# Cancer spectrum in men with germline *BRCA1* and *BRCA2* pathogenic variants: Results from the Consortium of Investigators of Modifiers of *BRCA1/BRCA2* (CIMBA)

## Subtitle: Cancer spectrum in male *BRCA1* and *BRCA2* pathogenic variant carriers

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**KEY POINTS**

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

**Findings -** In this large retrospective study, 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.

**ABSTRACT**

**IMPORTANCE:** The limited data on cancer phenotypes in men with germline *BRCA1/2* pathogenic variants (PVs) has 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:** Retrospective cohort.

**SETTING:** The study population was 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).

**PARTICIPANTS:** 6,902 men, including 3,651 *BRCA1* and 3,251 *BRCA2* PV carriers, older than 18 years. Clinical data and pathological characteristics were collected.

**EXPOSURE(S), MAIN OUTCOME(S) AND MEASURE(S):** *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:** Overall, 1,634 cancers were diagnosed in 1,376 of 6,902 men (19.9%), the majority (922/1,376, 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% Confidence Interval (CI) 2.81 to 3.70, *P*<.001), as well as developing two (OR 7.97, 95% CI 5.47 to 11.60, P<.001) and three (OR 19.60, 95% CI 4.64 to 82.89, P<.001) primary tumors.

A higher frequency of breast (OR 5.47, 95% CI 4.06 to 7.37, P<.001) and prostate (OR 1.39, 95% CI 1.09 to 1.78, P=.008) cancers was associated with a higher probability of being a *BRCA2* PV. Among cancers other than breast and prostate, pancreatic cancer was associated with a higher probability (OR 3.00, 95% CI 1.55 to 5.81, P=.001), and colorectal cancer with a lower probability (OR 0.47, 95% CI 0.29 to 0.78, P=.003) of being a *BRCA2* PV carrier.

**CONCLUSIONS AND RELEVANCE:** Significant differences in 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.

## INTRODUCTION

While there are a substantial number of studies on cancer risks and cancer spectrum in female carriers of germline pathogenic variants (PVs) in *BRCA1* (MIM# 113705) and *BRCA2* (MIM# 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 1-5% for *BRCA1* and 5-10% for *BRCA2* PV carriers, *versus* 0.1% in the general male population [2,3,6-8]. Additionally, *BRCA1* and *BRCA2* PVs have been estimated to account for <1% and ~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], whilst other studies did not find any increased risk [16-18]. PVs 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 and are based on handfuls of cases in a limited number of families.

*BRCA1/2*-associated tumors in men exhibit specific pathological features and poor clinical outcome. A specific *BRCA2*-associated breast cancer phenotype, hallmarked by high histopathological 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 prostate cancer patients [27]. There is also some evidence suggesting that patients with *BRCA1/2*-associated pancreatic cancer may exhibit worse prognosis, compared with non-carriers [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 in order 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, 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 cancer risks of cancers other than breast and prostate in male *BRCA1/2* PV carriers.

## PATIENTS AND METHODS

### *CIMBA Study Participants*

Investigators collaborating through CIMBA (Consortium of Investigators of Modifiers of *BRCA1/2*, 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 6,902 male *BRCA1/2* PV carriers collected by 53 study-groups in 33 countries from 1966 to 2017 (**eTables 1 and 2**).

Data collected for each individual included year of birth, a unique family identifier, ethnicity, age at cancer diagnosis, primary tumor site (ICD-10 coding), age at last observation, and clinical data from medical, pathology or tumor registry records [25]. The majority of individuals (77%) reported herein are self-reported as white Caucasian, with other ethnicities not as equally represented (**eTable 3**). Recruited *BRCA1* or *BRCA2* PV carriers include probands and tested family members (**eTable 4**). Data on first- 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**). A signed informed consent was obtained from all study participants, as part of the approved protocol 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 one 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 to the odds of being a *BRCA2* PV carrier in the unaffected. In practice, under a univariate analysis this can be interpreted

as the ratio of odds (OR) of a *BRCA2* carrier being affected compared to 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 inter cancer intervals were assessed by the non-parametric Mann-Whitney test.

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 *versus* all cancers but breast; prostate cancer *versus* all cancers but prostate; cancers at other sites *versus* 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 *versus* all other cancers; melanoma *versus* all other cancers; pancreatic cancer *versus* all other cancers). To assess the potential impact 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 pre-specified 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 was included in all analyses as a surrogate for year of genetic testing, based on the groupings: $\leq$2000, 2001-2010, >2010, in order to account for ascertainment biases due to differential genetic testing approaches and inclusion criteria over time. A logistic regression adjusted also for proband status, estimated considering as probands individuals with cancer diagnosis date preceding interview prior genetic testing date, was performed. To assess the potential impact 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, each

389 variable grouped as positive, negative or unknown family history. A robust variance approach was
390 used to allow for dependencies between related individuals. P-values $\leq$.05 were considered
391 statistically significant. All analyses were carried out using Stata v13 software.
392

## RESULTS

The series included 6,902 men with PVs in *BRCA1* (n=3,651, 52.9%) or *BRCA2* (n=3,251, 47.1%). Of the 6,902 male *BRCA1/2* PV carriers, 1,376 (19.9%) had at least one cancer diagnosis, the majority of whom (67%) harbored a *BRCA2* PV. Age distribution is reported in **eFigure 1**.

Of the 1,376 carriers with cancer, 1,144 (83.1%) were diagnosed with one cancer, 206 (15%) had two, and 26 (<2%) had three independent cancer diagnoses, respectively (**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 two 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 to 3.70, *P*<.001). Similarly, developing multiple cancers, particularly two (OR 7.97, 95% CI 5.47 to 11.60, P<.001) and three (OR 19.60, 95% CI 4.64 to 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**).

Among male *BRCA2* PV carriers with more than one cancer diagnosis, significantly shorter median inter cancer intervals were observed for cases with a first diagnosis of breast (5 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%, respectively) (**Table 2 and eTable 7**). 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**). Non-breast and non-prostate 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%), 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 1,634 cancers were reported in the 1,376 affected individuals, of which 494 (30.2%) in *BRCA1* and 1,140 (69.8%) 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 to 7.37, P<.001) and prostate (OR 1.39, 95% CI 1.09 to 1.78, P=.008) cancers, and a lower frequency of cancers other than breast and prostate combined (OR 0.22, 95% CI 0.18 to 0.28, P<.001) were associated with a higher probability of being a *BRCA2,* rather than a *BRCA1,* PV carrier. Specifically, 643 of 1,634 tumors (39.4%) were in sites other than breast and prostate, of which 319 (64.6%) were diagnosed in *BRCA1* and 324 (28.4%) in *BRCA2* PV carriers (**Table 3**).

Considering cancers other than breast and prostate, more than 60 different cancer sites were reported (**eTable 8**). The most common non-breast and non-prostate cancer types (>60 diagnoses each) were non-melanoma 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 and eTable 8**). Cancer phenotype varied between *BRCA1* and *BRCA2* PV carriers (**Figure 2 and Table 3**). In particular, among the non-breast and non-prostate cancers, pancreatic cancer was associated with a higher probability of being a *BRCA2* carrier (OR 3.00, 95% CI 1.55 to 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 to 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**). Similar findings were also obtained in analyses omitting cancer diagnoses occurring more than 5 years prior to study recruitment (**eTable 10**).

## DISCUSSION

Men with *BRCA1/2* PVs represent an under-investigated group which 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 versus BRCA1* PV carriers. Being affected with cancer and to develop multiple cancer types at younger ages was associated with a higher probability of being a *BRCA2* PV carrier.

Inter-cancer 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 inter cancer 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* PV carriers [29].

Current National Comprehensive Cancer Network (NCCN) [32], European Society for Medical Oncology (ESMO, August 2016) [33], and American Society of Clinical Oncology (ASCO 2017) [34] guidelines recommend annual clinical breast examination starting at age 30-35 years, and clinical prostate cancer screening, particularly for *BRCA2* PV carriers, starting at age 40-45 years. ASCO 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 PSA 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 PSA 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 non-breast and non-prostate cancers, pancreatic cancer was associated with a higher probability of being a *BRCA2* PV carrier. This observation reinforces the evidence of a gender-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 NCCN and ESMO 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, the majority 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.

There are some limitations to the current study. Firstly, this study was largely retrospective and data may have been not systematically collected. Secondly, cases were mostly recruited from high-risk clinics and/or high-risk families, and hence a selection bias towards 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 performed based on cancer types or cancer family history and genetic testing approaches and inclusion criteria might have changed over time. In order 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 impact 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 arising in male *BRCA2* PV carriers, particularly breast and pancreatic cancers.

The present study design does not allow for inference on the associations of specific cancer types in men with *BRCA1* or *BRCA2* PVs, due 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 in order to refine clinical management strategies.

## CONCLUSIONS

Our results, derived from analyses of the largest available male *BRCA1/2* PV carrier data set, provide reliable data on 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 towards evidence-based guidelines and may help to refine existing recommendations in terms of specifying distinct surveillance guidelines for men with either *BRCA1* or *BRCA2* PVs.

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**Access to data and data analysis**

Prof. Laura Ottini had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Dr. Valentina Silvestri, PhD, Sapienza University of Rome, conducted and is responsible for the data analysis.

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967 **FIGURE LEGENDS**

968

969 **Figure 1: Cancer diagnoses in male *BRCA1* and *BRCA2* PV carriers.**

970 Type of cancer diagnoses reported in the 1,376 affected male *BRCA1* (N=454) and *BRCA2*

971 (N=922) PV carriers in CIMBA.

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973 **Figure 2: Spectrum of cancers other than breast and prostate in male *BRCA1* and *BRCA2***

974 **PV carriers.**

975 Cancer sites other than breast and prostate with more than five reported diagnoses, in the whole

976 series of male *BRCA1/2* PV carriers within the CIMBA dataset. Significant differences between

977 *BRCA1* and *BRCA2* are indicated by an asterisk.

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**Table 1**: Cancer diagnosis in male *BRCA1/2* PV carriers within CIMBA dataset and Odds Ratios (ORs) in predicting *BRCA2* PV carrier status.

| | Total N | % | BRCA1 | % | BRCA2 | % | adjusted OR (95% CI)[a] | P-value |
|---|---|---|---|---|---|---|---|---|
| **Total Number of Male Carriers** | **6,902** | | **3,651** | | **3,251** | | | |
| **Unaffected** | 5,526 | 80.1 | 3,197 | 87.6 | 2,329 | 71.6 | ref | |
| **Affected** | 1,376 | 19.9 | 454 | 12.4 | 922 | 28.4 | **3.23 (2.81-3.70)** | **<.001** |
| **Cases with 1 cancer diagnosis** | **1,144** | **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 | 0.0 | 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 | 0.0 | | |
| **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 | 0.0 | 5 | 20.8 | | |
| Bilateral Breast and Cancer Other than Breast and Prostate | 7 | 26.9 | 0 | 0.0 | 7 | 29.2 | | |
| Prostate cancer and Two Cancers Other than Breast and Prostate | 1 | 3.8 | 1 | 50.0 | 0 | 0.0 | | |
| Breast, Prostate and Cancer Other than Breast and Prostate | 13 | 50.0 | 1 | 50.0 | 12 | 50.0 | | |

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

**Table 2:** Age at first cancer diagnosis according to cancer site and *BRCA1/2* PV in the 1,376 affected male carriers within CIMBA dataset.

| | Total Carriers | | | *BRCA1* PV carriers | | | *BRCA2* PV carriers | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | N | % | Median age at diagnosis (IQR) | N | % | Median age at diagnosis (IQR) | N | % | Median age at diagnosis (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) | 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** |

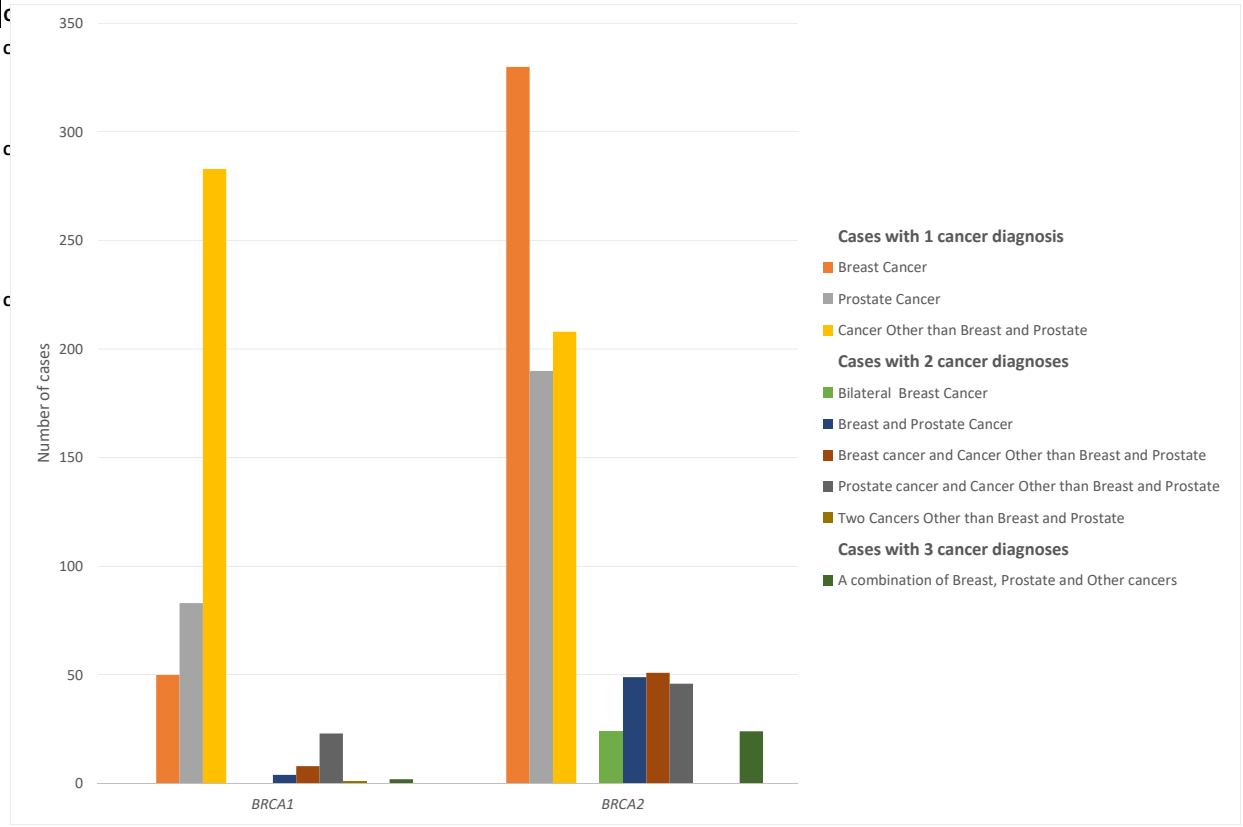
IQR, inter quartile range

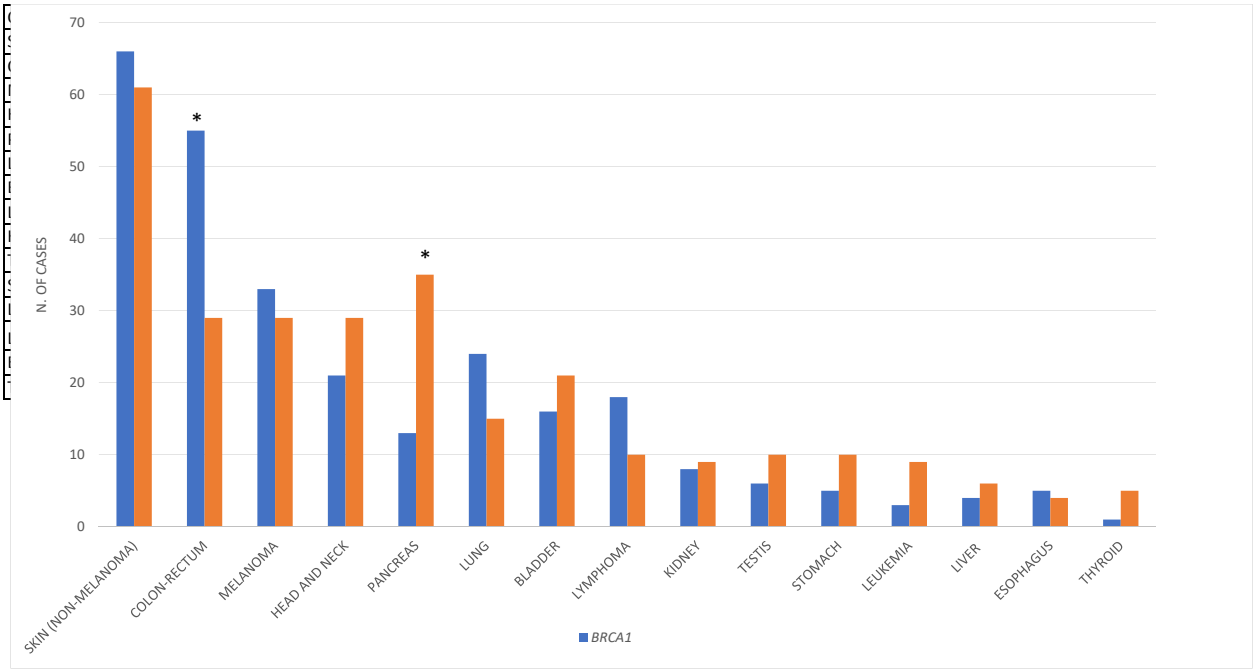
[a]Mann-Whitney test for the comparison of median age at first cancer diagnosis between male *BRCA1* and *BRCA2* PV carriers. Statistically significant results in bold.

**Table 3:** Analysis restricted to the total tumors reported in the 1,376 affected male *BRCA1/2* PV carriers within CIMBA dataset and ORs in predicting *BRCA2* PV carrier status.

| | Total | % | *BRCA1* | % | *BRCA2* | % | adjusted OR (95 CI)[a] | P-value |
|---|---|---|---|---|---|---|---|---|
| **All cancers** | **1,634** | | **494** | | **1,140** | | ref | |
| **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** |

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


350
300
250
200
150
100
50
0
Number of cases
BRCA1
BRCA2
Cases with 1 cancer diagnosis
Breast Cancer
Prostate Cancer
Cancer Other than Breast and Prostate
Cases with 2 cancer diagnoses
Bilateral Breast Cancer
Breast and Prostate Cancer
Breast cancer and Cancer Other than Breast and Prostate
Prostate cancer and Cancer Other than Breast and Prostate
Two Cancers Other than Breast and Prostate
Cases with 3 cancer diagnoses
A combination of Breast, Prostate and Other cancers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N. OF CASES
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SKIN (NON-MELANOMA)
COLON-RECTUM
MELANOMA
HEAD AND NECK
PANCREAS
LUNG
BLADDER
LYMPHOMA
KIDNEY
TESTIS
STOMACH
LEUKEMIA
LIVER
ESOPHAGUS
THYROID
BRCA1