Skin cancer risk in patients with *BRCA* mutations

To the Editor: Patients with germline BReast CAncer gene (*BRCA*) mutations have a well-documented risk of cancers, such as breast, ovarian, prostate, and pancreatic.[1] Studies evaluating the association between *BRCA* mutations and skin cancer risk report inconsistent results and are limited by surveillance bias.[2]

We used Optum's deidentified Clinformatics Data Mart Database (January 2007- June 2022, with approximately 62 million patients). We included patients with current procedural terminology codes for *BRCA* genetic testing. We considered patients to have evidence of *BRCA* mutation if they had at least one *genetic susceptibility to breast or ovarian cance*r International Classification of

Table I. Patient characteristics by *BRCA* status

Patient characteristic	Full cohort	No evidence of *BRCA* mutation	Evidence of *BRCA* mutation
Overall	71,092	64,630 (90.9%)	6462 (9.1%)
Age (mean ± SD)	49.1 ± 14.7	49.3 ± 14.7	47.0 ± 14.4
Age category			
<40	20,343 (28.6%)	18,193 (28.1%)	2150 (33.3%)
40-50	17,918 (25.2%)	16235 (25.1%)	1683 (26.0%)
50-59	15,560 (21.9%)	14,193 (22.0%)	1367 (21.2%)
60+	17,271 (24.3%)	16,009 (24.8%)	1262 (19.5%)
Sex			
Female	64,226 (90.3%)	58,254 (90.1%)	5972 (92.4%)
Male	6860 (9.6%)	6370 (9.9%)	490 (7.6%)
Region			
Northeast	7959 (11.2%)	7215 (11.2%)	744 (11.5%)
Midwest	13,288 (18.7%)	11,797 (18.3%)	1491 (23.1%)
South	35,601 (50.1%)	32,645 (50.5%)	2956 (45.7%)
West	14,140 (19.9%)	12,875 (19.9%)	1265 (19.6%)
Unknown	104 (0.1%)	98 (0.2%)	6 (0.1%)
History of skin cancer			
No	67,337 (94.7%)	61,157 (94.6%)	6180 (95.6%)
Yes	3755 (5.3%)	3473 (5.4%)	282 (4.4%)
History of AK			
No	68,378 (96.2%)	62,142 (96.2%)	6236 (96.5%)
Yes	2714 (3.8%)	2488 (3.8%)	226 (3.5%)
Race			
Asian	1993 (2.8%)	1822 (2.8%)	171 (2.6%)
Black	7870 (11.1%)	7214 (11.2%)	656 (10.2%)
Hispanic	7180 (10.1%)	6596 (10.2%)	584 (9.0%)
White	51,166 (72.0%)	46,359 (71.7%)	4807 (74.4%)
Unknown	2883 (4.1%)	2639 (4.1%)	244 (3.8%)
Skin cancer outcomes during follow-up*			
All skin cancer	3328 (4.7%)	3020 (4.7%)	308 (4.8%)
All keratinocyte carcinoma†	3094 (4.4%)	2812 (4.4%)	282 (4.4%)
BCC	1998 (2.8%)	1805 (2.8%)	193 (3.0%)
SCC	1353 (1.9%)	1240 (1.9%)	113 (1.8%)
All melanoma	362 (0.5%)	321 (0.5%)	41 (0.6%)
Melanoma in situ	180 (0.3%)	155 (0.2%)	25 (0.4%)
Invasive melanoma	225 (0.3%)	200 (0.3%)	25 (0.4%)

AK, Actinic keratosis; *BRCA*, BReast CAncer gene.
*Listed are the number of patients who had at least one of each skin cancer type.
†All keratinocyte carcinomas include BCC (basal cell carcinoma) and SCC (squamous cell carcinoma).

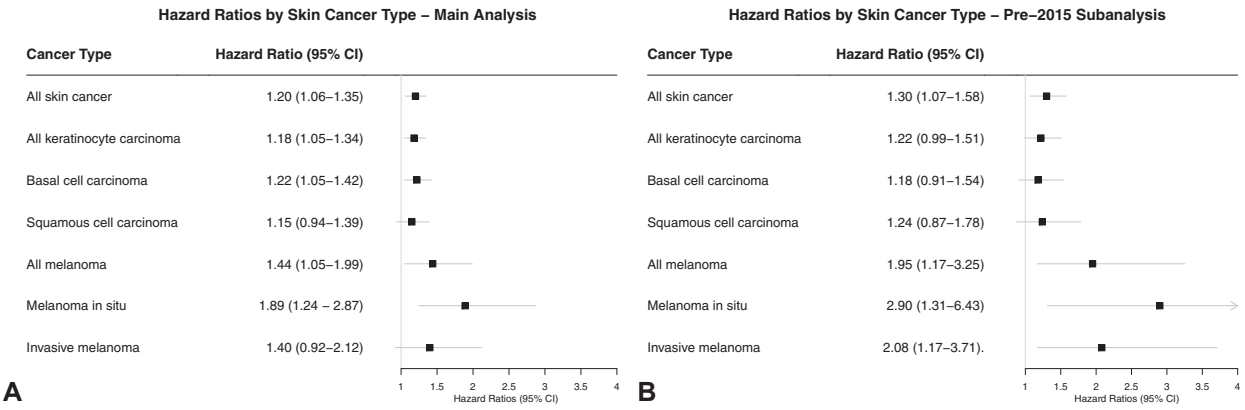

Fig 1. Hazard ratios by skin cancer type for main (**A**) and secondary (**B**; pre-2015 subanalysis) cohorts. Results of multivariable competing risks regression including adjustment variables: age, gender, race, region, history of skin cancer, and history of actinic keratosis. All keratinocyte carcinomas include BCC (basal cell carcinoma) and SCC (squamous cell carcinoma).

Diseases (ICD) code (Z15.01, Z15.02, V84.01, V84.02) 3 months prior or up to 3 years after *BRCA* test date. As some ICD codes may identify patients with non-*BRCA* mutations on multigene panels, we performed a secondary analysis limited to patients who received *BRCA* testing prior to 2015, when multigene panels were less common.[3] Skin cancer outcomes were identified using ICD codes plus same-day treatment current procedural terminology codes for keratinocyte carcinoma and melanoma.[4] Patients with solid organ transplant, HIV, or active breast, ovarian, pancreatic, or prostate cancer in the 6 months prior *BRCA* test date were excluded. We evaluated patient demographics and performed adjusted competing risks regression (competing risk of death) for risk of skin cancer comparing patients with evidence of *BRCA* mutation to those without.

There were 71,092 patients that met inclusion criteria. The mean age at *BRCA* testing was 49.1 (SD: 14.7) with a mean follow-up of 3.2 (SD: 2.1) years, and 9.1% ($n = 6462$) had a *BRCA* mutation (Table I). *BRCA* mutation was associated with a hazard ratio (HR) of 1.19 (95% CI: 1.06 − 1.34) for skin cancer overall, 1.42 (95% CI: 1.02-1.97) for melanoma, and 1.18 (95% CI: 1.04-1.33) for keratinocyte carcinoma in adjusted competing risks regression. Fig 1 shows results for skin cancer outcome subgroups (statistically significantly increased HRs for BCC and melanoma *in situ*) and for secondary analysis (statistically significantly increased HRs for all skin cancer and for melanoma, including *in situ* and invasive).

BRCA mutation was associated with an approximately 20% increased risk of skin cancer and approximately 40% increased risk of melanoma. Prior work on *BRCA* and skin cancer has been limited by surveillance bias.[2] This is important as many skin cancers are nonfatal and may be asymptomatic, and patients with higher health care utilization have higher risks of skin cancer.[5] Although we are not able to fully distinguish between surveillance bias and real biologic effect, we attempted to minimize surveillance bias by only including patients who received *BRCA* testing.

Using claims data limits the distinguishability between *BRCA1* and *BRCA2,* and identifying *BRCA* mutations in claims data is not yet validated. Although patients were tested for *BRCA*, we cannot confirm that the ICD codes reflect a positive *BRCA* test result, as this ICD code can represent other mutations. However, when we limited our cohort to prior to 2015, we found congruent results.

This study supports a positive association between *BRCA* mutations and skin cancer, which may represent a biologic effect rather than a surveillance bias effect.

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Conflicts of interest

None disclosed.

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