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Cancer Risks Associated With Germline *PALB2* Pathogenic Variants: An International Study of 524 Families

Xin Yang, PhD[1]; Goska Leslie, MEng[1]; Alicja Doroszuk, BA[2]; Sandra Schneider, PhD[2]; Jamie Allen, PhD[1]; Brennan Decker, PhD[1,3,4]; Alison M. Dunning, PhD[5]; James Redman, BSc[2]; James Scarth, BA[2]; Inga Plaskocinska, MSt[2]; Craig Luccarini, BSc[5]; Mitul Shah, MSc[5]; Karen Pooley, PhD[1]; Leila Dorling, PhD[1]; Andrew Lee, MSci[1]; Muriel A. Adank, MD, PhD[6]; Julian Adlard, MD, PhD[7]; Kristiina Aittomäki, MD, PhD[8]; Irene L. Andrulis, PhD[9]; Peter Ang, MD[10]; Julian Barwell, MBBS, PhD[11]; Jonine L. Bernstein, PhD[12]; Kristie Bobolis, MD[13]; Åke Borg, PhD[14]; Carl Blomqvist, MD, PhD[15]; Kathleen B.M. Claes, PhD[16]; Patrick Concannon, PhD[17]; Adeline Cuggia, MSc[18,19]; Julie O. Culver, MS[20]; Francesca Damiola, PhD[21]; Antoine de Pauw, PhD[22]; Orland Diez, PhD[23]; Jill S. Dolinsky, MS[24]; Susan M. Domchek, MD[25,26]; Christoph Engel, MD[27]; D. Gareth Evans, MD[28]; Florentia Fostira, PhD[29]; Judy Garber, MD[26,30]; Lisa Golmard, PharmD, PhD[22]; Ellen L. Goode, PhD[31]; Stephen B. Gruber, MD, PhD[32]; Eric Hahnen, PhD[33,34]; Christopher Hake, MD[13]; Tuomas Heikkinen, PhD[35]; Judith E. Hurley, MD[36]; Ramunas Janavicius, MD, PhD[37,38]; Zdenek Kleibl, MD, PhD[39]; Petra Kleiblova, MD, PhD[39,40]; Irene Konstantopoulou, PhD[29]; Anders Kvist, PhD[14]; Holly Laduca, MS[24]; Ann S.G. Lee, DPhil[11,41,42]; Fabienne Lesueur, PhD[43]; Eamonn R. Maher, MD[2]; Arto Mannermaa, PhD[44]; Siranoush Manoukian, MD[45]; Rachel McFarland, BS[24,46]; Wendy McKinnon, MS[47]; Alfons Meindl, PhD[48]; Kelly Metcalfe, PhD[49]; Nur Aishah Mohd Taib, MD[50]; Jukka Moilanen, MD, PhD[51]; Katherine L. Nathanson, MD[25]; Susan Neuhausen, PhD[52]; Pei Sze Ng, BSc[50,53]; Tu Nguyen-Dumont, PhD[54,55]; Sarah M. Nielsen, MS[56]; Florian Obermair, MD[57]; Kenneth Offit, MD, PhD[26,58]; Olufunmilayo I. Olopade, MD[56]; Laura Ottini, MD[59]; Judith Penkert, MD[60]; Katri Pylkäs, PhD[61]; Paolo Radice, PhD[62]; Susan J. Ramus, PhD[63,64]; Vilius Rudaitis, MD[37]; Lucy Side, MD[65]; Rachel Silva-Smith, MS[66]; Valentina Silvestri, PhD[59]; Anne-Bine Skytte, MD, PhD[67]; Thomas Slavin, MD[13,68]; Jana Soukupova, PhD[39]; Carlo Tondini, MD[69]; Alison H. Trainer, MD, PhD[70,71]; Gary Unzeitig, MD[13]; Lydia Usha, MD[13]; Thomas van Overeem Hansen, PhD[72,73]; James Whitworth, MD[2]; Marie Wood, MD[47]; Cheng Har Yip, MBBS[53]; Sook-Yee Yoon, MA[53]; Amal Yussuf, BS[24]; George Zogopoulos, MD, PhD[18,19]; David Goldgar, PhD[74]; John L. Hopper, PhD[75]; Georgia Chenevix-Trench, PhD[76]; Paul Pharoah, MD, PhD[1]; Sophia H.L. George, PhD[77]; Judith Balmaña, MD, PhD[23,26]; Claude Houdayer, PhD[22,78]; Paul James, MD, PhD[70,71]; Zaki El-Haffaf, MD[79]; Hans Ehrencrona, MD, PhD[80,81]; Marketa Janatova, PhD[39]; Paolo Peterlongo, PhD[82]; Heli Nevanlinna, PhD[35]; Rita Schmutzler, MD[33,34]; Soo-Hwang Teo, PhD[50,53]; Mark Robson, MD[26,83]; Tuya Pal, MD[84]; Fergus Couch, PhD[26,85]; Jeffrey N. Weitzel, MD, PhD[13,68]; Aaron Elliott, PhD[24]; Melissa Southey, PhD[54,55]; Robert Winqvist, PhD[61]; Douglas F. Easton, PhD[1]; William D. Foulkes, MBBS, PhD[18,86]; Antonis C. Antoniou, PhD[1]; and Marc Tischkowitz, MD, PhD[2]

abstract

PURPOSE To estimate age-specific relative and absolute cancer risks of breast cancer and to estimate risks of ovarian, pancreatic, male breast, prostate, and colorectal cancers associated with germline *PALB2* pathogenic variants (PVs) because these risks have not been extensively characterized.

METHODS We analyzed data from 524 families with *PALB2* PVs from 21 countries. Complex segregation analysis was used to estimate relative risks (RRs; relative to country-specific population incidences) and absolute risks of cancers. The models allowed for residual familial aggregation of breast and ovarian cancer and were adjusted for the family-specific ascertainment schemes.

RESULTS We found associations between *PALB2* PVs and risk of female breast cancer (RR, 7.18; 95% CI, 5.82 to 8.85; $P = 6.5 \times 10^{-76}$), ovarian cancer (RR, 2.91; 95% CI, 1.40 to 6.04; $P = 4.1 \times 10^{-3}$), pancreatic cancer (RR, 2.37; 95% CI, 1.24 to 4.50; $P = 8.7 \times 10^{-3}$), and male breast cancer (RR, 7.34; 95% CI, 1.28 to 42.18; $P = 2.6 \times 10^{-2}$). There was no evidence for increased risks of prostate or colorectal cancer. The breast cancer RRs declined with age (P for trend = 2.0×10^{-3}). After adjusting for family ascertainment, breast cancer risk estimates on the basis of multiple case families were similar to the estimates from families ascertained through population-based studies (P for difference = .41). On the basis of the combined data, the estimated risks to age 80 years were 53% (95% CI, 44% to 63%) for female breast cancer, 5% (95% CI, 2% to 10%) for ovarian cancer, 2%-3% (95% CI females, 1% to 4%; 95% CI males, 2% to 5%) for pancreatic cancer, and 1% (95% CI, 0.2% to 5%) for male breast cancer.

CONCLUSION These results confirm *PALB2* as a major breast cancer susceptibility gene and establish substantial associations between germline *PALB2* PVs and ovarian, pancreatic, and male breast cancers. These findings will facilitate incorporation of *PALB2* into risk prediction models and optimize the clinical cancer risk management of *PALB2* PV carriers.

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ASSOCIATED CONTENT

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

Germline pathogenic variants (PVs) in *PALB2*[1] were first associated with an increased risk of breast cancer (BC) more than a decade ago.[2-4] This was confirmed by multiple studies that culminated into a large international study by the *PALB2* Interest Group (PALB2-IG), which estimated the absolute risk of BC to be 14% by 50 years of age and 44% by 80 years of age on the basis of data from 154 families.[5] *PALB2* is now included on BC gene panels,[6] and clinical testing for germline *PALB2* PVs in the context of female BC is standard of care,[7] although gaps in our understanding of risk for other cancers remain.

Beyond BC, germline PVs in *PALB2* have been associated with pancreatic cancer (PaC)[8,9] and gastric cancer.[10-12] Possible associations with ovarian (OC)[13] and colorectal cancer (CRC)[14] have been suggested, but the statistical evidence is weak. Guidelines for the management of *PALB2*-associated BC risk exist,[7,15] but risk estimates for other cancers are based on small numbers and have large imprecision. Here, we use cancer family history data from 524 families comprising 17,906 individuals to refine age-specific cancer risks for BC and, for the first time to our knowledge, to estimate risks of OC, PaC, male breast cancer (MBC), prostate cancer (PrC), and CRC.

METHODS

Families

Data on 764 families were obtained through study groups that participated in PALB2-IG. Families included at least 1 member with a *PALB2* PV, and those with a known PV in *BRCA1*/*BRCA2* were excluded. Variants were considered pathogenic only if they were predicted to lead to a truncated protein, and *PALB2* missense variants were excluded. Studies were grouped using two types of ascertainment schemes: through cancer family clinics or families participating in research studies on the basis of having multiple affected members and through BC or OC series unselected for cancer family history. Participants provided informed consent in accordance with institutional review board policies and local practices at each participating center. The Data Supplement lists families by study group and details of study-specific ascertainment criteria.

Statistical Analysis

Complex segregation analysis was used to estimate cancer-specific relative risks (RRs) by fitting genetic models to the cancer inheritance patterns and observed genotypes in families. We estimated RRs for BC, OC, MBC, PaC, PrC, CRC, and all other cancers combined. Pedigree likelihoods were constructed and maximized using the pedigree analysis software Mendel version 3.3.[16]

For the main analysis, family members were followed from birth until age at diagnosis of first cancer (excluding nonmelanoma skin cancer) because cancer incidence can change after first cancer diagnosis. Otherwise, they were followed until age at death, age at last follow-up, age at risk-reducing mastectomy (RRM) in the BC analyses, risk-reducing salpingo-oophorectomy (RRBSO) in the OC analyses (if RRM/RRBSO occurred at least 1 year before cancer diagnosis), or age 80 years, whichever occurred first. Individuals diagnosed with BC, OC, MBC, PaC, PrC, or CRC were assumed to be affected by that cancer type at the age of diagnosis. Individuals with another subsequent cancer diagnosis were censored at the cancer diagnosis at their youngest age and for the purpose of the analysis, were considered to be affected with other cancer (Data Supplement). Noninformative families, in which no additional information beyond the data relevant to the ascertainment was available, were excluded from the analysis.

Two types of genetic susceptibility models were fitted: a single gene model that assumed that all familial aggregation of cancer is due to *PALB2* and a mixed single-gene/polygenic model that also allowed for a residual familial component because of other unobserved genetic effects in addition to *PALB2*. We fitted these models using country- and cohort-specific population age-specific incidences and constrained the overall cancer age-specific incidences over all assumed genetic effects in the model to agree with the population age-specific incidences[17] (Data Supplement).

Because family ascertainment criteria varied across studies, we adjusted for ascertainment for each family separately using an ascertainment-free approach in which likelihoods are computed conditional on any data that may be relevant to the ascertainment, which ensures consistent estimates[18-20] (Data Supplement). Nested models were compared using the likelihood ratio test (LRT), and non-nested models were compared using the Akaike information criterion (AIC). Equivalence of RR estimates between multiple-case and population-based families was assessed using the LRT. All statistical tests were two sided. To adjust for the testing of associations with 7 cancer types, we calculated the Benjamini-Hochberg (BH)–adjusted *P* value for a false discovery rate of .05.[21] We also derived the posterior distribution for the effect estimate (relative risks) for nominally significant associations to estimate the probability that the true effect is greater than an RR of 1.5.

RESULTS

Families

A total of 764 families with at least one member with a *PALB2* PV were identified through the PALB2-IG (Data Supplement). After adjustment for ascertainment and excluding the noninformative families, 524 families from 44 study centers in 21 countries were included in the analysis. Of these, 363 were multiple-case families, and 161 were from population-based studies of individuals with BC or OC. The eligible families included 8,830 females (852 with *PALB2* PVs) and 9,076 males (124 with *PALB2* PVs; Data

Supplement). One hundred sixty-one different PVs were identified, the most frequent being c.3113G>A (61 families). Twenty-three deletions or duplications of whole exons were observed, all of which were clustered in the PALB2 WD40 domain (Data Supplement).

Risk Models

The genetic models that included a residual (polygenic) familial component for BC or OC provided a better fit to the data than the single gene (AIC for single gene model, 10,687.50 *v* 10,662.08 for the BC polygenic model and 10,681.93 for the OC polygenic model). Therefore, the results presented herein are based on the models that assumed a single gene plus residual familial component for BC or OC.

BC Risk

The estimated BC RR was 7.18 (95% CI, 5.82 to 8.85; $P = 6.5 \times 10^{-76}$; BH-adjusted $P = 4.6 \times 10^{-75}$) when it was assumed to be constant with age (Table 1). When separate RRs were estimated for each decade of age, there was a suggestion that the RRs decreased with age; however, this model did not fit significantly better than the model with a constant RR (LRT, $df = 5$; $P = .20$; Table 1). We also fitted a model where the logRR was assumed to be a linear function of age from 20 to 79 years (AIC, 10,654.54; Table 1). This model gave a better fit than the model with a constant logRR ($P = 2.0 \times 10^{-3}$) or the model where logRR was assumed to be a linear function up to age 50 years and constant thereafter, which allowed for a threshold effect (AIC, 10,656.38). Under the linear trend model, the BC logRR estimate decreased with age ($P = 2.0 \times 10^{-3}$) from 13.10 at age 25 years to 4.69 at age 75 years. The absolute risk of developing BC was 16.9% (95% CI, 13.3% to 21.3%) to age 50 years and 52.8% (95% CI, 43.7% to 62.7%) to age 80 years, assuming that all women had the calendar period incidences experienced by a woman born during 1950-1959 (Fig 1A; Table 2).

We investigated whether BC risks varied by birth cohort. Compared with women born before 1940, the estimated RR was 2.09 (95% CI, 1.38 to 3.15) for women born during 1940-1969 and 4.02 (95% CI, 2.54 to 6.38) for women born after 1969. Under this model, the absolute risk of developing BC was estimated to be 6.9% (95% CI, 4.6% to 10.2%) to age 50 years and 29.5% (95% CI, 21.0% to 40.4%) to age 80 years for those born in 1930-1939 and 17.4% (95% CI, 12.9% to 23.1%) to age 50 years and 57.7% (95% CI, 45.0% to 71.2%) to age 80 years for those born in 1950-1959. The risk to age 50 years was 34.3% (95% CI, 25.7% to 44.9%) for those born after 1969 (Fig 1B).

OC Risk

The estimated OC RR was 2.91 (95% CI, 1.40 to 6.04; $P = 4.1 \times 10^{-3}$; BH-adjusted $P = .014$) when the RR was assumed to be constant with age (Table 1). There was a suggestion of a higher OC RR in ages 60-79 years (RR, 4.63; 95% CI, 1.82 to 11.77) compared with ages 30-59 years (RR, 1.93; 95% CI, 0.62 to 6.03), but this model did not fit significantly better than the model with a constant RR (LRT, $df = 1$; $P = 0.24$). The absolute risk of developing OC for women born during 1950-1959 was 0.6% (95% CI, 0.3% to 1.3%) to age 50 years and 4.8% (95% CI, 2.4% to 9.7%) to age 80 years (Fig 2; Table 2).

PaC Risk

The RR of PaC was estimated to be 2.37 (95% CI, 1.24 to 4.50; $P = .0087$; BH-adjusted $P = .020$; Table 1). The number of individuals with PaC was too small to obtain age-specific RR estimates with any precision. Under this model, the absolute risk of developing PaC to age 80 years for a person born during 1950-1959 was 2.2% (95% CI, 1.2% to 4.2%) for females and 2.8% (95% CI, 1.5% to 5.3%) for males (Fig 2; Table 2).

MBC Risk

The estimated MBC RR was 7.34 (95% CI, 1.28 to 42.18; $P = .026$; BH-adjusted $P = .036$; Table 1), and the corresponding absolute risk of developing MBC to age 80 years for men born during 1950-1959 was 0.9% (95% CI, 0.2% to 4.9%; Fig 2; Table 2).

PrC, CRC, and Other Cancer Risk

The PrC RR was estimated to be 0.42 (95% CI, 0.21 to 0.84; $P = .014$; BH-adjusted $P = .025$). There was no significant association with CRC (RR, 0.97; 95% CI, 0.51 to 1.87; $P = .93$; BH-adjusted $P = .93$; Table 1). The results remained similar when separate CRC RRs were estimated for males and females (LRT, $P = .74$). The estimated RR of all other cancers was 0.76 (95% CI, 0.58 to 0.99; $P = .039$; BH-adjusted $P = .046$).

Predicted Risks by Family History

The most parsimonious models included a residual familial component for BC or OC. As a result, the predicted absolute risks of developing BC or OC differed by cancer family history. For example, the predicted absolute risk of developing BC by age 80 years varies from 52% (95% CI, 42% to 62%) for a female with an unaffected mother at age 50 years and unaffected maternal grandmother at age 70 years to 76% (95% CI, 69% to 83%) for a female with two affected first-degree relatives (Table 3). Similarly, the predicted risk of developing OC by age 80 years varies from 5% (95% CI, 2% to 10%) for a female with no family history of OC in first- and second-degree relatives to 16% (95% CI, 8% to 28%) for a female whose mother and sister developed OC at age 50 years (Table 3).

DISCUSSION

Robust quantification of cancer risks is critical for the optimum clinical management of persons with germline PVs in *PALB2*. Using the largest worldwide collection of people with *PALB2* PVs (976 from 524 families) to our

TABLE 1. Estimated Cancer RRs for *PALB2* Pathogenic Variant Carriers Under Different Models and Best Fit Models

Cancer	Model Considered	Age (years)	*PALB2* RR (95% CI)	*P*	Best Fit Model
Female breast	Age-constant model	20-79	7.18 (5.82 to 8.85)	6.5×10^{-76}	
	Age-specific model, separate parameters for each decade of age	20-29	9.96 (3.30 to 30.10)	.2*	
		30-39	11.25 (7.42 to 17.05)		
		40-49	7.29 (5.18 to 10.26)		
		50-59	7.44 (5.43 to 10.20)		
		60-69	6.56 (4.52 to 9.53)		
		70-79	4.84 (2.80 to 8.36)		
	Age-trend model[a,b]	25	13.10 (8.68 to 19.75)	2×10^{-3}**	Yes
		35	10.67 (7.84 to 14.51)		
		45	8.69 (6.89 to 10.94)		
		55	7.07 (5.72 to 8.75)		
		65	5.76 (4.43 to 7.50)		
		75	4.69 (3.28 to 6.70)		
Ovarian	Age-constant model	30-79	2.91 (1.40 to 6.04)	4.1×10^{-3}	Yes
	Age-specific model	30-59	1.93 (0.62 to 6.03)	.24**	
		60-79	4.63 (1.82 to 11.77)		
Pancreatic	Age-constant model	30-79	2.37 (1.24 to 4.50)	.0087	Yes
Male breast	Age-constant model	30-79	7.34 (1.28 to 42.18)	.026	Yes
Prostate	Age-constant model	30-79	0.42 (0.21 to 0.84)	.0140	Yes
Colorectal	Age-constant model	30-79	0.97 (0.51 to 1.87)	.93	Yes
Other	Age-constant model	20-79	0.76 (0.58 to 0.99)	.039	Yes

Abbreviation: RR, relative risk.

[a]$\log RR = \alpha + \beta(\text{age} - 20)$, where $\alpha = 2.68$ (95% CI, 0.24 to 2.21) and $\beta = -0.021$ (95% CI, −0.033 to −0.0077).

[b]Cohort effect: before 1940, RR = 1; 1940-1969, RR = 2.09 (95% CI, 1.38 to 3.15); after 1969, RR = 4.02 (95% CI, 2.54 to 6.38).

*Likelihood ratio test comparing against the model with a constant relative risk, $df = 5$.

**Likelihood ratio test comparing against the model with a constant relative risk, $df = 1$.

knowledge, we have firmly established the place of *PALB2* as an important nonsyndromic BC gene after *BRCA1* and *BRCA2*. We also found significantly increased risks of OC, PaC, and MBC, and for the first time to our knowledge, we provide risk estimates for these. The posterior probabilities for the RR parameter estimates being > 1.5 were 0.96 for MBC, 0.89 for OC, and 0.87 for PaC (Data Supplement). No increased risks for PrC, CRC, or other cancers were identified.

Previously published studies provided BC odds ratio (OR) or hazard ratio estimates for women with *PALB2* PVs that ranged from 3.40 to 12.67 (Data Supplement). This variation is likely due to differences in study designs and chance caused by small sample sizes. Here, by using a modified segregation analysis approach that adjusts appropriately for ascertainment, the estimated BC RR was found to vary from 13.1 at young ages to 4.69 for older ages, all in the range of other reported estimates. The absolute risk of developing BC to age 80 years was 53% (95% CI, 44% to 63%; Fig 1A; Table 1). Both the RR and the present absolute risk estimates were somewhat higher than those reported in the previous PALB2-IG study in 154 families,[5] which shared 77 families with the current study. When risks were estimated separately for multiple-case families and population-based families, the BC risk estimates were slightly higher for multiple-case families but not significantly different after adjusting for ascertainment ($P = .41$; Data Supplement).

There has been conflicting evidence for the role of *PALB2* in OC predisposition; 2 observational studies that implicated an association with *PALB2* lacked unaffected or matched controls.[22,23] Other studies reported RRs of 0.96-5.53, but none were significant.[5,13,24,25] Here, we show that *PALB2* PVs are associated with a moderate risk of OC (RR, 2.91; $P = 4.1 \times 10^{-3}$) and that the estimated absolute risk of developing OC to age 80 years was approximately 5%.

Models that allow for a residual familial component in addition to the *PALB2*-attributable risk provided a better fit to the data for both BC and OC. This is consistent with previous analyses of BC and OC risks for both *PALB2* and *BRCA1/BRCA2* and strongly suggests other genetic or environmental factors shared in families that modify these risks for *PALB2*.[5,26-29] The combined effects of common genetic variants identified through genome-wide

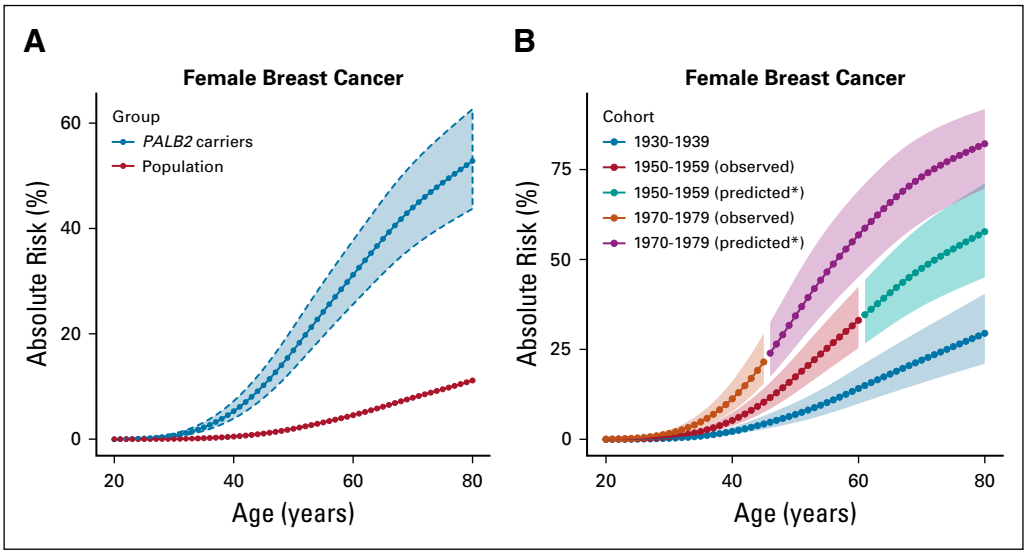

FIG 1. Estimated absolute risk of developing breast cancer for women with germline *PALB2* pathogenic variants (PVs) by age under (A) a model that assumes no cohort effect (blue, the risk for women with *PALB2* PVs; red, the risk in the United Kingdom general population, assuming that population incidences are applicable to individuals born between 1950 and 1959) and (B) a model that allows for cohort-specific relative risk parameters. The dotted curves and shaded area show the 95% CI. (*) Assuming that the relative risk estimates apply to the unobserved age ranges for women born in these cohorts.

association studies, summarized as a polygenic risk score (PRS), have been shown to modify BC and OC risks women with *BRCA1/BRCA2* PVs,[30] which explains part of this residual familial component. It is likely that a PRS will also modify the risk associated with *PALB2* PVs, thus further improving risk prediction.

We included cohort- and country-specific cancer population incidences in our models to reflect the baseline cancer incidence changes over time and across countries. Despite this, the BC RR estimates varied by both birth cohort and age, with higher RRs observed for more recent birth cohorts and younger ages, consistent with previous findings.[5,31,32] The higher RR of BC for women born more recently might reflect under-reporting of cancers in earlier decades; changes in lifestyle, reproductive, or other environmental factors; or more intensive cancer surveillance in recent decades. No evidence for variation in OC risks by age or birth cohort was observed, but the number of individuals with OC (n = 104) limited statistical power.

The absolute risks presented here were obtained by applying estimated RRs to United Kingdom population cancer incidences, so they would be applicable to women from populations with similar age-specific cancer incidences. If the RRs are assumed to be constant across populations, then the estimated absolute risk will be lower for populations with lower cancer incidences.

Previous observational studies of *PALB2* in familial PaC reported conflicting results.[8,9,33-36] The current analysis confirms the association with PaC and is the first in our knowledge to quantify it, with an RR estimate of 2.30 (albeit with wide confidence limits), which translates to an absolute risk of 2%-3% by age 80 years (Fig 2; Table 2). Previous studies observed a higher prevalence of *PALB2* PVs in MBC,[5,37-39] and the results presented here confirm an increased MBC risk (RR, 7.34; 95% CI, 1.28 to 42.18).

No previous study that we know of has demonstrated statistically significant associations of *PALB2* with PrC risk,[25,40-42] and our analysis points to a weak association with decreased risk. Because families were primarily ascertained through female individuals with BC and OC, this result might reflect under-reporting of PrC in these families, and the same phenomenon could explain the slightly decreased risk for all other cancers. Studies have observed germline *PALB2* PVs in patients with CRC who underwent gene panel testing,[14,43] and while a case-control analysis found a higher frequency of *PALB2* PVs in cases with CRC (OR estimate, 3.4), the evidence of association was weak ($P = .034$), and the results were not replicated in cases with early-onset CRC.[44] Here, we did not find evidence of an association with CRC.

The current study has several limitations. Retrospective kin-cohort studies are susceptible to possible biases related to self-reported family histories of cancer. Under-reporting of cancer in families is a common problem,[45] which might partly explain the results for cancers beyond breast, ovary, and pancreas. Of the individuals with cancer in the data set, age at diagnosis was missing for 5.5% and could not be inferred by other available information. We assumed that

TABLE 2. Estimated Age-Specific Cancer Incidences and Absolute Risks for Persons With *PALB2* Pathogenic Variants

Age (years)	Female Breast Cancer	Ovarian Cancer	Male Breast Cancer	Female Pancreatic Cancer	Male Pancreatic Cancer
Estimated Incidence (per 1,000 person-years) for Persons With *PALB2* Pathogenic Variants (95% CI)[a]					
30	2 (1 to 3)	0.09 (0.04 to 0.2)	0.002 (0.0004 to 0.01)	0.006 (0.003 to 0.01)	0.007 (0.004 to 0.01)
40	9 (7 to 11)	0.3 (0.1 to 0.6)	0.02 (0.004 to 0.1)	0.03 (0.01 to 0.05)	0.04 (0.02 to 0.09)
50	18 (14 to 22)	0.7 (0.3 to 1)	0.07 (0.01 to 0.4)	0.1 (0.06 to 0.2)	0.2 (0.1 to 0.4)
60	20 (16 to 25)	1 (0.6 to 3)	0.2 (0.03 to 1)	0.4 (0.2 to 0.8)	0.6 (0.3 to 1)
70	19 (14 to 25)	2 (0.8 to 4)	0.4 (0.07 to 2)	1 (0.5 to 2)	1 (0.6 to 2)
79	17 (11 to 25)	2 (1 to 4)	0.6 (0.1 to 3)	2 (0.8 to 3)	2 (1 to 4)
Estimated Absolute Risk (%) for Persons With *PALB2* Pathogenic Variants (95% CI)[a]					
30	0.7 (0.5 to 1)	0.02 (0.02 to 0.02)	0.0001 (0.0001 to 0.0001)	0.0009 (0.0009 to 0.0009)	0.002 (0.002 to 0.002)
40	5 (4 to 7)	0.2 (0.1 to 0.4)	0.009 (0.002 to 0.05)	0.01 (0.008 to 0.03)	0.02 (0.01 to 0.04)
50	17 (13 to 21)	0.6 (0.3 to 1)	0.05 (0.008 to 0.3)	0.07 (0.04 to 0.1)	0.1 (0.06 to 0.2)
60	31 (26 to 38)	2 (0.8 to 3)	0.2 (0.03 to 0.9)	0.3 (0.2 to 0.6)	0.5 (0.2 to 0.9)
70	44 (37 to 52)	3 (1 to 6)	0.4 (0.07 to 2)	1 (0.5 to 2)	1 (0.7 to 3)
80	53 (44 to 63)	5 (2 to 10)	0.9 (0.2 to 5)	2 (1 to 4)	3 (2 to 5)

[a]Assuming population calendar and cohort-specific incidences for an individual born between 1950 and 1959. Mortality is not accounted for in absolute risk estimates.

these individuals developed the cancer at the average age at diagnosis of the corresponding cancer in the data set. To examine the effect of this assumption, we performed a sensitivity analysis that censored those individuals at age 0 (ie, effectively ignoring these diagnoses from the analysis). The results remained similar for all cancers except

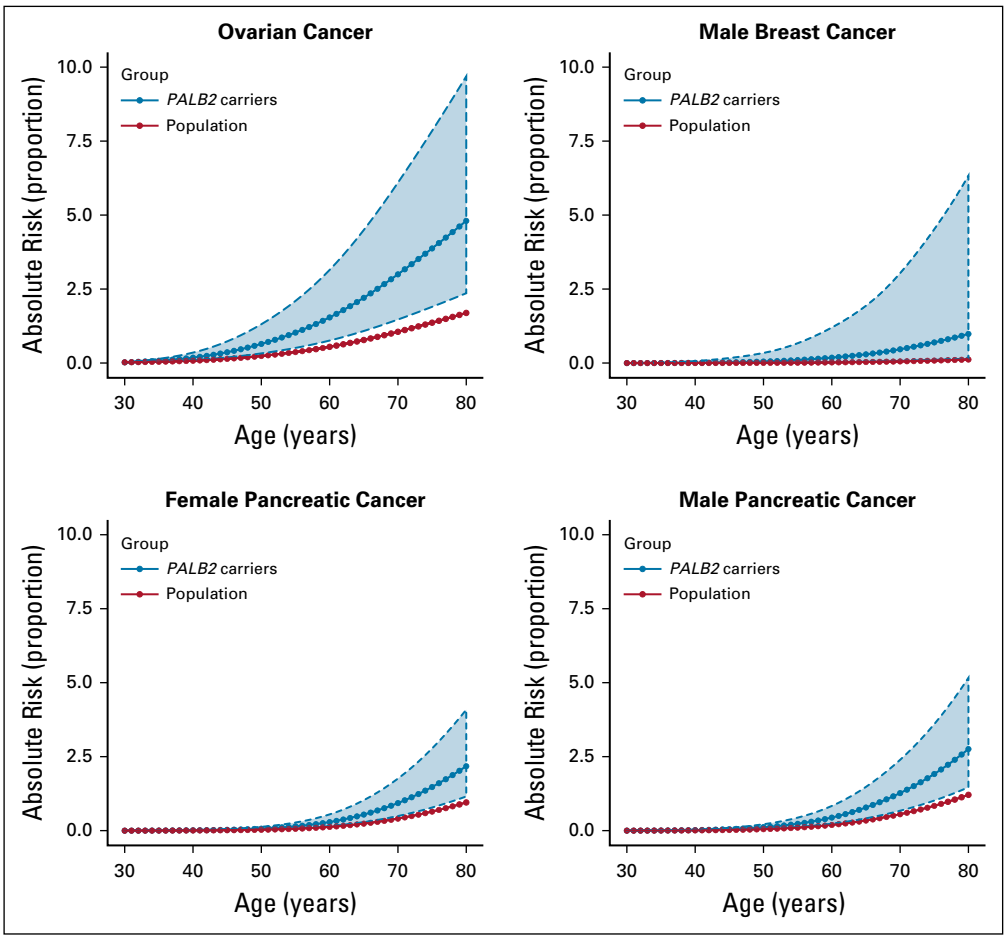

FIG 2. Estimated absolute risk of developing ovarian, pancreatic, and male breast cancer for individuals with *PALB2* pathogenic variants PVs and in the general population by age (assuming that population incidences are applicable to individuals born between 1950 and 1959). The dotted curves and shaded area show the 95% CI.

TABLE 3. Cumulative Risk of Developing Breast Cancer and Ovarian Cancer for Women With *PALB2* Pathogenic Variants by Family History

Cancer Type and Age (years)	Cumulative Risk of Developing Cancer for Women With *PALB2* Pathogenic Variants, % (95% CI)				
	Without Considering Family History	Mother Unaffected at Age 50 Years, Maternal Grandmother Unaffected at Age 70 Years	Mother Affected at Age 35 Years	Mother and Sister Affected at Age 50 Years	Mother and Maternal Grandmother Affected at Age 50 Years
Breast					
30	0.7 (0.5 to 1)	0.7 (0.5 to 1)	1 (1 to 2)	2 (1 to 2)	1 (1 to 2)
35	2 (2 to 3)	2 (1 to 3)	4 (3 to 6)	5 (4 to 6)	4 (3 to 5)
40	5 (4 to 7)	5 (4 to 7)	9 (7 to 12)	11 (9 to 13)	9 (7 to 12)
45	10 (8 to 13)	10 (7 to 12)	18 (14 to 22)	20 (17 to 24)	17 (14 to 21)
50	17 (13 to 21)	16 (13 to 20)	28 (23 to 34)	31 (27 to 36)	27 (23 to 32)
55	24 (20 to 30)	23 (19 to 28)	38 (32 to 45)	43 (38 to 48)	38 (32 to 43)
60	31 (26 to 38)	30 (25 to 36)	47 (40 to 55)	52 (47 to 58)	47 (41 to 53)
65	38 (32 to 46)	37 (30 to 44)	56 (48 to 63)	61 (55 to 67)	55 (49 to 62)
70	44 (37 to 52)	43 (35 to 51)	62 (54 to 71)	68 (61 to 74)	62 (55 to 69)
75	49 (41 to 59)	47 (39 to 57)	67 (58 to 76)	72 (66 to 79)	67 (59 to 74)
80	53 (44 to 63)	52 (42 to 62)	71 (62 to 80)	76 (69 to 83)	71 (63 to 79)
Ovarian					
35	0.1 (0.1 to 0.1)	0.1 (0.1 to 0.1)	0.2 (0.1 to 0.3)	0.3 (0.2 to 0.5)	0.2 (0.1 to 0.3)
40	0.2 (0.1 to 0.4)	0.2 (0.1 to 0.4)	0.4 (0.2 to 0.7)	0.7 (0.4 to 1)	0.5 (0.3 to 0.8)
45	0.4 (0.2 to 0.7)	0.4 (0.2 to 0.7)	0.8 (0.4 to 1)	1 (0.7 to 2)	0.9 (0.5 to 2)
50	0.7 (0.3 to 1)	0.6 (0.3 to 1)	1 (0.7 to 3)	2 (1 to 4)	2 (0.8 to 3)
55	1 (0.5 to 2)	1 (0.5 to 2)	2 (1 to 4)	4 (2 to 7)	3 (1 to 5)
60	2 (0.8 to 3)	2 (0.8 to 3)	3 (2 to 6)	5 (3 to 10)	4 (2 to 7)
65	2 (1 to 5)	2 (1 to 4)	4 (2 to 9)	8 (4 to 14)	5 (3 to 10)
70	3 (1 to 6)	3 (1 to 6)	6 (3 to 12)	10 (5 to 19)	7 (4 to 14)
75	4 (2 to 8)	4 (2 to 8)	8 (4 to 15)	13 (7 to 24)	9 (5 to 17)
80	5 (2 to 10)	5 (2 to 10)	9 (5 to 18)	16 (8 to 28)	11 (6 to 21)

PaC, where the estimated RR was attenuated to 1.84 (95% CI, 0.87 to 3.91) as a result of excluding 10 of the 99 individuals with PaC (Data Supplement). The risk of a second primary BC in women previously diagnosed with *PALB2*-associated BC could not be determined from the available data, although it remains an important issue to assess in future studies.

PALB2 interacts closely with BRCA1 and BRCA2 in the homologous recombination (HR) DNA repair pathway where the sequence of recruitment to DNA is BRCA1, PALB2, and then BRCA2.[46] This suggests that *PALB2* and *BRCA2* might have similar cancer risks because BRCA2 needs PALB2 to be recruited in HR repair. Our results show a similar BC birth cohort effect to that previously observed in women with *BRCA1*/*BRCA2* PVs,[32] and the BC-specific age incidences follow a similar pattern to that seen in *BRCA2*[47] (Table 2), where incidences increase with age and reach a constant level from age 50 years onward. The observed associations with MBC and PaC and the moderate risk of OC are also reminiscent of the pattern seen in *BRCA2*, which presumably reflects tissue-specific differences in DNA repair mechanisms and highlights the importance of conducting such studies for each susceptibility gene.

The cumulative risk estimates for BC in women with *PALB2* PVs overlap with *BRCA1/BRCA2*, for whom RRM is typically offered as an option, and here we provide critical data that allow refinement of RRM guidelines for *PALB2*. Risk estimates for OC are somewhat lower than for *BRCA1/BRCA2*, and here the family history of OC would be an important factor when considering RRBSO. Given the similarity in the cancer spectrum and underlying biology, we expect that cancer drugs effective in persons with *BRCA1* or *BRCA2* PVs may also be effective for those with *PALB2* PVs,[48,49] and clinical trials currently are addressing this (eg, ClinicalTrials.gov identifier: NCT03344965).

To our knowledge, this is the largest study of *PALB2*-associated cancer risks to date, and has allowed us to refine BC risk estimates and, for the first time, to provide estimates for OC, PaC, and MBC risk. This advance in knowledge warrants the inclusion of *PALB2* in cancer gene panels and will facilitate better cancer risk management of women and men with germline PVs in this gene.

AFFILIATIONS

[1]Centre for Cancer Genetic Epidemiology, Department of Public Health and Primary Care, University of Cambridge, Cambridge, United Kingdom
[2]Department of Medical Genetics, NIHR Cambridge Biomedical Research Centre, and Cancer Research UK Cambridge Centre, University of Cambridge, Cambridge, United Kingdom
[3]Cancer Genetics Branch, National Human Genome Research Institute, National Institutes of Health, Bethesda, MD
[4]Department of Pathology, Brigham and Women's Hospital, Boston, MA
[5]Centre for Cancer Genetic Epidemiology, Department of Oncology,University of Cambridge, Cambridge, United Kingdom
[6]Family Cancer Clinic, The Netherlands Cancer Institute–Antoni van Leeuwenhoek Hospital, Amsterdam, the Netherlands
[7]Yorkshire Regional Genetics Service, Chapel Allerton Hospital, Leeds, United Kingdom
[8]Department of Clinical Genetics, Helsinki University Hospital, University of Helsinki, Helsinki, Finland
[9]Lunenfeld-Tanenbaum Research Institute of Mount Sinai Hospital, Toronto, Ontario, Canada
[10]Laboratory of Molecular Oncology, Division of Cellular and Molecular Research, National Cancer Centre Singapore, Singapore
[11]Leicestershire Clinical Genetics Service, University Hospitals of Leicester NHS Trust, Leicester, United Kingdom
[12]Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY
[13]Clinical Cancer Genomics Community Research Network, City of Hope, Duarte, CA
[14]Division of Oncology and Pathology, Department of Clinical Sciences Lund, Lund University, Lund, Sweden
[15]Department of Oncology, Helsinki University Hospital, University of Helsinki, Helsinki, Finland
[16]Centre for Medical Genetics, Ghent University, Ghent, Belgium
[17]University of Florida Genetics Institute, University of Florida, Gainesville, FL
[18]The Research Institute of the McGill University Health Centre, McGill University, Montreal, Quebec, Canada
[19]The Goodman Cancer Research Centre, McGill University, Montreal, Quebec, Canada
[20]Keck School of Medicine, University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA
[21]Biopathologie, Centre Léon Bérard, Lyon, France
[22]Service de Génétique, Institut Curie, Paris, France
[23]Oncogenetics Group, Clinical and Molecular Genetics Area, Vall d'Hebron Institute of Oncology (VHIO), University Hospital, Vall d'Hebron, Barcelona, Spain
[24]Ambry Genetics, Aliso Viejo, CA
[25]Department ofMedicine, Abramson Cancer Center, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA
[26]Prospective Registry of Multiplex Testing (PROMPT), United States and Europe
[27]Institute for Medical Informatics, Statistics and Epidemiology, University of Leipzig, Leipzig, Germany
[28]Division of Evolution and Genomic Sciences, University of Manchester; Manchester Centre for Genomic Medicine, St Mary's Hospital–Manchester University Hospitals NHS Foundation Trust; and Manchester Academic Health Science Centre, Manchester, United Kingdom
[29]Molecular Diagnostics Laboratory, INRASTES, National Centre for Scientific Research "Demokritos," Athens, Greece
[30]Dana-Farber Cancer Institute, Boston, MA
[31]Department of Health Sciences Research, Mayo Clinic, Rochester, MN
[32]City of Hope National Medical Center, Duarte, CA
[33]Center for Molecular Medicine Cologne (CMMC), University of Cologne, Cologne, Germany
[34]Center for Hereditary Breast and Ovarian Cancer, University Hospital of Cologne, Cologne, Germany
[35]Department of Obstetrics and Gynecology, Helsinki University Hospital, University of Helsinki, Helsinki, Finland
[36]Division of Medical Oncology, Sylvester Comprehensive Cancer Center, University of Miami Miller School of Medicine, Miami, FL
[37]Hematology, Oncology and Transfusion Medicine Center, Department of Molecular and Regenerative Medicine, Vilnius University Hospital Santariskiu Clinics, Vilnius, Lithuania
[38]State Research Institute Innovative Medicine Center, Vilnius, Lithuania
[39]Institute of Biochemistry and Experimental Oncology, First Faculty of Medicine, Charles University and General University Hospital in Prague, Prague, Czech Republic
[40]Institute of Biology and Medical Genetics, First Faculty of Medicine, Charles University, Prague, Czech Republic
[41]Department of Physiology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore
[42]SingHealth Duke-NUS Oncology Academic Clinical Programme (ONCO ACP), Duke-NUS Medical School, Singapore
[43]INSERM U900, Institut Curie, PSL University, Mines ParisTech, Paris, France
[44]Institute of Clinical Medicine, Pathology and Forensic Medicine, University of Eastern Finland, Kuopio, Finland
[45]Unit of Medical Genetics, Department of Medical Oncology and Hematology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy
[46]Department of Epidemiology, University of California, Irvine, Irvine, CA
[47]Familial Cancer Program, The University of Vermont Cancer Center, Burlington, VT
[48]Department of Gynecology and Obstetrics, Ludwig-Maximilians University of Munich, Munich, Germany
[49]Lawrence S. Bloomberg Faculty of Nursing, University of Toronto, Toronto, Ontario, Canada
[50]University Malaya Cancer Research Institute, Faculty of Medicine, University Malaya, Kuala Lumpur, Malaysia
[51]Department of Clinical Genetics, Oulu University Hospital, Medical Research Center Oulu and PEDEGO Research Unit, University of Oulu, Oulu, Finland
[52]Department of Population Sciences, Beckman Research Institute, City of Hope, Duarte, CA
[53]Cancer Research Malaysia, Subang Jaya Selangor, Malaysia
[54]Department of Clinical Pathology, The University of Melbourne, Melbourne, Victoria, Australia
[55]Precision Medicine, School of Clinical Sciences at Monash Health, Monash University, Clayton, Victoria, Australia
[56]Center for Clinical Cancer Genetics, The University of Chicago, Chicago, IL
[57]Institute of Medical Genetics, Kepler University Hospital Linz and Laboratory for Molecular Biology and Tumor Cytogenetics, Ordensklinikum Linz, Linz, Austria
[58]Clinical Genetics Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY
[59]Department of Molecular Medicine, University La Sapienza, Rome, Italy
[60]Department of Human Genetics, Hannover Medical School, Hannover, Germany
[61]Laboratory of Cancer Genetics and Tumor Biology, Cancer and Translational Medicine Research Unit, Biocenter Oulu, University of Oulu, and Northern Finland Laboratory Centre, Oulu, Finland
[62]Unit of Molecular Basis of Genetic Risk and Genetic Testing, Department of Research, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy
[63]School of Women's and Children's Health, Faculty of Medicine, University of New South Wales Sydney, Sydney, New South Wales, Australia
[64]The Kinghorn Cancer Centre, Garvan Institute of Medical Research, Sydney, New South Wales, Australia
[65]Wessex Clinical Genetics Service, Princess Anne Hospital, Southampton, United Kingdom

[66]Department of Genetics, University of MiamiMiller School of Medicine, Miami, FL
[67]Department of Clinical Genetics, Aarhus University Hospital, Aarhus, Denmark
[68]Department of Medical Oncology, Division of Clinical Cancer Genomics, City of Hope, Duarte, CA
[69]Unit of Medical Oncology, Department of Oncology and Hematology,Papa Giovanni XXIII Hospital, Bergamo, Italy
[70]Sir Peter MacCallum Department of Oncology, The University of Melbourne, Melbourne, Victoria, Australia
[71]Parkville Familial Cancer Centre, Peter MacCallum Cancer Center, Melbourne, Victoria, Australia
[72]Department of Clinical Genetics, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark
[73]Center for Genomic Medicine, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark
[74]Huntsman Cancer Institute, Department of Population Health Sciences, University of Utah, Salt Lake City, UT
[75]Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, The University of Melbourne, Melbourne, Victoria, Australia
[76]Department of Genetics and Computational Biology, QIMR Berghofer Medical Research Institute, Brisbane, Queensland, Australia
[77]Department of Obstetrics, Gynecology and Reproductive Sciences, Division of Gynecologic Oncology, Sylvester Comprehensive Cancer Center, University of Miami Miller School of Medicine, Miami, FL
[78]Genetics Department, F76000 and Normandy University, UNIROUEN, INSERM U1245, Normandy Centre for Genomic and Personalized Medicine, Rouen University Hospital, Rouen, France
[79]Department of Genetics, Centre Hospitalier de l'Université de Montréal, Montreal, Quebec, Canada
[80]Department of Clinical Genetics and Pathology, Department of Laboratory Medicine, Office for Medical Services, Lund, Sweden
[81]Division of Clinical Genetics, Department of Laboratory Medicine, Lund University, Lund, Sweden
[82]Genome Diagnostics Program, IFOM–The FIRC Institute for Molecular Oncology, Milan, Italy
[83]Breast Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY
[84]Vanderbilt-Ingram Cancer Center, Division of Genetic Medicine, Department of Medicine, Vanderbilt University Medical Center, Nashville, TN
[85]Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN
[86]Departments of Human Genetics, Oncology, and Medicine, McGill University, Montreal, Quebec, Canada

CORRESPONDING AUTHOR

Marc Tischkowitz, MD, PhD, Department of Medical Genetics, Box 238, Level 6, Addenbrooke's Treatment Centre, Cambridge Biomedical Campus, Cambridge CB2 0QQ, United Kingdom; e-mail: mdt33@cam.ac.uk.

EQUAL CONTRIBUTION

A.C.A and M.T. contributed equally to this work and are co-corresponding authors.

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DATA SHARING

All mutation data will be deposited in the Leiden Open Variation Database https://www.lovd.nl (open access)

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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AUTHOR CONTRIBUTIONS

Conception and design: Arto Mannermaa, John L. Hopper, Paul Pharoah, Zaki El-Haffaf, Tuya Pal, Melissa Southey, Robert Winqvist, Douglas F. Easton, William D. Foulkes, Antonis C. Antoniou, Marc Tischkowitz
Financial support: Ellen L. Goode, George Zogopoulos, John L. Hopper, Melissa Southey, Antonis C. Antoniou, Marc Tischkowitz
Administrative support: Alicja Doroszuk, D. Gareth Evans, Arto Mannermaa, John L. Hopper, Jeffrey N. Weitzel, Melissa Southey, Marc Tischkowitz
Provision of study material or patients: Alison M. Dunning, Mitul Shah, Muriel A. Adank, Julian Adlard, Peter Ang, Jonine L. Bernstein, Kristie Bobolis, Åke Borg, Kathleen B.M. Claes, Patrick Concannon, Adeline Cuggia, Francesca Damiola, Antoine de Pauw, Orland Diez, D. Gareth Evans, Florentia Fostira, Judy Garber, Stephen B. Gruber, Eric Hahnen, Zdenek Kleibl, Petra Kleiblova, Irene Konstantopoulou, Anders Kvist, Holly Laduca, Ann S.G. Lee, Fabienne Lesueur, Eamonn R. Maher, Arto Mannermaa, Siranoush Manoukian, Wendy McKinnon, Nur Aishah Mohd Taib, Katherine L. Nathanson, Susan Neuhausen, Pei Sze Ng, Florian Obermair, Kenneth Offit, Olufunmilayo I. Olopade, Judith Penkert, Katri Pylkäs, Paolo Radice, Susan J. Ramus, Anne-Bine Skytte, Thomas Slavin, Jana Soukupova, Gary Unzeitig, Lydia Usha, James Whitworth, Marie Wood, Cheng Har Yip, Sook-Yee Yoon, Amal Yussuf, George Zogopoulos, John L. Hopper, Georgia Chenevix-Trench, Paul Pharoah, Sophia H.L. George, Paul James, Marketa Janatova, Heli Nevanlinna, Rita Schmutzler, Soo-Hwang Teo, Mark Robson, Fergus Couch, Jeffrey N. Weitzel, Melissa Southey, Robert Winqvist, Douglas F. Easton, William D. Foulkes, Antonis C. Antoniou, Marc Tischkowitz
Collection and assembly of data: Goska Leslie, Alicja Doroszuk, Sandra Schneider, Jamie Allen, Brennan Decker, Alison M. Dunning, James Redman, James Scarth, Inga Plaskocinska, Craig Luccarini, Mitul Shah, Karen Pooley, Muriel A. Adank, Julian Adlard, Irene L. Andrulis, Peter Ang, Julian Barwell, Jonine L. Bernstein, Kristie Bobolis, Åke Borg, Carl Blomqvist, Kathleen B.M. Claes, Patrick Concannon, Adeline Cuggia, Julie O. Culver, Francesca Damiola, Antoine de Pauw, Orland Diez, Jill S. Dolinsky, Susan M. Domchek, Christoph Engel, D. Gareth Evans, Judy Garber, Lisa Golmard, Ellen L. Goode, Stephen B. Gruber, Eric Hahnen, Christopher Hake, Tuomas Heikkinen, Judith E. Hurley, Ramunas Janavicius, Zdenek Kleibl, Petra Kleiblova, Irene Konstantopoulou, Anders Kvist, Holly Laduca, Ann S.G. Lee, Fabienne Lesueur, Eamonn R. Maher, Arto Mannermaa, Siranoush Manoukian, Rachel McFarland, Wendy McKinnon, Alfons Meindl, Kelly Metcalfe, Nur Aishah Mohd Taib, Jukka Moilanen, Katherine L. Nathanson, Susan Neuhausen, Pei Sze Ng, Tu Nguyen-Dumont, Sarah M. Nielsen, Florian Obermair, Kenneth Offit, Olufunmilayo I. Olopade, Laura Ottini, Judith Penkert, Katri Pylkäs, Paolo Radice, Susan J. Ramus, Vilius Rudaitis, Lucy Side, Rachel Silva-Smith, Valentina Silvestri, Anne-Bine Skytte, Thomas Slavin, Jana Soukupova, Carlo Tondini, Alison H. Trainer, Gary Unzeitig, Lydia Usha, James Whitworth, Marie Wood, Cheng Har Yip, Sook-Yee Yoon, Amal Yussuf, George Zogopoulos, David Goldgar, John L. Hopper, Georgia Chenevix-Trench, Paul Pharoah, Sophia H.L. George, Judith Balmaña, Claude Houdayer, Paul James, Zaki El-Haffaf, Hans Ehrencrona, Marketa Janatova, Paolo Peterlongo, Heli Nevanlinna, Rita Schmutzler, Soo-Hwang Teo, Mark Robson, Tuya Pal, Fergus Couch, Jeffrey N. Weitzel, Aaron Elliott, Melissa Southey, Robert Winqvist, William D. Foulkes, Antonis C. Antoniou, Marc Tischkowitz
Data analysis and interpretation: Xin Yang, Jamie Allen, Brennan Decker, Leila Dorling, Andrew Lee, Jonine L. Bernstein, Carl Blomqvist, Susan M. Domchek, D. Gareth Evans, Florentia Fostira, Eric Hahnen, Irene Konstantopoulou, Arto Mannermaa, Tu Nguyen-Dumont, Thomas Slavin, George Zogopoulos, Georgia Chenevix-Trench, Zaki El-Haffaf, Tuya Pal,

Jeffrey N. Weitzel, Melissa Southey, Robert Winqvist, Antonis C. Antoniou, Marc Tischkowitz
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

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SWE-BRCA (The Swedish BRCA1 & BRCA2 Study Collaborators): Gothenburg, Sahlgrenska University Hospital: Zakaria Einbeigi; Linköping University Hospital: Marie Stenmark-Askmalm and Ekaterina Kuchinskaya; Lund University Hospital: Hans Ehrencrona, Therese Törngren, Anders Kvist, and Åke Borg; Stockholm, Karolinska University Hospital: Brita Arver, Annika Lindblom, and Emma Tham; Umeå University Hospital: Beatrice Melin; and Uppsala University Hospital: Ylva Paulsson-Karlsson. Z.K., P.K., J.S., and M.J. were supported by grants from the Ministry of Health of the Czech Republic (NV16-29959A) and Charles University projects PROGRES Q28/LF1 and SVV2019/260367. We thank clinical geneticists Kamila Vesela, Ales Panczak, and Jaroslav Kotlas from the Institute of Biology and Medical Genetics and Michal Vocka from the Department of Oncology, First Faculty of Medicine, Charles University, and General University Hospital in Prague for their valuable contribution to the study. 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R.W. is supported by the Academy of Finland (project grant 318337 and Center of Excellence grant 251314), the Finnish Cancer Foundation, the Sigrid Jusélius Foundation, the University of Oulu, and the special Government Funding of Oulu University Hospital grants. K.Py. is supported by Academy of Finland Research Fellow grant 314183 and the Finnish Cancer Foundation. A.Ma. is supported by special Government Funding of Kuopio University Hospital grants, the Cancer Fund of North Savo, the Finnish Cancer Foundation, and the strategic funding of the University of Eastern Finland. 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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Cancer Risks Associated With Germline *PALB2* Pathogenic Variants: An International Study of 524 Families

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Alicja Doroszuk
Employment: AstraZeneca
Research Funding: AstraZeneca
Travel, Accommodations, Expenses: AstraZeneca

Brennan Decker
Stock and Other Ownership Interests: Avidea Technologies
Consulting or Advisory Role: Foundation Medicine, Avidea Technologies

Inga Plaskocinska
Employment: IQVIA
Honoraria: IQVIA

Andrew Lee
Patents, Royalties, Other Intellectual Property: Inventor of the BOADICEA model, which is commercialized by Cambridge Enterprise (part of the University of Cambridge). Currently, the model is licensed to the company FamHis. I have received royalties from this commercialization.

Peter Ang
Consulting or Advisory Role: Roche Pharma AG, Eli Lilly, Novartis

Julian Barwell
Honoraria: AstraZeneca, Merck
Consulting or Advisory Role: Deerfield Management
Travel, Accommodations, Expenses: AstraZeneca

Åke Borg
Honoraria: Roche
Travel, Accommodations, Expenses: Roche, AstraZeneca

Kathleen B.M. Claes
Consulting or Advisory Role: AstraZeneca (Ins)

Patrick Concannon
Stock and Other Ownership Interests: Amgen
Patents, Royalties, Other Intellectual Property: 6,458,534 Gene associated with Nijmegen breakage syndrome, a gene product and methods for their use filed April 27, 1999; 5,955,279 Ataxia-telangiectasia: mutations in the ATM gene filed June 13, 1997; 5,770,372 Detection of mutations in the human ATM gene filed November 20, 1996
Other Relationship: 10X Genomics (Inst), CELLINK (Inst), Canon USA (Inst), Illumina (Inst)

Adeline Cuggia
Consulting or Advisory Role: AstraZeneca

Jill S. Dolinsky
Employment: Ambry Genetics

Susan M. Domchek
Honoraria: AstraZeneca, Clovis Oncology, Bristol-Myers Squibb
Research Funding: AstraZeneca (Inst), Clovis Oncology (Inst), PharmaMar (Inst)

D. Gareth Evans
Honoraria: AstraZeneca

Judy Garber
Consulting or Advisory Role: Novartis (I), GTx (I), Helix BioPharma, Konica Minolta, Aleta BioTherapeutics (I), H3 Biomedicine (I), Kronos Bio (I)
Research Funding: Novartis (I), Ambry Genetics, Invitae Genetics, Myriad Genetics
Other Relationship: Susan G. Komen for the Cure (I), American Association for Cancer Research, Diane Helis Henry Medical Foundation (I), James P. Wilmot Foundation (I), Adrienne Helis Malvin Medical Research Foundation (I), Breast Cancer Research Foundation, Facing our Risk of Cancer Empowered

Stephen B. Gruber
Employment: Brogent
Leadership: Brogent
Stock and Other Ownership Interests: Brogent, Fulgent Therapeutics
Consulting or Advisory Role: Myriad Genetics, Fulgent Therapeutics
Research Funding: Myriad Genetics (Inst)

Tuomas Heikkinen
Employment: Bayer AG

Irene Konstantopoulou
Speakers' Bureau: AstraZeneca
Research Funding: AstraZeneca

Holly Laduca
Employment: Ambry Genetics
Stock and Other Ownership Interests: Ambry Genetics

Eamonn R. Maher
Consulting or Advisory Role: Illumina
Travel, Accommodations, Expenses: Illumina

Sarah M. Nielsen
Employment: Invitae
Stock and Other Ownership Interests: Invitae
Consulting or Advisory Role: AstraZeneca, Merck, Myriad Genetics
Speakers' Bureau: AstraZeneca
Travel, Accommodations, Expenses: Myriad Genetics, AstraZeneca

Olufunmilayo I. Olopade
Employment: CancerIQ (I)
Leadership: CancerIQ
Stock and Other Ownership Interests: CancerIQ, Tempus
Research Funding: Novartis (Inst), Roche (Inst), Genentech (Inst)
Other Relationship: Tempus, Color Genomics, Roche, Genentech, Bio Ventures for Global Health
Open Payments Link: https://openpaymentsdata.cms.gov/physician/olopade

Vilius Rudaitis
Travel, Accommodations, Expenses: MSD Oncology, Roche

Lucy Side
Research Funding: Myriad Genetics (Inst)

Carlo Tondini
Consulting or Advisory Role: Myriad Genetics
Speakers' Bureau: Amgen
Travel, Accommodations, Expenses: Roche, Genentech, Novartis, Celgene

Lydia Usha
Consulting or Advisory Role: Agendia, Myriad Genetics
Patents, Royalties, Other Intellectual Property: Patent in relationship to an adverse effect of a pharmaceutical agent. The patent has not generated any royalties or other reimbursements (Inst).
Travel, Accommodations, Expenses: Myriad Genetics

Thomas van Overeem Hansen
Honoraria: Pfizer

James Whitworth
Consulting or Advisory Role: SellmerDiers Sperm Bank

Marie Wood
Consulting or Advisory Role: Heron Therapeutics (Inst), AstraZeneca (Inst)

Sook-Yee Yoon
Research Funding: AstraZeneca (Inst)

Amal Yussuf
Employment: Ambry Genetics

George Zogopoulos
Consulting or Advisory Role: Ipsen, AstraZeneca
Research Funding: Diazon Pharmaceuticals
Patents, Royalties, Other Intellectual Property: TC-PTP inhibitors as APC activators for immunotherapy
Travel, Accommodations, Expenses: Baxalta

Paul Pharoah
Patents, Royalties, Other Intellectual Property: The PREDICT breast cancer prognostic model is licensed to OncoAssist by the University of Cambridge. I receive a share of the fees. I receive a share of the fees for a patent held by the University of Cambridge of a 7-single nucleotide polymorphism polygenic risk assay.

Judith Balmaña
Consulting or Advisory Role: AstraZeneca, Pfizer
Research Funding: AstraZeneca (Inst), PharmaMar (Inst)
Patents, Royalties, Other Intellectual Property: European patent request submitted (EP17382884.9) not related to this work
Travel, Accommodations, Expenses: AstraZeneca, PharmaMar

Hans Ehrencrona
Consulting or Advisory Role: AstraZeneca
Travel, Accommodations, Expenses: AstraZeneca

Rita Schmutzler
Honoraria: AstraZeneca, Clovis Oncology
Consulting or Advisory Role: AstraZeneca
Travel, Accommodations, Expenses: AstraZeneca

Soo-Hwang Teo
Speakers' Bureau: AstraZeneca

Mark Robson
Honoraria: AstraZeneca
Consulting or Advisory Role: McKesson, AstraZeneca
Research Funding: AstraZeneca (Inst), Myriad Genetics (Inst), Invitae (Inst), AbbVie (Inst), Tesaro (Inst), Medivation (Inst)
Travel, Accommodations, Expenses: AstraZeneca, Pfizer
Other Relationship: Research to Practice, Clinical Care Options, Physician Education Resource
Uncompensated Relationships: Merck, Pfizer, Daiichi Sankyo
Open Payments Link: https://openpaymentsdata.cms.gov/physician/612669/summary

Fergus Couch
Consulting or Advisory Role: AstraZeneca
Speakers' Bureau: Ambry Genetics, QIAGEN, GRAIL
Travel, Accommodations, Expenses: GRAIL, QIAGEN
Other Relationship: Ambry Genetics

Jeffrey N. Weitzel
Speakers' Bureau: AstraZeneca

Aaron Elliott
Employment: Ambry Genetics
Leadership: Ambry Genetics

Douglas F. Easton
Patents, Royalties, Other Intellectual Property: Royalties from BOADICEA risk prediction tool (Inst)

William D. Foulkes
Research Funding: AstraZeneca (Inst)

Antonis C. Antoniou
Patents, Royalties, Other Intellectual Property: Inventor of the BOADICEA model, which has been licensed to Cambridge Enterprise for commercialization. May receive royalties if commercialization is realized.

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