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Characterization of the Cancer Spectrum in Men With Germline *BRCA1* and *BRCA2* Pathogenic Variants

Results From the Consortium of Investigators of Modifiers of BRCA1/2 (CIMBA)

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IMPORTANCE The limited data on cancer phenotypes in men with germline *BRCA1* and *BRCA2* pathogenic variants (PVs) have hampered the development of evidence-based recommendations for early cancer detection and risk reduction in this population.

OBJECTIVE To compare the cancer spectrum and frequencies between male *BRCA1* and *BRCA2* PV carriers.

DESIGN, SETTING, AND PARTICIPANTS Retrospective cohort study of 6902 men, including 3651 *BRCA1* and 3251 *BRCA2* PV carriers, older than 18 years recruited from cancer genetics clinics from 1966 to 2017 by 53 study groups in 33 countries worldwide collaborating through the Consortium of Investigators of Modifiers of BRCA1/2 (CIMBA). Clinical data and pathologic characteristics were collected.

MAIN OUTCOMES AND MEASURES *BRCA1/2* status was the outcome in a logistic regression, and cancer diagnoses were the independent predictors. All odds ratios (ORs) were adjusted for age, country of origin, and calendar year of the first interview.

RESULTS Among the 6902 men in the study (median [range] age, 51.6 [18-100] years), 1634 cancers were diagnosed in 1376 men (19.9%), the majority (922 of 1,376 [67%]) being *BRCA2* PV carriers. Being affected by any cancer was associated with a higher probability of being a *BRCA2*, rather than a *BRCA1*, PV carrier (OR, 3.23; 95% CI, 2.81-3.70; $P < .001$), as well as developing 2 (OR, 7.97; 95% CI, 5.47-11.60; $P < .001$) and 3 (OR, 19.60; 95% CI, 4.64-82.89; $P < .001$) primary tumors. A higher frequency of breast (OR, 5.47; 95% CI, 4.06-7.37; $P < .001$) and prostate (OR, 1.39; 95% CI, 1.09-1.78; $P = .008$) cancers was associated with a higher probability of being a *BRCA2* PV carrier. Among cancers other than breast and prostate, pancreatic cancer was associated with a higher probability (OR, 3.00; 95% CI, 1.55-5.81; $P = .001$) and colorectal cancer with a lower probability (OR, 0.47; 95% CI, 0.29-0.78; $P = .003$) of being a *BRCA2* PV carrier.

CONCLUSIONS AND RELEVANCE Significant differences in the cancer spectrum were observed in male *BRCA2*, compared with *BRCA1*, PV carriers. These data may inform future recommendations for surveillance of *BRCA1/2*-associated cancers and guide future prospective studies for estimating cancer risks in men with *BRCA1/2* PVs.

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Supplemental content

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While there are a substantial number of studies on cancer risks and the cancer spectrum in female carriers of germline pathogenic variants (PVs) in *BRCA1* (OMIM 113705) and *BRCA2* (OMIM 600185),[1-4] data on male *BRCA1/2* PV carriers are limited and have primarily focused on breast and/or prostate cancers. Population-based studies have shown that *BRCA1* and *BRCA2* PVs account for up to 2% and 13% of male breast cancer cases, respectively.[5] The lifetime risk of male breast cancer has been estimated at 1% to 5% for *BRCA1* and 5% to 10% for *BRCA2* PV carriers, vs 0.1% in the general male population.[2,3,6-8] Additionally, *BRCA1* and *BRCA2* PVs have been estimated to account for less than 1% and approximately 2% of incident prostate cancer diagnoses, respectively.[9,10] Estimates of lifetime prostate cancer risk associated with *BRCA1* and *BRCA2* PVs vary, with some studies reporting higher risk for male *BRCA2* PV carriers,[10-15] while other studies did not find any increased risk.[16-18] Pathogenic variants in *BRCA1* and, more frequently, in *BRCA2* have been reported in male patients diagnosed with other cancer types.[13,14,19-24] However, current risk estimates for cancers other than breast and prostate are based on handfuls of cases in a limited number of families.

BRCA1/2-associated tumors in men exhibit specific pathologic features and poor clinical outcome. A specific *BRCA2*-associated breast cancer phenotype, hallmarked by high histopathologic grade, a feature suggestive of biological aggressiveness, has been reported in men.[25] Compared with age-matched controls, men with *BRCA1/2*-associated prostate cancer more frequently have early-onset (<65 years) and aggressive disease.[15,26] Specifically, *BRCA2* PVs were identified as an independent negative prognostic factor in patients with prostate cancer.[27] There is also some evidence suggesting that patients with *BRCA1/2*-associated pancreatic cancer may exhibit worse prognosis compared with noncarriers.[28] In the aggregate, these observations highlight the need for large collaborations to improve and expand data on the cancer spectrum in male *BRCA1/2* PV carriers to optimize guidelines for cancer risk management in this group.[29]

The Consortium of Investigators of Modifiers of BRCA1/2 (CIMBA) is an international collaboration that has collected data on female and male *BRCA1/2* PV carriers.[30] Using this series, to our knowledge the largest collected worldwide, we aimed to characterize the spectrum of cancers diagnosed in male *BRCA1/2* PV carriers and identify differences between *BRCA1* and *BRCA2* PV carriers. Such information could form the foundation for future screening and surveillance recommendations regarding *BRCA1/2*-associated cancers in men and for future studies aimed to estimate lifetime risks of cancers other than breast and prostate in male *BRCA1/2* PV carriers.

Key Points

Question Are there cancer phenotype differences between male *BRCA1* and *BRCA2* pathogenic variant carriers?

Findings In this cohort study of 6902 men with a *BRCA1* or *BRCA2* pathogenic variant, being affected by cancer, particularly breast, prostate, and pancreatic cancers and developing multiple primary tumors, was associated with a higher probability for a man of being a *BRCA2*, rather than a *BRCA1*, pathogenic variant carrier.

Meaning Surveillance programs in men with *BRCA1* and *BRCA2* pathogenic variants should be tailored in light of these gene-specific cancer phenotype differences. These results may inform the design of prospective studies on cancer risks in male *BRCA1* and *BRCA2* pathogenic variant carriers.

Methods

CIMBA Study Participants

Investigators collaborating through CIMBA (http://cimba.ccge.medschl.cam.ac.uk/) have collected data on men older than 18 years who carry pathogenic and likely pathogenic *BRCA1* or *BRCA2* variants, with the majority of carriers identified and recruited via cancer genetics clinics.[25] Variant pathogenicity was defined as previously described.[31] The present study includes data from 6902 male *BRCA1/2* PV carriers collected by 53 study groups in 33 countries from 1966 to 2017 (eTables 1 and 2 in the Supplement).

Data collected for each individual included year of birth, a unique family identifier, ethnicity, age at cancer diagnosis, primary tumor site (*International Statistical Classification of Diseases and Related Health Problems, Tenth Revision [ICD-10]* coding), age at last observation, and clinical data from medical, pathology, or tumor registry records.[25] Most individuals (77%) reported herein are self-reported as white Caucasian, with other ethnicities not as equally represented (eTable 3 in the Supplement). Recruited *BRCA1* or *BRCA2* PV carriers include probands and tested family members (eTable 4 in the Supplement). Data on first-degree and second-degree family history of male breast, prostate, and female breast cancer were also collected and were available for a subset of individuals (eTable 5 in the Supplement). Written informed consent was obtained from all study participants, as part of the protocol approved by the individual ethics committees at the participating centers.

Statistical Methods

The primary objective was to compare cancer diagnoses between male *BRCA1* and *BRCA2* PV carriers. We used logistic regression to estimate the association between *BRCA1/2* PV status (outcome) and cancer diagnosis (independent variable). Individuals with no cancer diagnosis at last follow-up were considered unaffected (reference group), whereas individuals with 1 or more diagnoses of cancer at any site were grouped as affected. This provides an estimate of the odds ratio (OR) comparing the odds of being a *BRCA2* PV carrier in the affected group to the odds of being a *BRCA2* PV carrier in the unaffected group. In practice, under a univariate analysis, this can be interpreted as the OR of a *BRCA2* carrier being affected compared with the odds of a *BRCA1* PV carrier being affected. Differences in age at first cancer diagnosis by cancer site (breast, prostate, other sites) between *BRCA1* and *BRCA2* PV carriers and in intercancer intervals were assessed by the nonparametric Mann-Whitney test.

Table 1. Cancer Diagnosis in Male *BRCA1/2* Pathogenic Variant (PV) Carriers Within CIMBA Data Set and Odds Ratios (ORs) in Predicting *BRCA2* PV Carrier Status

	No. (%)				
	Total (N = 6902)	*BRCA1* (n = 3651)	*BRCA2* (n = 3251)	Adjusted OR (95% CI)[a]	*P* value
Unaffected	5526 (80.1)	3197 (87.6)	2329 (71.6)	1.00 [Reference]	
Affected	1376 (19.9)	454 (12.4)	922 (28.4)	3.23 (2.81-3.70)	<.001
Cases with 1 cancer diagnosis	1144 (83.1)	416 (91.6)	728 (79.0)	2.77 (2.40-3.20)	<.001
Breast cancer	380 (33.2)	50 (12.0)	330 (45.3)		
Prostate cancer	273 (23.9)	83 (20.0)	190 (26.1)		
Cancer other than breast and prostate	491 (42.9)	283 (68.0)	208 (28.6)		
Cases with 2 cancer diagnoses	206 (15.0)	36 (8.0)	170 (18.4)	7.97 (5.47-11.60)	<.001
Bilateral breast cancer	24 (11.7)	0	24 (14.1)		
Breast and prostate cancer	53 (25.7)	4 (11.1)	49 (28.8)		
Breast cancer and cancer other than breast and prostate	59 (28.6)	8 (22.2)	51 (30.0)		
Prostate cancer and cancer other than breast and prostate	69 (33.5)	23 (63.9)	46 (27.1)		
Two cancers other than breast and prostate	1 (0.5)	1 (2.8)	0		
Cases with 3 cancer diagnoses	26 (1.9)	2 (0.4)	24 (2.6)	19.60 (4.64-82.89)	<.001
Bilateral breast and prostate cancer	5 (19.2)	0	5 (20.8)		
Bilateral breast and cancer other than breast and prostate	7 (26.9)	0	7 (29.2)		
Prostate cancer and 2 cancers other than breast and prostate	1 (3.8)	1 (50.0)	0		
Breast, prostate, and cancer other than breast and prostate	13 (50.0)	1 (50.0)	12 (50.0)		

Abbreviation: CIMBA, Consortium of Investigators of Modifiers of BRCA1/2.

[a] Analyses adjusted for age at cancer diagnosis/last follow-up, country of origin, and calendar year of interview.

A separate cancer-only logistic regression was performed (using the same approach described above) restricted to affected individuals in which all tumors arising in affected male carriers were taken into consideration. The independent variables were defined as the cancer site (breast cancer vs all cancers but breast; prostate cancer vs all cancers but prostate; cancers at other sites vs breast and prostate cancers). A further analysis was performed, including only tumors at sites other than breast and prostate to address possible ascertainment bias of breast and prostate cancers. In this analysis, the independent variables were specific cancer sites, namely colorectal cancer, melanoma, and pancreatic cancer (colorectal cancer vs all other cancers; melanoma vs all other cancers; pancreatic cancer vs all other cancers). To assess the potential influence of survival bias, these analyses were also repeated after omitting cancer diagnoses occurring more than 5 years prior to study recruitment.

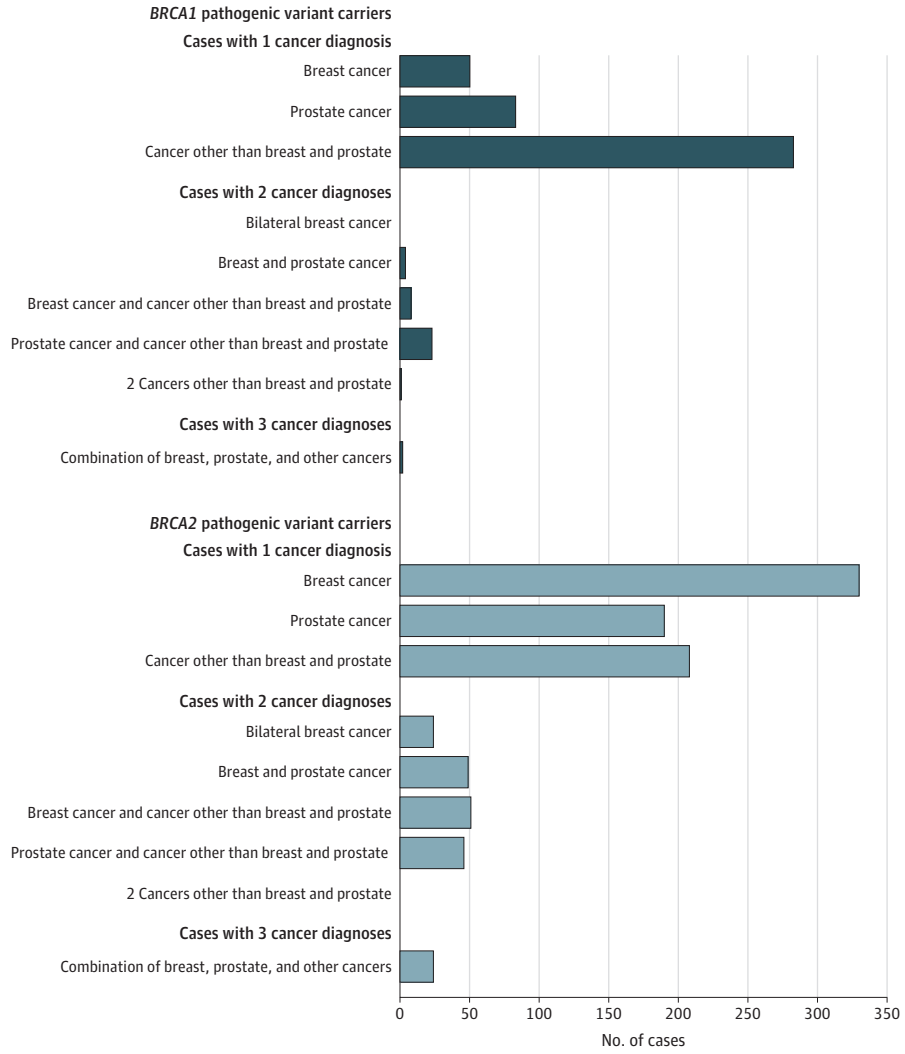
Confounders included in the logistic regression models were prespecified and were chosen on the basis of previous studies on CIMBA male carrier series[25,31] and by considering factors related to the study design. All analyses were adjusted for age at cancer diagnosis (affected individuals) or age at last follow-up (unaffected individuals) and country of origin. In addition, adjustments for calendar year of the first interview were included in all analyses as a surrogate for year of genetic testing, based on the groupings of 2000 or earlier, 2001-2010, and after 2010, to account for ascertainment biases owing to differential genetic testing approaches and inclusion criteria over time. A logistic regression adjusted also for proband status, estimated considering as probands individuals with a cancer diagnosis date preceding interview prior genetic testing date, was performed. To assess the potential influence of family history, analyses were repeated adjusting for family history of male breast cancer, female breast cancer, and prostate cancer, all included as separate covariates, with each variable grouped as positive, negative, or unknown family history. A robust variance approach was used to allow for dependencies between related individuals. *P* values of .05 or less were considered statistically significant. All analyses were carried out using Stata, version 13 (StataCorp).

Results

The series included 6902 men with PVs in *BRCA1* (n = 3651 [52.9%]) or *BRCA2* (n = 3251 [47.1%]). Of the 6902 male *BRCA1/2* PV carriers, 1376 (19.9%) had at least 1 cancer diagnosis, the majority of whom (67.0%) harbored a *BRCA2* PV. Median (range) age in the whole series was 51.6 (18-100) years. Age distribution is reported in the eFigure in the Supplement.

Of the 1376 carriers with cancer, 1144 (83.1%) were diagnosed with 1 cancer, 206 (15.0%) had 2 cancers, and 26 (1.9%) had 3 independent cancer diagnoses (**Table 1**). The number and type of cancer diagnoses varied greatly depending on which gene was mutated (Table 1 and **Figure 1**). Notably, all individuals diagnosed with 2 independent breast cancers had a *BRCA2* PV. Overall, being affected by any cancer was associated with a higher probability of being a *BRCA2*, rather than a *BRCA1*, PV carrier (OR, 3.23; 95% CI, 2.81-3.70; $P < .001$). Similarly, de-

Figure 1. Cancer Diagnoses in Male *BRCA1* and *BRCA2* Pathogenic Variant Carriers



Type of cancer diagnoses reported in the 1376 affected male *BRCA1* (n = 454) and *BRCA2* (n = 922) pathogenic variant carriers in the Consortium of Investigators of Modifiers of BRCA1/2 data set.

veloping multiple cancers, particularly 2 (OR, 7.97; 95% CI, 5.47-11.60; $P < .001$) and 3 (OR, 19.60; 95% CI, 4.64-82.89; $P < .001$) primary tumors, was associated with a higher probability of being a *BRCA2* PV carrier in analyses adjusted for age, country of origin, and calendar year of interview (Table 1). Analyses adjusted also for family history of male breast cancer, female breast cancer, and prostate cancer gave similar results (eTable 6 in the Supplement).

Among male *BRCA2* PV carriers with more than 1 cancer diagnosis, significantly shorter median intercancer intervals were observed for cases with a first diagnosis of breast (5.0 years) or prostate (3.4 years) cancers compared with cases with a first diagnosis of other cancers (7 years; Mann-Whitney test $P = .03$ and $P = .005$, respectively). Focusing on the first cancer diagnosed, breast (n = 485 [35.3%]) and prostate (n = 337 [24.5%]) cancers represented the majority of all first diagnoses (**Table 2**). Both breast and prostate cancers occurred more frequently in *BRCA2* PV carriers (46.4% and 25.6%, respectively) compared with *BRCA1* PV carriers (12.5% and 22.3%) (Table 2; eTable 7 in the Supplement). Median age at first cancer diagnosis was 61.5 years for breast cancer and 63.2 years for prostate cancer and were similar for *BRCA1* and *BRCA2* PV carriers (Table 2). Nonbreast and nonprostate cancers combined (n = 554) represented 40.2% of all first cancer diagnoses, with a median age at diagnosis of 59.2 years (Table 2). The proportion of cancers other than breast and prostate taken together is larger in *BRCA1* PV carriers (65.2%) compared with *BRCA2* PV carriers (28.0%), while mean age at first diagnosis was statistically significantly older in *BRCA1* (61.8 years) compared with *BRCA2* PV carriers (56.5 years; Mann-Whitney test $P = .003$).

A total of 1634 cancers were reported in the 1376 affected individuals, of which 494 (30.2%) were in *BRCA1* PV carriers and 1140 (69.8%) were in *BRCA2* PV carriers (**Table 3**). The analysis restricted to affected individuals and adjusted for age, country of origin, and calendar year of interview showed that a higher frequency of breast (OR, 5.47; 95% CI, 4.06-7.37; $P < .001$) and prostate (OR, 1.39; 95% CI, 1.09-1.78; $P = .008$) cancers, and a lower frequency of cancers other than breast and prostate combined (OR,

Table 2. Age at First Cancer Diagnosis According to Cancer Site and *BRCA1/2* Pathogenic Variant (PV) Status in the 1376 Affected Male Carriers Within CIMBA Data Set

	Total carriers		*BRCA1* PV carriers		*BRCA2* PV carriers		
Cancer diagnosis	No. (%)	Age at diagnosis, median (IQR)	No. (%)	Age at diagnosis, median (IQR)	No. (%)	Age at diagnosis, median (IQR)	*P* value[a]
Male breast cancer	485 (35.3)	61.5 (16.0)	57 (12.5)	61.0 (20.0)	428 (46.4)	61.5 (15.3)	.87
Prostate cancer	337 (24.5)	63.2 (12.5)	101 (22.3)	65.0 (12.0)	236 (25.6)	63.1 (12.2)	.09
Cancers other than breast and prostate	554 (40.2)	59.2 (19.6)	296 (65.2)	61.8 (20.0)	258 (28.0)	56.5 (20.3)	.003

Abbreviations: CIMBA, Consortium of Investigators of Modifiers of BRCA1/2; IQR, interquartile range.

[a] Mann-Whitney test for the comparison of median age at first cancer diagnosis between male *BRCA1* and *BRCA2* PV carriers.

Table 3. Analysis Restricted to the Total Tumors Reported in the 1376 Affected Male *BRCA1/2* Pathogenic Variant (PV) Carriers Within CIMBA Data Set and Odds Ratios (ORs) in Predicting *BRCA2* PV Carrier Status

	No. (%)			Adjusted OR (95% CI)[a]	
Cancer diagnosis	Total	*BRCA1*	*BRCA2*		*P* value
All cancers	1634	494	1140	1.00 [Reference]	
Male breast cancer	577 (35.3)	63 (12.7)	514 (45.1)	5.47 (4.06-7.37)	<.001
Prostate cancer	414 (25.3)	112 (22.7)	302 (26.5)	1.39 (1.09-1.78)	.008
Cancers other than breast and prostate	643 (39.4)	319 (64.6)	324 (28.4)	0.22 (0.18-0.28)	<.001
Colorectal cancer	84 (13.1)	55 (17.2)	29 (9.0)	0.47 (0.29-0.78)	.003
Melanoma	62 (9.6)	33 (10.3)	29 (9.0)	0.76 (0.43-1.34)	.35
Pancreatic cancer	48 (7.5)	13 (4.1)	35 (10.8)	3.00 (1.55-5.81)	.001

Abbreviation: CIMBA, Consortium of Investigators of Modifiers of BRCA1/2.

[a] Analyses adjusted for age at cancer diagnosis/last follow-up, country of origin and calendar year of interview.

0.22; 95% CI, 0.18-0.28; $P < .001$) were associated with a higher probability of being a *BRCA2*, rather than a *BRCA1*, PV carrier. Specifically, 643 of 1634 tumors (39.4%) were in sites other than breast and prostate, of which 319 (64.6%) were diagnosed in *BRCA1* PV carriers and 324 (28.4%) were diagnosed in *BRCA2* PV carriers (Table 3).

Considering cancers other than breast and prostate, more than 60 different cancer sites were reported (eTable 8 in the Supplement). The most common nonbreast and nonprostate cancer types (>60 diagnoses each) were nonmelanoma skin cancer, colorectal cancer and melanoma; other frequently reported cancer types (>30 diagnoses each) were head and neck, pancreatic, lung, and bladder cancers (**Figure 2**; eTable 8 in the Supplement). Cancer phenotype varied between *BRCA1* and *BRCA2* PV carriers (Figure 2 and Table 3). In particular, among the nonbreast and nonprostate cancers, pancreatic cancer was associated with a higher probability of being a *BRCA2* carrier (OR, 3.00; 95% CI, 1.55-5.81; $P = .001$), and colorectal cancer was associated with a lower probability of being a *BRCA2* PV carrier (OR, 0.47; 95% CI, 0.29-0.78; $P = .003$), in analyses adjusted for age, country of origin, and calendar year of interview (Table 3). No statistically significant differences in the frequencies of other cancer diagnoses between *BRCA1* and *BRCA2* PV carriers were found. Analyses adjusted also for family history of male breast cancer, female breast cancer, and prostate cancer gave similar results (eTable 9 in the Supplement). Similar findings were also obtained in analyses omitting cancer diagnoses occurring more than 5 years prior to study recruitment (eTable 10 in the Supplement).

Discussion

Men with *BRCA1/2* PVs represent an underinvestigated group that poses clinical challenges. The paucity of data on cancers arising in male *BRCA1/2* PV carriers has limited the development of evidence-based clinical guidelines for surveillance and prevention in men harboring *BRCA1/2* PVs.[29]

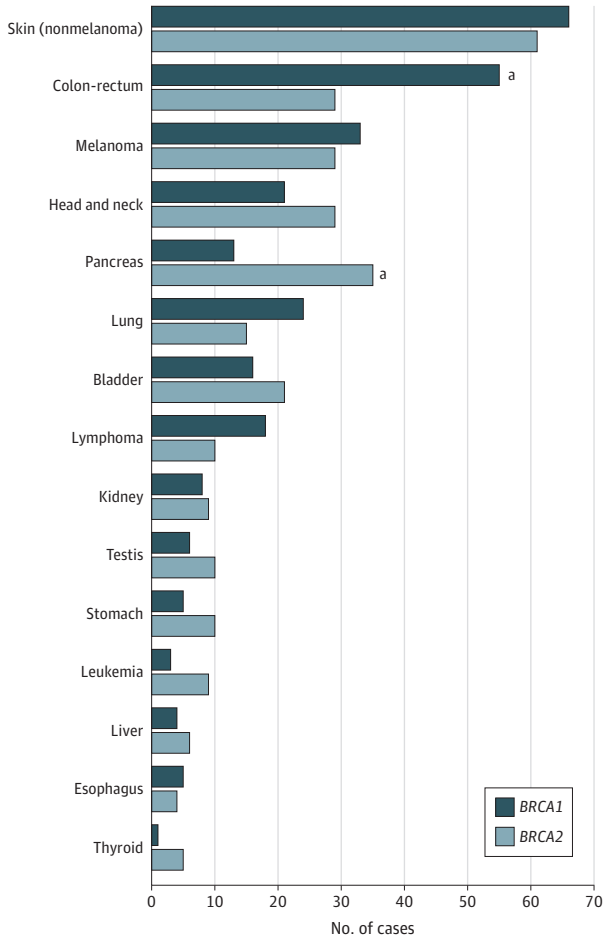
By taking advantage of data collected through CIMBA, we characterized the cancer spectrum in male *BRCA1/2* PV carriers and compared *BRCA1* with *BRCA2* PV carriers in terms of number, site, and age of cancer diagnoses. We believe this study comprises the largest series of male *BRCA1/2* PV carriers collected worldwide to date.

Our results highlight specific, unique differences in the cancer spectrum of male *BRCA2* vs *BRCA1* PV carriers. Being affected with cancer and developing multiple cancer types at younger ages was associated with a higher probability of being a *BRCA2* PV carrier.

Intercancer intervals were shorter in male *BRCA2* PV carriers with a first diagnosis of breast or prostate cancers, compared with other cancers, thus suggesting that *BRCA2*-associated breast and prostate cancers may have a worse prognosis. However, age difference at first diagnosis, being older for breast or prostate cancer compared with the other cancers, may affect intercancer intervals.

While recommended guidelines for early detection and cancer risk reduction for female *BRCA1/2* PV carriers are evidence based,[32] only limited recommendations, based on low-level evidence or expert opinion, are available for male *BRCA1/2*

Figure 2. Spectrum of Cancers Other Than Breast and Prostate in Male *BRCA1* and *BRCA2* Pathogenic Variant (PV) Carriers



Cancer sites other than breast and prostate with >5 reported diagnoses in the whole series of male *BRCA1/2* PV carriers within the Consortium of Investigators of Modifiers of BRCA1/2 data set.

[a] Significant differences between *BRCA1* and *BRCA2*.

PV carriers.[29] Current National Comprehensive Cancer Network (NCCN),[32] European Society for Medical Oncology (August 2016),[33] and American Society of Clinical Oncology (2017)[34] guidelines recommend annual clinical breast examination starting at age 30 to 35 years, and clinical prostate cancer screening, particularly for *BRCA2* PV carriers, starting at age 40 to 45 years. American Society of Clinical Oncology recommendations also suggest consideration of baseline mammograms on an individual basis.[34]

Recent studies have shown that mammography can detect clinically occult breast cancer when screening high-risk men, including *BRCA1/2* PV carriers.[35-37] Moreover, interim results from the International Prospective Prostate Cancer Screening (IMPACT) study have shown that the use of systematic prostate-specific antigen screening can detect clinically significant prostate cancers in male *BRCA2* PV carriers.[38] Based on those findings and on our data demonstrating that male *BRCA2* PV carriers more frequently develop breast and prostate cancers as a first or second tumor, future guidelines should consider recommending mammography and systematic prostate-specific antigen testing for male *BRCA2* PV carriers, although formal evaluation of these screening strategies is warranted in this set.

Our data also show that among the nonbreast and nonprostate cancers, pancreatic cancer was associated with a higher probability of being a *BRCA2* PV carrier. This observation reinforces the evidence of a sex-independent association between *BRCA2* PVs and pancreatic cancer.[14,19,20] Our findings are consistent with those from previous studies of families with *BRCA2* PVs showing that the spectrum of cancers for male carriers is largely attributable to the excess of breast, prostate, and pancreatic cancers.[19]

A prospective study on screening protocols for male *BRCA1/2* PV carriers suggested a role for screening for pancreatic cancer in addition to prostate and breast cancer.[24] Both National Comprehensive Cancer Network and European Society for Medical Oncology guidelines suggest individualizing screening for pancreatic cancer based on family specific-cancer history.[32-34] Our results provide further evidence to consider screening for pancreatic cancer in male *BRCA2* PV carriers. However, given the lack of data regarding the effectiveness of any pancreatic cancer screening program, male *BRCA2* PV carriers should be strongly encouraged to participate in clinical trials evaluating such screening strategies.[33]

In our study, most of the commonly reported cancers in male *BRCA1/2* PV carriers are also common in the general population and are possibly associated with environmental or lifestyle risk factors, such as smoking, although a role of gene-environment interactions in increasing cancer risks may be suggested.[39-42] However, country-specific environmental influences and lifestyle factors cannot be excluded. The absence of reliable risk estimates in *BRCA1/2* PV carriers for these cancers, especially for colorectal cancer,[43] leads to uncertainty about appropriate screening protocols. Nevertheless, education and awareness regarding signs and symptoms of these cancer types and strict adherence to population screening guidelines are highly warranted for male *BRCA1/2* PV carriers.

Limitations

There are some limitations to the current study. First, this study was largely retrospective, and data may not have been systematically collected. Second, cases were mostly recruited from high-risk clinics and/or high-risk families, and hence a selection bias toward having more affected individuals seems likely. However, the proportions of *BRCA1* and *BRCA2* PV carriers, as well as affected to unaffected ratios, are consistent with previously reported series of male *BRCA1/2* PV carriers.[2,7-9,14] Furthermore, the series included male carriers, both family probands and members, collected by different centers, and ascertainment bias may have occurred.

We assumed similar biases for *BRCA1/2*; thus, the study was designed to compare *BRCA1* with *BRCA2* PV carriers. However, *BRCA1/2* genetic testing might have been per-

formed based on cancer types or cancer family history, and genetic testing approaches and inclusion criteria might have changed over time. To account for such biases, different models, adjusted for cancer family history, proband status, and calendar year of the first interview, were performed. To assess the potential influence of survival bias, key analyses were repeated considering only cancer diagnoses within 5 years from study recruitment.

A high number of *BRCA1/2* mutations is reported in our series. Recently, an association between specific regions of *BRCA2* and prostate cancer risk was demonstrated.[31] Genotype-phenotype associations deserve to be further investigated for other cancers, particularly breast and pancreatic, arising in male *BRCA2* PV carriers.

The present study design does not allow for inference on the associations of specific cancer types in men with *BRCA1* or *BRCA2* PVs owing to the lack of a similar comparison group without PVs. Thus, associations between the observed cancer types and *BRCA1* or *BRCA2* PVs could not be analyzed, and age-specific cancer risks for male carriers could not be estimated. Further research, ideally large prospective studies, to obtain reliable cancer risk estimates in male *BRCA1/2* PV carriers is urgently needed to refine clinical management strategies.

Conclusions

Our results, derived from analyses of the largest available (to our knowledge) male *BRCA1/2* PV carrier data set, provide reliable data on the cancer spectrum in male *BRCA1* and *BRCA2* PV carriers. Being affected by any cancer and developing multiple cancers, particularly breast, prostate, and pancreatic cancers, was associated with a higher probability of being a *BRCA2*, rather than a *BRCA1*, PV carrier. These data may represent a step toward evidence-based guidelines and may help to refine existing recommendations in specifying distinct surveillance guidelines for men with either *BRCA1* or *BRCA2* PVs.

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