were carried out for each cancer type, using a logistic regression model adjusted for age at entry, sex, and hospital location (Table 2). We observed four significant associations after Bonferroni correction [$P < 2.78 \times 10^{-3}$ ($= 0.05/18$)]: between *BRCA1* pathogenic variants and thyroid cancer [odds ratio (OR) 5.25, 95% CI

Table 1. Characteristics of the participants

	Patients			Controls		
	$n = 3489$[a]			$n = 38\ 842$		
	Female	Male	Total	Female	Male	Total
Participants, *n* (%)	1107 (31.7)	2382 (68.3)	3489 (100.0)	17 012 (43.8)	21 830 (56.2)	38 842 (100.0)
Age at entry, median years (IQR)	69.0 (61.0-76.0)	72.0 (65.0-77.0)	71.0 (64.0-77.0)	65.0 (55.0-73.0)	70.0 (64.0-76.0)	68.0 (60.0-75.0)
Cancer type						
Bladder	160	983	1143	—	—	—
Bone	38	44	82	—	—	—
Brain	104	97	201	—	—	—
Head and neck	127	773	900	—	—	—
Sarcoma	18	23	41	—	—	—
Skin	127	207	334	—	—	—
Testis	—	79	79	—	—	—
Thyroid	541	204	745	—	—	—
Ureter	17	42	59	—	—	—
Smoking history						
Smoking	243	1934	2177	3709	16 237	19 946
Nonsmoking	854	425	1279	13 019	5131	18 150
Unknown	10	23	33	284	462	746
Alcohol drinking history						
Drinking	275	1694	1969	4661	14 452	19 113
Nondrinking	819	658	1477	11 982	6798	18 780
Unknown	13	30	43	369	580	949

IQR, interquartile range.
[a]The number of cases was 3584; 95 patients (2.7%) had two cancer types.

2.06-13.38, $P = 5.22 \times 10^{-4}$]; between *BRCA2* pathogenic variants and bladder cancer (OR 4.67, 95% CI 2.57-8.47, $P = 4.27 \times 10^{-7}$), head and neck cancer (OR 3.89, 95% CI 2.01-7.53, $P = 5.74 \times 10^{-5}$), and skin cancer (OR 6.13, 95% CI 2.47-15.24, $P = 9.44 \times 10^{-5}$). We also observed an association of $P < 0.05$ between *BRCA2* pathogenic variants and thyroid cancer (OR 3.04, 95% CI 1.23-7.55, $P = 0.02$), but it was not considered significant after Bonferroni correction, requiring more careful interpretation. For the four associated cancer types, we also carried out analyses in a series of models: (i) unadjusted; (ii) adjusted for age at entry, sex, hospital location; (iii) adjusted for age at entry, sex, hospital location, drinking status; (iv) adjusted for age at entry, sex, hospital location, smoking status; and (v) adjusted for age at entry, sex, hospital location, drinking status, and smoking status. The ORs remained comparable after any adjustments in analysis for each associated cancer type (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2026.106900). In the analysis among the regions of head and neck cancer shown in Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2026.106900, *BRCA2* pathogenic variants were significantly associated with pharyngeal and laryngeal cancer (OR 4.65, 95% CI 2.23-9.70, $P = 4.31 \times 10^{-5}$). An exploratory analysis

Table 2. Associations between pathogenic variants in *BRCA1/2* and nine less common cancer types

Cancer type	Number of cases[a]	*BRCA1*				*BRCA2*			
		Number of pathogenic variant carriers (%)		OR[b,c] (95% CI)	*P* value[b,c]	Number of pathogenic variant carriers (%)		OR[b,c] (95% CI)	*P* value[b,c]
		Case ($n = 3549$[a])	Control ($n = 38\ 288$)			Case ($n = 3549$[a])	Control ($n = 38\ 288$)		
Bladder	1130	3 (0.27)	58 (0.15)	1.58 (0.49-5.11)	*0.45*	*13 (1.15)*	*103 (0.27)*	***4.67 (2.57-8.47)***	***4.27 × 10⁻⁷***
Bone	79	0 (0.00)	58 (0.15)	NA	*NA*	*1 (1.27)*	*103 (0.27)*	*4.77 (0.66-34.72)*	*0.12*
Brain	201	1 (0.50)	58 (0.15)	3.26 (0.45-23.75)	*0.27*	*1 (0.50)*	*103 (0.27)*	*2.04 (0.28-14.69)*	*0.48*
Head and neck	897	1 (0.11)	58 (0.15)	0.64 (0.09-4.65)	*0.66*	*10 (1.12)*	*103 (0.27)*	***3.89 (2.01-7.53)***	***5.74 × 10⁻⁵***
Sarcoma	41	0 (0.00)	58 (0.15)	NA	*NA*	*0 (0.00)*	*103 (0.27)*	*NA*	*NA*
Skin	331	2 (0.60)	58 (0.15)	3.92 (0.95-16.23)	*0.06*	*5 (1.51)*	*103 (0.27)*	***6.13 (2.47-15.24)***	***9.44 × 10⁻⁵***
Testis	79	0 (0.00)	40 (0.19)	NA	*NA*	*0 (0.00)*	*67 (0.31)*	*NA*	*NA*
Thyroid	734	5 (0.68)	58 (0.15)	***5.25 (2.06-13.38)***	***5.22 × 10⁻⁴***	*5 (0.68)*	*103 (0.27)*	***3.04 (1.23-7.55)***	***0.02***
Ureter	57	0 (0.00)	58 (0.15)	NA	NA	1 (1.75)	103 (0.27)	7.27 (0.99-53.41)	0.05

CI, confidence interval; NA, not applicable; OR, odds ratio.
[a]The number of cases was 3549; 95 patients had two cancer types.
[b]A logistic regression model with adjustment for age at entry, sex, and hospital location was used. A Bonferroni-corrected threshold of significance was applied with a *P* value $< 2.78 \times 10^{-3}$ (i.e. 0.05/18).
[c]The results with a *P* value < 0.05 are shown in bold, and results that fall below the Bonferroni-corrected threshold (*P* value $< 2.78 \times 10^{-3}$) are also shown in italics.

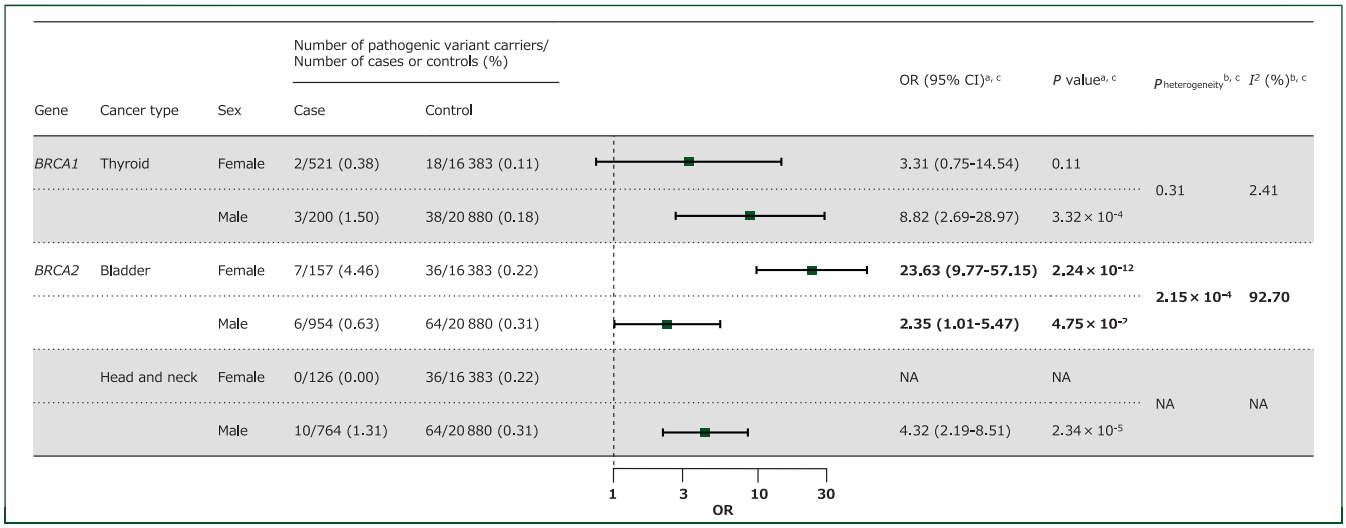

Figure 1. Associations between pathogenic variants in *BRCA1/2* and three cancer types stratified by sex. CI, confidence interval; NA, not applicable; OR, odds ratio. [a]A logistic regression model with adjustment for age at entry, hospital location, smoking status, and drinking status was used. [b]The heterogeneity of associations between females and males was evaluated using the Cochran Q statistic and I^2 statistic in a random-effects model. [c]The results with $P_{heterogeneity} < 0.05$ are shown in bold.

observed an association with $P < 0.05$ for nasal cavities and paranasal sinuses (OR 11.74, 95% CI 1.57-87.61, $P = 0.02$).

Sex-stratified association analysis for cancer types linked to BRCA1/2 pathogenic variants

Among cancer types associated with *BRCA1/2* pathogenic variants, thyroid, bladder, and head and neck cancers are recognized to have sex differences in incidence and response to treatment. In addition, smoking and drinking status are widely recognized as epidemiological risk factors for sex-specific presentation of these cancers.[15] Therefore, further analyses stratified by sex with adjustment for smoking and drinking status were carried out (Figure 1). For bladder cancer, the impact of *BRCA2* pathogenic variants was greater in females [number of carriers (n) = 7; OR 23.63, 95% CI 9.77-57.15] than in males ($n = 6$; OR 2.35, 95% CI 1.01-5.47), with significant heterogeneity ($P_{heterogeneity} = 2.15 \times 10^{-4}$; $I^2 = 92.70\%$). Female bladder cancer patients with *BRCA2* pathogenic variants had no past medical history of breast or ovarian cancer. For thyroid cancer, there was a trend for the OR to be higher in males ($n = 3$; OR 8.82, 95% CI 2.69-28.97) than in females ($n = 2$; OR 3.31, 95% CI 0.75-14.54), though heterogeneity was not statistically significant ($P_{heterogeneity} = 0.31$; $I^2 = 2.41\%$). In our study, *BRCA2* carriers were not observed among females with head and neck cancer. These results should be cautiously interpreted, including the possibility of insufficient statistical power due to the small number of carriers.

Lifetime cumulative risk of each cancer type

The estimated cumulative risk of cancer up to 85 years of age was calculated for carriers and noncarriers of *BRCA1/2* pathogenic variants in the four significantly associated cancer types (Figure 2). For *BRCA1* carriers, the cumulative risk of thyroid cancer was 10.1%. For *BRCA2* carriers, the cumulative risk was 9.0% in skin cancer and 8.3% in head and neck cancer. The cumulative risk of bladder cancer was estimated separately for females and males, at 12.8% and 5.6%, respectively.

DISCUSSION

This study identified significant associations between pathogenic variants in *BRCA1* or *BRCA2* and four less common cancer types: thyroid, bladder, head and neck, and skin. While the association between *BRCA2* and cutaneous melanoma is described in the National Comprehensive Cancer Network (NCCN) guidelines,[3] studies on other cancer types remain limited. In an analysis of *BRCA1/2* families, Li et al. observed a tendency for associations between *BRCA2* and bladder cancer [relative risk (RR) 1.71, 95% CI 0.75-3.89]; however, no significant association was observed for thyroid and head and neck cancers with *BRCA1/2*.[1] Although an analysis of *BRCA2* families in the Dutch population suggested an association with pharyngeal cancer (RR 7.3, 95% CI 2.0-18.6),[17] another analysis of *BRCA2* families in ∼3000 Caucasians showed no association with buccal cavity and pharyngeal cancers (RR 2.26, 95% CI 1.09-4.58, $P = 0.06$),[5] showing inconsistent results. The low incidence of these cancers may contribute to the lack of definitive associations. While previous family-based studies included <200 cases with a carrier status for less common cancers,[1,5,17] our study included >300 cases of associated cancers, highlighting the importance of sample size.

Our identification of associations between *BRCA1/2* pathogenic variants and four less common cancer types highlights the potential of expanded personalized medicine, including surveillance options and using PARP inhibitors. Bladder and head and neck cancers have poor prognosis, with a 5-year survival rate of 5%-20% for metastatic cases.[18] Advanced bladder cancer is often resistant to chemotherapy and immune checkpoint inhibitors.[19] Also,

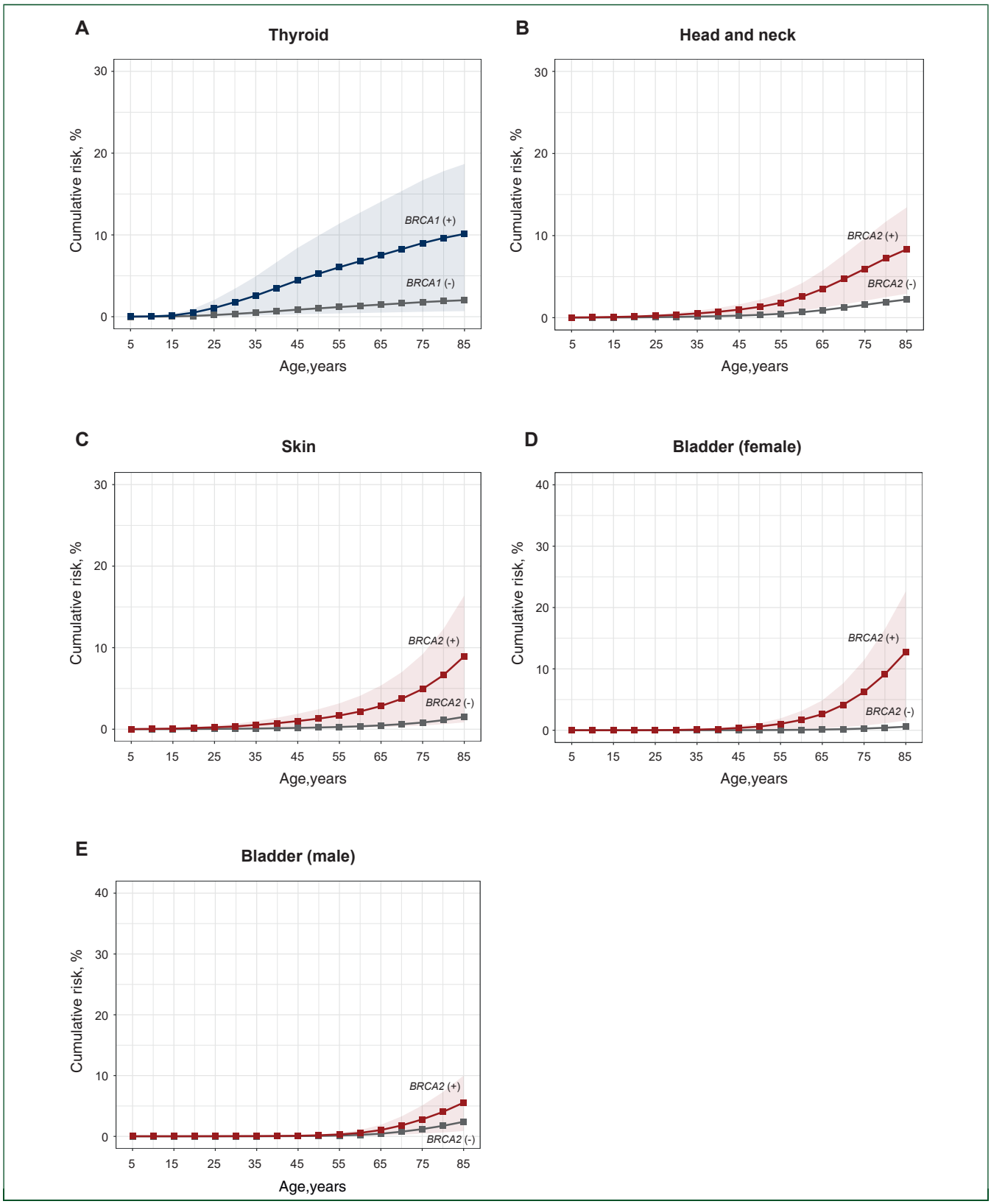

Figure 2. Cumulative risk of each cancer type associated with pathogenic variants in *BRCA1/2*. The cumulative risks up to the age of 85 years were estimated for carriers and noncarriers of pathogenic variants in (A) *BRCA1* for thyroid cancer, (B) *BRCA2* for head and neck cancer, (C) *BRCA2* for skin cancer, (D) *BRCA2* for female bladder cancer, and (E) *BRCA2* for male bladder cancer. *BRCA1* (+) and *BRCA2* (+) indicate pathogenic variant carriers in *BRCA1* and *BRCA2*, respectively. *BRCA1* (−) and *BRCA2* (−) indicate individuals without pathogenic variants in *BRCA1* and *BRCA2*, respectively.

>50% of head and neck cancer patients are already in advanced stages at diagnosis, limiting treatment options.[20] Early detection and expanded treatment options may improve the prognosis for these cancer types. The association between *BRCA2* and cutaneous melanoma is described in the NCCN guidelines based on Caucasian data.[3] In Japan, melanoma accounts for 7.2% of skin cancer patients, which is small compared with squamous- (43.9%) and basal-cell carcinoma (37.2%) with a relatively good prognosis.[21] Given that similar proportions are expected to be collected from BioBank Japan[13] and *BRCA2* carrier frequency in melanoma is reported to be <1% in Caucasian populations,[22] our results may not be limited to the effect of melanoma. Further studies are needed to provide more precise personalized medicine for these cancer types.

Our study revealed that *BRCA2* pathogenic variants had a greater impact on the risk of bladder cancer in females than in males. A previous family-based study in Caucasians observed no association between *BRCA2* pathogenic variants and bladder cancer overall, but there was a trend toward higher RR in females than in males [females 4.07 (95% CI 1.09-15.21); males 1.26 (95% CI 0.46-3.47)].[1] However, no statistically significant sex difference was observed ($P = 0.20$),[1] likely because of the limited sample size. Regarding sex differences in the effect of *BRCA1/2* pathogenic variants, the risk of *BRCA2* pathogenic variants for breast cancer is higher in males,[2] while it is unclear for other cancer types. Environmental factors such as smoking and drinking history may influence sex differences in the effect of pathogenic variants.[15] Our analysis observed the sex differences in the effect of pathogenic variants despite considering these factors. Another possibility is that the observed sex differences might be influenced by cystitis, more prevalent in females. It has been suggested that inflammation promotes carcinogenesis based on DNA damage.[23,24] Considering this finding, individuals with reduced DNA damage-repair capacity by *BRCA2* pathogenic variants could have interactively increased the risk of bladder cancer due to genomic instability from repeated cystitis. This interaction may explain the greater impact of *BRCA2* pathogenic variants observed in females than in males. Although prevention and treatment of cystitis could be important for pathogenic variant carriers, further studies are needed.

There are some limitations. Firstly, we used self-reported medical histories, which might have been affected by information bias and misclassification bias. However, participants provided self-reports without knowledge of their carrier status for pathogenic variants. Therefore, information bias is unlikely to affect the associations between pathogenic variants and each cancer type. Previous reports in BioBank Japan also demonstrated comparable genetic evidence from physician-based and self-reported data, suggesting limited misclassification bias in this study.[25,26] Secondly, due to limited clinical information, we could not sufficiently evaluate associations with lethality or aggressiveness. Therefore, we referred to the data from the Center for Cancer Genomics and Advanced Therapeutics (C-CAT), which has collected data of patients with advanced cancer after standard treatment.[27] We observed three *BRCA2* carriers among 122 bladder cancer patients. One patient died ~2 years after diagnosis, while the other two patients survived for 3-4 years and remain alive to date (Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2026.106900). These results suggest that *BRCA2*-associated bladder cancer is not necessarily limited to lethal cases. Also, no *BRCA1* carriers were observed in 158 advanced thyroid cancer patients after standard treatment in C-CAT. Considering these findings, large-scale analyses using more detailed clinical information are required to clarify the clinical severity characteristics of *BRCA2*-associated cancers, while establishing screening criteria based on carrier status requires more cautious discussion.

Conclusions

This study identified significant associations between pathogenic variants in *BRCA1/2* and four less common cancer types, with significant sex differences in the risk of pathogenic variants for bladder cancer. These results suggest the potential for expanding and more precise personalized medicine.

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DISCLOSURE

The authors have declared no conflicts of interest.

DATA SHARING

The sequence data that support the findings of this study will be deposited in the NBDC human database (NBDC Research ID: hum0014) and be available under the NBDC Data Sharing Policy (controlled-access data Type-1) after this paper is accepted.

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