Cancer Risks Associated With BRCA1 and BRCA2 Pathogenic Variants

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PURPOSE To provide precise age-specific risk estimates of cancers other than female breast and ovarian cancers associated with pathogenic variants (PVs) in BRCA1 and BRCA2 for effective cancer risk management.

METHODS We used data from 3,184 BRCA1 and 2,157 BRCA2 families in the Consortium of Investigators of Modifiers of BRCA1/2 to estimate age-specific relative (RR) and absolute risks for 22 first primary cancer types adjusting for family ascertainment.

RESULTS BRCA1 PVs were associated with risks of male breast (RR = 4.30; 95% CI, 1.09 to 16.96), pancreatic (RR = 2.36; 95% CI, 1.51 to 3.68), and stomach (RR = 2.17; 95% CI, 1.25 to 3.77) cancers. Associations with colorectal and gallbladder cancers were also suggested. BRCA2 PVs were associated with risks of male breast (RR = 44.0; 95% CI, 21.3 to 90.9), stomach (RR = 3.69; 95% CI, 2.40 to 5.67), pancreatic (RR = 3.34; 95% CI, 2.21 to 5.06), and prostate (RR = 2.22; 95% CI, 1.63 to 3.03) cancers. The stomach cancer RR was higher for females than males (6.89 v 2.76; P = .04). The absolute risks to age 80 years ranged from 0.4% for male breast cancer to approximately 2.5% for pancreatic cancer for BRCA1 carriers and from approximately 2.5% for pancreatic cancer to 27% for prostate cancer for BRCA2 carriers.

CONCLUSION In addition to female breast and ovarian cancers, BRCA1 and BRCA2 PVs are associated with increased risks of male breast, pancreatic, stomach, and prostate (only BRCA2 PVs) cancers, but not with the risks of other previously suggested cancers. The estimated age-specific risks will refine cancer risk management in men and women with BRCA1/2 PVs.

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INTRODUCTION It is well established that pathogenic variants (PVs) in BRCA1 and BRCA2 (BRCA1/2) are associated with increased risks of breast and ovarian cancers in women for which reliable risk estimates are available.1,2 Accrued evidence indicates that BRCA1/2 PVs are also associated with pancreatic cancer3,4 and male breast cancer risks5,6,7 and that BRCA2 PVs are associated with prostate cancer risk, particularly aggressive prostate cancer, whereas the association between BRCA1 PVs and prostate cancer risk is still debated.2,8,9,10,11,12,13

Associations with risks for other cancers have also been
CONTEXT

Key Objective
The associations of pathogenic variants (PVs) in BRCA1 and BRCA2 with cancers other than female breast and ovarian cancers remain uncertain. Precise risk estimates are required to inform effective cancer risk management. This study investigates the associations between the risks of 22 cancers and BRCA1/2 PVs using data from 5,341 families segregating BRCA1 or BRCA2 PVs.

Knowledge Generated
BRCA1 and BRCA2 PVs are associated with increased risks of male breast, pancreatic, and stomach cancers; male BRCA2 carriers are also at increased prostate cancer risk. No associations were found with risks of other cancers. The cumulative risks to age 80 years ranged from 0.4% for male breast cancer to approximately 2.5% for pancreatic cancer for BRCA1 carriers and from approximately 2.5% for pancreatic cancer to 27% for prostate cancer for BRCA2 carriers.

Relevance
The findings provide age-specific cancer risk estimates and will allow for improved cancer risk assessment of male and female carriers.

METHODS
Study Sample
Data on 7,618 families with at least one family member having a BRCA1 or BRCA2 PV were obtained from 26 study groups in the Consortium of Investigators of Modifiers of BRCA1/2 (Data Supplement, online only).23 Only families with a clearly PV identified were included.24 The majority of families (7,281) were ascertained through an index individual attending cancer family clinics, mainly because of having multiple affected relatives, and 337 families were ascertained through an index case with breast or ovarian cancer, unselected for family history. All index individuals were age ≥ 18 years. For each family member, data including familial relationship, BRCA1/2 PV status, sex, year of birth, and years or age at pedigree data collection, death, and cancer diagnoses were collected (Data Supplement). All participants provided written informed consent and participated in studies at the host institutions under ethically approved protocols.

Statistical Analysis
BRCA1 and BRCA2 families were analyzed separately. Complex segregation analysis,25 which considered the observed phenotype and observed or inferred genotype information of all family members, was used to estimate relative risks (RRs) for 22 first primary cancer sites, excluding female breast and ovarian cancers (Table 1). This involved comparing the observed cancer incidences for carriers with the age-, country- and birth cohort-specific population incidences (Cancer Incidence in Five Continents26); thus, the estimated RRs were equivalent to standardized incidence ratios. Noncarriers were assumed to develop the cancers according to population incidences. Pedigree likelihoods were constructed and maximized using the pedigree analysis software MENDEL.27 Individuals were followed from birth until the age of the first primary cancer diagnosis, death, age at pedigree-data collection, risk-reducing mastectomy and/or salpingo-oophorectomy (if these occurred at least 1 year before breast or ovarian cancer diagnoses, respectively), or age 80 years, whichever occurred first. Missing year of birth and cancer diagnosis age were imputed (Data Supplement). Each individual was assumed to be at risk of developing the cancer of interest, as well as breast or ovarian cancer. The RRs for female breast and ovarian cancers were assumed...
| Cancer Site                  | BRCA1 Families, No. | BRCA2 Families, No. |
|-----------------------------|---------------------|---------------------|
|                             | Carriers (n = 1,508) | Noncarriers (n = 1,716) | Untested (n = 44,396) | Carriers (n = 1,063) | Noncarriers (n = 1,064) | Untested (n = 30,032) |
|                             | Males | Females | Total | Males | Females | Total |
| Bladder                     | 123   | 6       | 6      | 79    | 1       | 5     | 26    | 72    | 5       | 1       | 48    | 4     | 2     | 12    |
| Brain and CNS               | 186   | 5       | 1      | 105   | 1       | 1     | 73    | 156   | 0       | 1       | 82    | 2     | 3     | 68    |
| Breast                      | 9,389 | 17      | 3      | 26    | 3,648   | 271   | 5,424 | 7,143 | 82      | 4       | 133   | 2,612 | 205   | 4,107 |
| Cervix uteri                | 187   | 0       | 0      | 0     | 34      | 20    | 133   | 125   | 0       | 0       | 0     | 26    | 10    | 89    |
| Colon-rectum                | 726   | 20      | 14     | 360   | 20      | 13    | 299   | 490   | 12      | 8       | 240   | 3     | 10    | 217   |
| Connective and soft tissue  | 20    | 1       | 0      | 7     | 1       | 1     | 11    | 11    | 0       | 0       | 4     | 1     | 0     | 6     |
| Corpus uteri                | 120   | 0       | 0      | 0     | 5       | 4     | 111   | 50    | 0       | 0       | 0     | 3     | 3     | 44    |
| Esophagus                   | 88    | 1       | 1      | 64    | 1       | 0     | 21    | 69    | 1       | 1       | 52    | 0     | 0     | 15    |
| Eye                         | 10    | 1       | 0      | 5     | 0       | 0     | 4     | 11    | 1       | 0       | 5     | 1     | 1     | 2     |
| Gallbladder and extrahepatic ducts | 27   | 0       | 0      | 11    | 0       | 1     | 15    | 18    | 0       | 0       | 9     | 2     | 1     | 6     |
| Head and neck               | 226   | 9       | 4      | 161   | 1       | 1     | 50    | 158   | 5       | 3       | 114   | 3     | 0     | 33    |
| Kidney                      | 117   | 3       | 2      | 82    | 2       | 0     | 28    | 76    | 3       | 2       | 50    | 1     | 1     | 19    |
| Leukemia                    | 198   | 2       | 3      | 101   | 2       | 1     | 89    | 150   | 3       | 1       | 76    | 3     | 1     | 66    |
| Lung                        | 746   | 13      | 6      | 567   | 2       | 5     | 153   | 504   | 6       | 7       | 376   | 4     | 0     | 111   |
| Lymphoma                    | 134   | 6       | 6      | 71    | 3       | 3     | 45    | 80    | 5       | 4       | 35    | 2     | 4     | 30    |
| Melanoma                    | 174   | 11      | 10     | 71    | 19      | 28    | 35    | 96    | 8       | 11      | 33    | 12    | 11    | 21    |
| Multiple myeloma            | 14    | 1       | 0      | 5     | 1       | 2     | 5     | 10    | 0       | 0       | 8     | 0     | 0     | 2     |
| Ovary                       | 2,743 | 0       | 0      | 885   | 28      | 1,830 | 827   | 0     | 0       | 0       | 293   | 18    | 516   |
| Pancreas                    | 252   | 9       | 2      | 146   | 4       | 1     | 90    | 266   | 12      | 2       | 151   | 8     | 2     | 91    |
| Prostate                    | 686   | 34      | 64     | 588   | 0       | 0     | 0     | 685   | 71      | 31      | 583   | 0     | 0     | 0     |
| Stomach                     | 463   | 5       | 0      | 263   | 0       | 0     | 195   | 387   | 5       | 2       | 243   | 4     | 0     | 133   |
| Testis                      | 47    | 1       | 2      | 44    | 0       | 0     | 0     | 38    | 4       | 1       | 33    | 0     | 0     | 0     |
| Thyroid                     | 58    | 1       | 0      | 12    | 9       | 8     | 28    | 47    | 0       | 0       | 11    | 14    | 6     | 16    |
| AFFECTED BY ANY CANCER       | 16,500| 144     | 123    | 2,762 | 4,577   | 391   | 8,503 | 11,354| 221     | 80      | 2,277 | 2,976 | 275   | 5,525 |
| Unaffected                  | 83,451| 1,364   | 1,593  | 41,634| 2,799   | 3,763 | 32,298| 56,300| 842     | 984     | 27,755| 2,055 | 2,095 | 22,569|
to be equal to previous estimates, therefore, we only estimated the RR for the cancer of interest. We fitted models in which the RRs were assumed to be constant with age, birth cohort, sex, and study group and separate models with sex-specific RRs. For cancers with significant associations, we investigated whether the RRs varied by age. RRs from the best fitting models were used to estimate age-specific absolute risks on the basis of UK cancer incidences in year 2008-2012 (Data Supplement).

Because family ascertainment varied across study groups, we adjusted for the ascertainment of each family separately using an ascertainment-assumption-free approach. Pedigree likelihoods were computed conditional on any data that may be relevant to the ascertainment (Data Supplement). Non-informative families, in which no additional information beyond the data relevant to the ascertainment was available, were excluded from analysis. Since cancer family history was self-reported, we assessed the possibility of systematic under-reporting of specific cancers at the individual study group level and concluded that demonstrated associations: (1) stratifying by geographical region (Asian countries v others); (2) including study groups with possible cancer under-reporting; (3) excluding individuals with missing age at diagnosis; (4) individuals with risk-reducing bilateral mastectomy and/or salpingo-oophorectomy were still considered to be at risk of developing the other cancers, except breast and ovarian cancers; and (5) assuming the data relevant to the ascertainment for clinic-based families do not include the family history of cancer of interest. To account for population differences in melanoma skin pigmentation, we also conducted sensitivity analyses for melanoma by using (1) only families from Australia, Northern Europe, and North America; (2) only families in which probands self-identified as White European; and (3) only the families satisfying both (1) and (2).

All statistical tests were two-sided, and associations with a nominal $P < .05$ were considered statistically significant.

### RESULTS

After ascertainment adjustment, 3,184 *BRCA1* families and 2,157 *BRCA2* families were informative for inclusion in the analysis, including 14,979 carriers, 9,296 noncarriers,
### TABLE 3. Sex-Specific RRs and 95% CIs for BRCA1 and BRCA2 Carriers From the Main Analysis

| Cancer Site               | BRCA1 Carriers | BRCA2 Carriers |
|---------------------------|----------------|----------------|
|                           | Male RR (95% CI) | Female RR (95% CI) | \( P \) for Difference* | Male RR (95% CI) | Female RR (95% CI) | \( P \) for Difference* |
| Bladder                   | 0.97 (0.34 to 2.78) | 0.53 (0.05 to 5.95) | .61 | 1.26 (0.46 to 3.47) | 4.07 (1.09 to 15.21) | .20 |
| Brain and CNS             | 0.72 (0.25 to 2.06) | 2.56 (0.98 to 6.67) | .11 | 0.48 (0.10 to 2.25) | 2.27 (0.83 to 6.21) | .09 |
| Colon-rectum              | 1.54 (0.98 to 2.42) | 1.34 (0.66 to 2.73) | .74 | 1.57 (0.90 to 2.74) | 0.89 (0.36 to 2.20) | .28 |
| Connective and soft tissue| 0.08 (0 to 196.37) | 1.61 (0.15 to 16.78) | .36 | 0 (0 to 3.5E+122) | 1.33 (0 to 3.851.9) | .53 |
| Esophagus                 | 0.88 (0.29 to 2.70) | 1.63 (0.13 to 20.17) | .68 | 1.12 (0.37 to 3.42) | 0.07 (0 to 3.18) | .13 |
| Eye                       | 1.98 (0.15 to 25.33) | NA | NA | 3.26 (0.29 to 36.23) | 6.19 (0.71 to 54.34) | .70 |
| Gallbladder and extrahepatic ducts | 3.75 (1.23 to 11.43) | 2.52 (0.36 to 17.56) | .71 | 2.35 (0.59 to 9.35) | 2.20 (0.49 to 9.92) | .95 |
| Head and neck             | 1.04 (0.41 to 2.64) | 1.69 (0.29 to 9.93) | .65 | 0.71 (0.19 to 2.73) | 0.83 (0 to 474.33) | .96 |
| Kidney                    | 1.35 (0.36 to 5.06) | 3.10 (0.74 to 12.93) | .41 | 0.19 (0.01 to 4.46) | 3.13 (0.37 to 26.16) | .27 |
| Leukemia                  | 1.03 (0.36 to 2.92) | NA | NA | 0.77 (0.23 to 2.60) | 1.85 (0.30 to 11.57) | .48 |
| Lung                      | 1.36 (0.79 to 2.33) | 1.43 (0.49 to 4.22) | .93 | 0.81 (0.39 to 1.69) | 2.84 (1.23 to 6.60) | .05 |
| Lymphoma                  | 0.69 (0.12 to 3.91) | 1.56 (0.33 to 7.43) | .49 | 0.78 (0.09 to 6.37) | 2.24 (0.13 to 39.84) | .64 |
| Melanoma                  | 0.44 (0.04 to 5.44) | 0.80 (0.13 to 5.06) | .70 | NA | 1.82 (0.43 to 7.71) | NA |
| Multiple myeloma          | 3.60 (1.00 to 12.96) | 2.04 (0.22 to 18.87) | .66 | 1.11 (0.13 to 9.46) | 0.01 (0 to 19.48) | .52 |
| Pancreas                  | 1.92 (1.12 to 3.28) | 4.27 (2.01 to 9.05) | .11 | 2.96 (1.78 to 4.94) | 4.34 (2.19 to 8.62) | .38 |
| Stomach                   | 1.67 (0.86 to 3.27) | 4.86 (2.13 to 11.08) | .08 | 2.76 (1.59 to 4.80) | 6.89 (3.71 to 12.78) | .04 |
| Thyroid                   | 0.05 (0 to 4,319.91) | 0.14 (0.01 to 1.78) | .88 | NA | 1.01 (0.25 to 4.19) | .31 |

Abbreviations: NA, No. of cancers too small to obtain a sex-specific estimate; RR, relative risk.

*\( P \) value by comparing the model of the same RR between males and females with its nested model of sex-specific RR.

and 153,323 untested individuals (Data Supplement). 61.3% of probands had self-reported ethnicity data. Of those, 77.0%, 11.5%, 4.7%, 3.3%, and 1.2% self-identified as White European, Asian, Ashkenazi Jewish, Hispanic, and Black, respectively. Prostate, lung, colorectal, stomach, and pancreatic cancers were the most common cancers in the data set, aside from breast and ovarian (Table 1). The age at diagnosis for each cancer by PV status is shown in the Data Supplement. After excluding study groups in which there was potential cancer under-reporting (Data Supplement), the proportions of families included in the estimation of cancer-specific risks varied from approximately 15% for lymphoma and multiple myeloma to > 90% for pancreatic and male breast cancers (Data Supplement).

Cancer Associations With BRCA1 PVs

BRCA1 PVs were associated with male breast (RR = 4.30; 95% CI, 1.09 to 16.96), gallbladder (RR = 3.34; 95% CI, 1.34 to 8.28), pancreatic (RR = 2.36; 95% CI, 1.51 to 3.68), stomach (RR = 2.17; 95% CI, 1.25 to 3.77), and colorectal (RR = 1.48; 95% CI, 1.01 to 2.16) cancers (Table 2). No association was found for prostate cancer (RR = 0.82; 95% CI, 0.54 to 1.27). No difference in the RR estimates by sex was observed for any of the 17 non-sex-specific cancers (all \( P > .07; \) Table 3).

A model with RRs stratified by age 65 years (Data Supplement) provided a significantly better fit for stomach cancer: RR = 3.50 (95% CI, 2.01 to 6.10) for age < 65 years and higher than 0.61 (95% CI, 0.16 to 2.30) for age ≥ 65 years (\( P \)-heterogeneity = .01). For male breast cancer, a model with RRs stratified by age decade provided a better fit than the model with an age-constant RR (\( P = .03 \)), but this was mainly driven by the lack of cases in the age group of 50-59 years (Data Supplement).

Cancer Associations With BRCA2 PVs

BRCA2 PVs were associated with increased risks of male breast (RR = 44.0; 95% CI, 21.3 to 90.9), stomach (RR = 3.69; 95% CI, 2.40 to 5.67), pancreatic (RR = 3.34; 95% CI, 2.21 to 5.06), and prostate (RR = 2.22; 95% CI, 1.63 to 3.03) cancers (Table 2). Female carriers had a higher risk of stomach cancer (RR = 6.89; 95% CI, 3.71 to 12.78) than male carriers (RR = 2.76; 95% CI, 1.59 to 4.80; \( P \)-heterogeneity = .04; Table 3).

A model with RRs stratified by age 65 years (Data Supplement) provided a significantly better fit for pancreatic cancer: RR = 4.92 (95% CI, 2.96 to 7.80) for age < 65 years and higher than 1.77 (95% CI, 0.87 to 3.58) for age ≥ 65 years (\( P \)-heterogeneity = .03). There was a suggestion that the prostate cancer RR was greater for...
TABLE 4. Age-Specific Absolute Risks (%) and 95% CIs of Primary Cancers With Significant Associations for BRCA1 and BRCA2 Carriers*

| Cancer Site | Sex | Age 50 Years | Age 60 Years | Age 70 Years | Age 80 Years |
|-------------|-----|--------------|--------------|--------------|--------------|
|             |     | Absolute risk (95% CI) for BRCA1 carriers |             |             |              |
| Breast      | Male| 0.02 (0.01 to 0.08) | 0.07 (0.02 to 0.3) | 0.2 (0.05 to 0.7) | 0.4 (0.1 to 1.5) |
| Pancreas    | Male| 0.1 (0.07 to 0.2) | 0.4 (0.3 to 0.7) | 1.3 (0.8 to 2.0) | 2.9 (1.9 to 4.5) |
|             | Female| 0.08 (0.05 to 0.1) | 0.3 (0.2 to 0.5) | 1.0 (0.6 to 1.5) | 2.3 (1.5 to 3.6) |
| Stomach     | Male| 0.2 (0.1 to 0.3) | 0.6 (0.3 to 1.0) | 1.1 (0.6 to 2.2) | 1.6 (0.7 to 4.0) |
|             | Female| 0.1 (0.06 to 0.2) | 0.3 (0.2 to 0.5) | 0.5 (0.3 to 0.9) | 0.7 (0.3 to 1.7) |

| Cancer Site | Sex | Age 50 Years | Age 60 Years | Age 70 Years | Age 80 Years |
|-------------|-----|--------------|--------------|--------------|--------------|
|             |     | Absolute risk (95% CI) for BRCA2 carriers |             |             |              |
| Breast      | Male| 0.2 (0.1 to 0.5) | 0.7 (0.4 to 1.5) | 1.8 (0.9 to 3.7) | 3.8 (1.9 to 7.7) |
| Pancreas    | Male| 0.2 (0.1 to 0.3) | 0.9 (0.5 to 1.4) | 2.0 (1.2 to 3.3) | 3.0 (1.7 to 5.4) |
|             | Female| 0.2 (0.09 to 0.2) | 0.6 (0.4 to 1.0) | 1.5 (0.9 to 2.5) | 2.3 (1.3 to 4.2) |
| Prostate    | Male| 0.2 (0.2 to 0.3) | 2.9 (2.1 to 3.9) | 12.6 (9.4 to 16.7) | 26.9 (20.5 to 34.7) |
| Stomach     | Male| 0.1 (0.08 to 0.2) | 0.5 (0.3 to 0.8) | 1.4 (0.8 to 2.3) | 3.5 (2.1 to 6.1) |
|             | Female| 0.2 (0.1 to 0.4) | 0.6 (0.3 to 1.0) | 1.3 (0.7 to 2.5) | 3.5 (1.9 to 6.4) |

*Absolute risks were calculated on the basis of UK cancer incidences in years 2008-2012 in the Cancer Incidence in Five Continents.26

Sensitivity Analysis

The results are described in detail in the Data Supplement. There was no significant difference in the RR estimates by geographical region. The observed cancer associations were robust to all sensitivity analyses, except for colorectal and gallbladder cancers. No association was found for melanoma even when analyses were restricted to families from Australia, Northern Europe, and North America or families in which probands self-identified as White European.

Absolute Risks

RRs from the main analysis best-fitting models were used to calculate age-specific absolute cancer risks (Table 4 and Fig 1). By age 80 years, the male breast cancer risk for BRCA1 and BRCA2 carriers was 0.4% (95% CI, 0.1 to 1.5) and 3.8% (95% CI, 1.9 to 7.7), respectively; the pancreatic cancer risk varied between 2.3% and 3.0% for both male and female BRCA1 and BRCA2 carriers; the stomach cancer risks were 1.6% (95% CI, 0.7 to 4.0) for male and 0.7% (95% CI, 0.3 to 1.7) for female BRCA1 carriers and approximately 3.5% for both male and female BRCA2 carriers. The prostate cancer risk associated with BRCA2 PVs was 26.9% (95% CI, 20.5 to 34.7) by age 80 years and 33.1% (95% CI, 25.5 to 42.2) by age 85 years.

DISCUSSION

This study assessed the risks associated with BRCA1/2 PVs for 22 first primary cancers, other than female breast and ovarian cancers, and further clarified the cancer spectrum associated with BRCA1/2 PVs. The associations of BRCA1/2 PVs with the risks of male breast and pancreatic cancers were confirmed and refined, as well as the association of prostate cancer with BRCA2 PVs, regardless of age and aggressiveness.

The lifetime male breast cancer risks were previously reported to be 2%-6% for BRCA1 and 7%-13% for BRCA2 carriers (Data Supplement).3,6-9,13 We estimated these risks to be somewhat lower, 0.4% (95% CI, 0.1 to 1.5) and 3.8% (95% CI, 1.9 to 7.7), respectively. The pancreatic cancer associations were consistent with previously reported RRs of 2-3 and lifetime risks of 1%-4% for BRCA1 carriers,3,4,6 and RRs of 3-6 and lifetime risks of 3%-5% for BRCA2 carriers (Data Supplement).2,5,8 Notably, the RR was higher for BRCA2 carriers age < 65 years.

Previous retrospective studies reported prostate cancer RRs of 2-6 and absolute risks of 17%-31% by age 80 years for BRCA2 carriers (Data Supplement).2,5,6,8,14-17 Our estimated absolute risk by age 85 years was 33%, lower than the recently reported prospective estimate of 60% by Nyberg et al.32 However, after adjusting for possible increased prostate-specific antigen screening effects in the prospective study, their estimate was 41% (95% CI, 22 to 59), consistent with our estimate. The present estimate is unlikely to be subject to increased screening biases since prostate cancer family history was retrospectively collected, and increased screening in relatives is unlikely to have taken place before the identification of BRCA2 PVs. The reported associations of BRCA1 PVs with prostate cancer risk are inconsistent, with RRs of 0.4-4, most not statistically significant.3,4,6,8,14-18,32,33 This study confirms that BRCA1 PVs are not associated with overall prostate cancer risk.

Among the suggested associations with other cancers, the association between BRCA1/2 PVs and stomach cancer is
Age-specific absolute risks (%) and 95% CIs of primary cancers on the basis of UK cancer incidences in years 2008-2012 for (A) BRCA1 and (B) BRCA2 carriers. Solid lines are the age-specific absolute risk estimates, and ribbons are the relevant 95% CIs.
under considerable debate. This study validated and further elucidated this association: there were associations with both BRCA1 and BRCA2 PVs, with RRs of 2.17 (3.50 for age < 65 years) and 3.69, respectively. Our estimates better refined the previously reported RRs of 2-7 for BRCA1 carriers and approximately 2.6 for BRCA2 carriers (Data Supplement). Notably, our findings showed that the stomach cancer RR for female BRCA2 carriers was higher than the estimate for male carriers although this translated in similar absolute risks, given the higher incidence of male stomach cancer in the general population. However, we cannot exclude the possibility that the higher female RR may be due to the misclassification of some ovarian cancers as stomach cancers.

Data in the current study come from either epidemiologic studies or families undergoing PV screening collected at genetics centers. Although individual studies and clinical genetic centers, where possible, confirmed reported cancer diagnoses in families through medical records or registries as part of standard clinical practice, cancer confirmation information is not available centrally and it was not feasible to collect this at such a large scale. However, a key advantage of the present study is the large sample size, which results in RR estimates with greater precision. Only a small number of family-based studies reported cancer confirmation rates. Our RR estimates for stomach cancer, which may be susceptible to a greater degree of misclassification bias than other cancers, are not significantly different from the estimates from studies that reported cancer confirmation. However, the present RRs have similar or greater precision than the published estimates from studies with high cancer confirmation rates (Data Supplement).

In the present study, previously suggested associations of BRCA1/2 PVs with risks of other genitourinary cancers and melanoma were not replicated. Although associations of BRCA1 PVs with colorectal and gallbladder cancers were observed, the results were not robust in the sensitivity analyses performed.

Increased risks of bone and liver cancer have also been reported for BRCA1 or BRCA2 carriers. However, liver and bone are common metastatic sites for breast, prostate, or pancreatic cancers and could be the presenting cancer. Since no pathology confirmation data were available, we did not examine these associations in the main analysis. If we assume that the reported bone and liver cancers in the data set are indeed first primaries, the data suggest no association with BRCA1 PVs, but that BRCA2 carriers are at seven-fold increased risk of bone cancer and five-fold increased risk of liver cancer without significant differences between males and females (Data Supplement). However, no conclusion for these associations can be drawn without pathology confirmation.

Overall, the estimated age-specific relative and absolute risks suggest that, in addition to breast and ovarian cancers, the clinical management of BRCA1/2 carriers should focus on cancer sites, which now show robust associations, such as prostate (BRCA2 carriers only), pancreatic, and possibly stomach cancers. Notably, although rare, pancreatic and stomach cancers are associated with poor prognosis and their incidences have been rising over time, and thus, our results highlight the importance of screening for upper gastrointestinal tract malignancies for BRCA1 and BRCA2 carriers, particularly for age < 65 years. On the other hand, some cancers previously taken into consideration for screening for BRCA1/2 carriers, like melanoma, may be reconsidered, to further optimize cancer prevention screening strategies and eventually reduce carriers’ distress. Given that the cancer risk associations were found for both male and female carriers, the results also suggest that male relatives of known BRCA1/2 carriers should be informed about their individual cancer risk and encouraged to be tested. It has been shown that knowing the germline BRCA1/2 PV status can influence treatment options for patients with cancer, leading to improved prognosis. For example, poly (ADP-ribose) polymerase inhibitor therapies that have been used successfully in the treatment of BRCA-related breast and ovarian cancers are now beginning to be used for pancreatic and prostate cancers, and in the near future, they might also be used for stomach cancer.

To avoid biases in the risk estimates related to the ascertainment of clinic-based families, on the basis of multiple affected family members, we used a conservative ascertainment adjustment approach by conditioning on the family histories of cancers of breast and ovary and the cancer site under investigation. When only family history of female breast and ovarian cancers was considered in the ascertainment, the RR estimates were somewhat higher for most cancers but with narrower CIs (Data Supplement). Therefore, conditioning on the family history of the cancer of interest is unlikely to have led to substantial underestimation of risk. A notable exception was male breast cancer, where much higher RR estimates were obtained. However, this estimate is most likely biased because male breast cancer family history has been an important factor in considering BRCA1/2 germline genetic testing since the discovery of BRCA1/2.

This study has several limitations. First, this is a retrospective family-based study, with self-reported cancer family history, which may be inaccurate. Second, 7%-40% of reported cancer cases had missing age at diagnosis, with stomach cancer having the largest proportion. To minimize these potential biases, we performed sensitivity analyses excluding any study groups in which under-reporting was likely and any cases with missing age at diagnosis, and conclusions remained similar for most cancers. Third, we presented our results without any multiple testing adjustment. However, even using a false discovery rate adjustment, all the observed associations for
BRCA2 carriers and the pancreatic cancer association for BRCA1 carriers had false discovery rates < 0.05. Fourth, the ethnicity of the family proband was not systematically collected by all studies because of variations in local data collection protocols. Among those with recorded ethnicity, in Asia-based studies, 97.7% of probands were Asian and in the rest of the studies 86.1%, 5.2%, 3.7%, 1.3%, and 1.1% of probands were White European, Ashkenazi, Hispanic, Black, and Asian, respectively. Therefore, the power to investigate the associations by all ethnic groups was limited. However, we did not find evidence of heterogeneity in the RRs by geographical region (Asia vs others). Whether our risk estimates are applicable to non-European populations requires further investigation. Fifth, we did not have data on other genetic and environmental factors, so we were unable to investigate the modification effects of these factors; therefore, our risk estimates should be interpreted as the average risks across all potential genetic and environmental modifiers.

In conclusion, this study confirms that, aside from female breast and ovarian cancers, BRCA1/2 PVs are associated with increased risks of breast cancer in men, and pancreatic and stomach cancers in both sexes, and that only BRCA2 carriers are at elevated prostate cancer risk. BRCA1/2 PVs were not associated with the risks of any other cancers previously suggested. The association results and estimated age-specific risks will improve the cancer risk management for men and women with BRCA1/2 PVs.
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REFERENCES

1. Kuchenbaecker KB, Hopper JL, Barnes DR, et al: Risks of breast, ovarian, and contralateral breast cancer for BRCA1 and BRCA2 mutation carriers. JAMA 317: 2402-2416, 2017
2. Breast Cancer Linkage Consortium: Cancer risks in BRCA2 mutation carriers. J Natl Cancer Inst 91:1310-1316, 1999
3. Brose MS, Rebbeck TR, Calzone KA, et al: Cancer risk estimates for BRCA1 mutation carriers identified in a risk evaluation program. J Natl Cancer Inst 94: 1365-1372, 2002
4. Thompson D, Easton DF: Cancer Incidence in BRCA1 mutation carriers. J Natl Cancer Inst 94:1358-1365, 2002
5. van Asperen CJ, Brohet RM, Meijers-Heijboer EJ, et al: Cancer risks in BRCA2 families: Estimates for sites other than breast and ovary. J Med Genet 42: 711-719, 2005
6. Risch HA, McLaughlin JR, Cole DE, et al: Population BRCA1 and BRCA2 mutation frequencies and cancer penetrances: A kin-cohort study in Ontario, Canada. J Natl Cancer Inst 98:1694-1706, 2006
7. Ferrone CR, Levine DA, Tang LH, et al: BRCA germline mutations in Jewish patients with pancreatic adenocarcinoma. J Clin Oncol 27:433-438, 2009
8. Morari A, O'Hara C, Khan S, et al: Risk of cancer other than breast or ovarian in individuals with BRCA1 and BRCA2 mutations. Fam Cancer 11:235-242, 2012
9. Tai YC, Domchek S, Parmigiani G, et al: Breast cancer risk among male BRCA1 and BRCA2 mutation carriers. J Natl Cancer Inst 99:1811-1814, 2007
10. Easton DF, Steele L, Fields P, et al: Cancer risks in two large breast cancer families linked to BRCA2 on chromosome 13q12-13. Am J Hum Genet 61:120-128, 1997
11. Thompson D, Easton D: Variation in cancer risks, by mutation position, in BRCA2 mutation carriers. Am J Hum Genet 68:410-419, 2001
12. Milne RL, Osozio A, Czajka TR, et al: The average cumulative risks of breast and ovarian cancer for carriers of mutations in BRCA1 and BRCA2 attending genetic counseling units in Spain. Clin Cancer Res 14:2861-2869, 2008
13. Evans DG, Susen wala I, Dawson J, et al: Risk of breast cancer in male BRCA2 carriers. J Med Genet 47:710-711, 2010
14. Gallagher DJ, Gaudet MM, Pai P, et al: Germline BRCA mutations denote a clinicopathologic subset of prostate cancer. Clin Cancer Res 16:2115-2121, 2010
15. Roed Nielsen H, Petersen J, Therkildsen C, et al: Increased risk of male cancer and identification of a potential prostate cancer cluster region in BRCA2. Acta Oncol 55:38-44, 2016
16. Oh M, Alkhushaym N, Fallatah S, et al: The association of BRCA1 and BRCA2 mutations with prostate cancer risk, frequency, and mortality: A meta-analysis. Prostate 79:880-895, 2019
17. Ford D, Easton DF, Bishop DT, et al: Risks of cancer in BRCA1-mutation carriers. Breast Cancer Linkage Consortium. Lancet 343:692-695, 1994
18. Phean CM, Pijper J, Lynch HT, et al: Incidence of colorectal cancer in BRCA1 and BRCA2 mutation carriers: Results from a follow-up study. Br J Cancer 110: 530-534, 2014
19. Struweing JP, Hartge P, Wacholder S, et al: The risk of cancer associated with specific mutations of BRCA1 and BRCA2 among Ashkenazi Jews. N Engl J Med 336:1401-1408, 1997
20. Daly MB, Pai T, Berry MP, et al: Genetic/familial high-risk assessment: Breast, ovarian, and pancreatic, version 2,2021, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 19:103-v110, 2021
21. Paluch-Shimon S, Cardoso F, Sessa C, et al: Prevention and screening in BRCA2 mutation carriers and other breast/ovarian hereditary cancer syndromes. ESMO Clinical Practice Guidelines for cancer prevention and screening. Ann Oncol 27:v103-v110, 2016
22. Chenex-Srench G, Milne RL, Antoniou AC, et al: An international initiative to identify genetic modifiers of cancer risk in BRCA1 and BRCA2 mutation carriers: The Consortium of Investigators of Modifiers of BRCA1 and BRCA2 (CIMBA). Breast Cancer Res 9:104, 2007
23. Consortium of Investigators of Modifiers of BRCA1/2: Eligibility. http://cimbca.ccge.medschl.cam.ac.uk/eligibility/
24. Antoniou AC, Casadei S, Heikkinen T, et al: Breast-cancer risk in families with mutations in PALB2. N Engl J Med 371:497-506, 2014
25. International Agency for Research on Cancer: Cancer incidence in five continents. http://ici5.iarc.fr
26. Lange K, Weeks D, Boehnke M: Programs for pedigree analysis: MENDEL, FISHER, and gEDE. Genet Epidemiol 5:471-472, 1988
27. Antoniou AC, Cunningham AP, Peto J, et al: The BOADICEA model of genetic susceptibility to breast and ovarian cancers: Updates and extensions. Br J Cancer 98:1457-1466, 2008
28. Cannings C, Thompson EA: Ascertaining in the sequential sampling of pedigrees. Clin Genet 12:208-212, 1977
29. Ewens WJ, Shute NC: A resolution of the ascertainment sampling problem. I. Theory. Theor Popul Biol 30:388-412, 1986
30. Shute NC, Ewens WJ: A resolution of the ascertainment sampling problem. III. Pedigrees. Am J Hum Genet 43:387-395, 1988
31. Nyberg T, Frost D, Barnowdale D, et al: Prostate cancer risks for male BRCA1 and BRCA2 mutation carriers: A prospective cohort study. Eur Urol 77:24-35, 2017
32. Agalliu I, Gem R, Leanza S, et al: Associations of high-grade prostate cancer with BRCA1 and BRCA2 founder mutations. Clin Cancer Res 15:1112-1120, 2009
33. Douglas FS, O’Dair LC, Robinson M, et al: The accuracy of diagnoses as reported in families with cancer: A retrospective study. J Med Genet 36:309-312, 1999
34. Rauscher EA, Dean M, Campbell-Salome GM: “I am uncertain about what my uncertainty even is”: Men’s uncertainty and information management of their BRCA-related cancer risks. J Genet Couns 27:1417-1427, 2018
35. Silvestri V, Leslie G, Barnes DR, et al: 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). JAMA Oncol 6:1-13, 2020
36. Tutt ANJ, Garber JE, Kaufman B, et al: Adjuvant olaparib for patients with BRCA1- or BRCA2-mutated breast cancer. N Engl J Med 384:2394-2405, 2021
37. Mateo J, Lord CJ, Serra V, et al: A decade of clinical development of PARP inhibitors in perspective. Ann Oncol 30:1437-1447, 2019
38. Stadler ZK, Maio A, Chakravarty D, et al: Therapeutic implications of germline testing in patients with advanced cancers. J Clin Oncol 39:2698-2709, 2021
39. Wang Y, Zheng K, Huang Y, et al: PARP inhibitors in gastric cancer: Beacon of hope. J Exp Clin Cancer Res 40:211, 2021
40. Kerber RA, Stlatten ML: Comparison of self-reported and database-linked family history of cancer data in a case-control study. Am J Epidemiol 146:244-248, 1997
41. Ziogas A, Anton-Culver H: Validation of family history data in cancer family registries. Am J Prev Med 24:190-198, 2003
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**Cancer Risks Associated With BRCA1 and BRCA2 Pathogenic Variants**

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