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# Breast-Cancer Risk in Families with Mutations in *PALB2*

A.C. Antoniou, S. Casadei, T. Heikkinen, D. Barrowdale, K. Pylkäs, J. Roberts, A. Lee, D. Subramanian, K. De Leeneer, F. Fostira, E. Tomiak, S.L. Neuhausen, Z.L. Teo, S. Khan, K. Aittomäki, J.S. Moilanen, C. Turnbull, S. Seal, A. Mannermaa, A. Kallioniemi, G.J. Lindeman, S.S. Buys, I.L. Andrulis, P. Radice, C. Tondini, S. Manoukian, A.E. Toland, P. Miron, J.N. Weitzel, S.M. Domchek, B. Poppe, K.B.M. Claes, D. Yannoukakos, P. Concannon, J.L. Bernstein, P.A. James, D.F. Easton, D.E. Goldgar, J.L. Hopper, N. Rahman, P. Peterlongo, H. Nevanlinna, M.-C. King, F.J. Couch, M.C. Southey, R. Winqvist, W.D. Foulkes, and M. Tischkowitz

## ABSTRACT

### BACKGROUND

Germline loss-of-function mutations in *PALB2* are known to confer a predisposition to breast cancer. However, the lifetime risk of breast cancer that is conferred by such mutations remains unknown.

### METHODS

We analyzed the risk of breast cancer among 362 members of 154 families who had deleterious truncating, splice, or deletion mutations in *PALB2*. The age-specific breast-cancer risk for mutation carriers was estimated with the use of a modified segregation-analysis approach that allowed for the effects of *PALB2* genotype and residual familial aggregation.

### RESULTS

The risk of breast cancer for female *PALB2* mutation carriers, as compared with the general population, was eight to nine times as high among those younger than 40 years of age, six to eight times as high among those 40 to 60 years of age, and five times as high among those older than 60 years of age. The estimated cumulative risk of breast cancer among female mutation carriers was 14% (95% confidence interval [CI], 9 to 20) by 50 years of age and 35% (95% CI, 26 to 46) by 70 years of age. Breast-cancer risk was also significantly influenced by birth cohort ($P<0.001$) and by other familial factors ($P=0.04$). The absolute breast-cancer risk for *PALB2* female mutation carriers by 70 years of age ranged from 33% (95% CI, 25 to 44) for those with no family history of breast cancer to 58% (95% CI, 50 to 66) for those with two or more first-degree relatives with breast cancer at 50 years of age.

### CONCLUSIONS

Loss-of-function mutations in *PALB2* are an important cause of hereditary breast cancer, with respect both to the frequency of cancer-predisposing mutations and to the risk associated with them. Our data suggest the breast-cancer risk for *PALB2* mutation carriers may overlap with that for *BRCA2* mutation carriers. (Funded by the European Research Council and others.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Tischkowitz at the Department of Medical Genetics, Box 134, Level 6, Addenbrooke's Treatment Centre, Addenbrooke's Hospital, Hills Rd., Cambridge CB2 0QQ, United Kingdom, or at mdt33@cam.ac.uk.

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PALB2 (PARTNER AND LOCALIZER OF BRCA2) was originally identified as a BRCA2-interacting protein that is crucial for key BRCA2 genome caretaker functions[1,2]; it was subsequently also shown to interact with BRCA1.[3] Biallelic germline loss-of-function mutations in *PALB2* (also known as *FANCN*) cause Fanconi's anemia, whereas monoallelic loss-of-function mutations are associated with an increased risk of breast cancer and pancreatic cancer.[4] Previous studies of familial breast cancer have yielded estimates of risk in association with loss-of-function mutations in *PALB2* that are two to four times as high as the risk among non–mutation carriers.[5-7] In Finland, the *PALB2* c.1592delT founder mutation was identified in approximately 1% of women with breast cancer who were not selected on the basis of a positive family history[6] and was associated with a risk of breast cancer that was increased by a factor of six, which is similar to the risk among carriers of deleterious *BRCA2* variants in the same country.[8] In Canada, the *PALB2* c.2323C→T (p.Glu775X) founder mutation was detected in approximately 0.5% of French-Canadian women with early-onset breast cancer who were not selected on the basis of a positive family history.[9] *PALB2* loss-of-function mutations have now been observed in persons from many countries and are found in 0.6 to 3.9% of families with a history of breast cancer, depending on the population.

Clinical testing for genes that confer a predisposition to breast cancer has been revolutionized by next-generation sequencing. Multigene panels that allow relatively inexpensive and rapid genetic profiling are now in widespread use. However, the usefulness of this technology for medical follow-up is limited by incomplete information on breast-cancer risk, even for well-documented genes. To obtain more precise and robust estimates of the cancer risk associated with loss-of-function mutations in *PALB2*, we collected data on mutation carriers and their relatives from multiple centers worldwide. The goal of our study was to estimate the risk of breast cancer associated with inherited loss-of-function mutations in *PALB2* on the basis of family data for mutation carriers from many locales, across multiple generations, and with differing family histories of cancer.

## METHODS

### FAMILIES

Families were identified through 14 participating research centers. Families were eligible for inclusion if at least one family member with breast cancer who tested negative for *BRCA1* and *BRCA2* mutations had a loss-of-function mutation in *PALB2*. Some families were ascertained through clinics for patients at high risk for breast cancer, and others were ascertained through screening of patients with breast cancer who were not selected on the basis of a positive family history. In instances in which *PALB2* testing was performed on a research basis, this was done with local institutional-review-board approval; family data were made anonymous before analysis for this project. Informed consent was obtained from participants in accordance with institutional-review-board policies and local practices at each participating center. Families with *PALB2* missense variants or with variants of uncertain pathogenicity were excluded from the study. The lists of participating centers and ascertainment criteria are provided in Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org.

### STATISTICAL ANALYSIS

The inheritance patterns of disease and genotypes in families were used to estimate the cancer risk conferred by *PALB2* loss-of-function mutations, with the use of modified complex-segregation-analysis methods.[10,11] Pedigree likelihoods were constructed with the use of the pedigree-analysis software Mendel, version 3.3,[12] and a maximum-likelihood approach was used to obtain parameter estimates.

For the main analysis, the phenotype of each female family member was defined by her age at breast-cancer diagnosis or, if she was unaffected, her age at last follow-up. Women were followed from 20 years of age until the age at diagnosis of breast, ovarian, or other cancer, age at death, age at last follow-up, or 80 years of age, whichever occurred first. For the analysis of breast-cancer risk, only women with a diagnosis of breast cancer (before a diagnosis of any other cancer) were assumed to be affected (see the Methods section in the Supplementary Appendix).

We used two main models of genetic susceptibility: a single-gene model in which all familial aggregation of breast cancer was assumed to be due to the *PALB2* loss-of-function mutations and a model in which genetic susceptibility to breast cancer was due to *PALB2* loss-of-function mutations and to a residual component representing other familial effects. Under each model, the incidence of breast cancer for person *i* was dependent on the underlying *PALB2* genotype and polygenotype (i.e., the genotype under the polygenic model) through a model of the form $\lambda_i(t) = \lambda_0(t) \exp[\beta(t) g_i + P_i]$, where $g_i = 0$ for persons without a *PALB2* mutation; $g_i = 1$ for carriers of a deleterious *PALB2* variant; $P_i$ is the residual familial component, assumed to be normally distributed with mean 0 and variance $\sigma_R^2$; and $\beta(t)$ is the age-specific log relative risk for carriers of a deleterious *PALB2* variant relative to the baseline breast-cancer incidence, $\lambda_0(t)$ (see the Methods section in the Supplementary Appendix). For all models allowing for a residual familial component, we constrained the sum of the variance in breast-cancer risk due to *PALB2* mutations and the residual variance, $\sigma_R^2$, to agree with external estimates of the total familial breast-cancer variance, $\sigma_P^2$, following the procedure described in detail elsewhere.[11] The total familial variance, $\sigma_P^2$, was assumed to be equal to 1.66, a value estimated in previous breast-cancer segregation analyses.[13,14]

Because families were ascertained in multiple ways, failure to adjust for the methods of ascertainment could have led to a biased estimation of cancer risk. To adjust for ascertainment, we used an ascertainment assumption–free approach[15-17] in which we evaluated each family separately. This involved dividing the data for each family into two components, one containing all the data potentially relevant to the ascertainment ($F_1$), and the other containing all the data not relevant to the ascertainment ($F_2$). For each family, we modeled the conditional likelihood, *L*, as being equal to $P(F_1, F_2)/P(F_1)$, where $P(F_1, F_2)$ is the probability of observing all data in the pedigree, and $P(F_1)$ is the probability of observing only data relevant to ascertainment in the pedigree (Table S2 in the Supplementary Appendix).

Specifically, for families identified through screening for *PALB2* mutations in population-based series of breast-cancer cases, we modeled the conditional likelihood of observing the phenotypes and genotypes in the families, given the *PALB2* mutation status, disease status, and age at diagnosis only of the index patient. For families identified through multiple affected members, we maximized the likelihood of observing the phenotypes and genotypes in the family, given all the disease phenotypes and the mutation status of the index family member. Family data contributed information to the analysis only if *PALB2* was genotyped in at least one family member in addition to the index patient. With this approach to adjustment for the method of ascertainment, 21 families that were ascertained through multiple affected members and in which no additional family members had been genotyped were excluded from the analysis. At some study centers, recruitment of families with multiple affected members was based on narrower criteria — for example, phenotypes of first-degree relatives or of first-degree and second-degree relatives only (Table S1 in the Supplementary Appendix). For these families, ascertainment adjustment was based on maximizing the likelihood of observing the phenotypes and genotypes in the family, given the disease phenotypes of relatives included in the ascertainment and the mutation status of the index family member.

Model parameters were expressed as the natural logarithm of the ratio of cancer incidence in *PALB2* mutation carriers relative to baseline cancer incidence. Parameters were estimated with the use of the maximum-likelihood method, and variances were obtained from the observed information matrix. All statistical tests were two-sided. A P value of 0.05 or less was considered to indicate statistical significance.

## RESULTS

### FAMILIES

Information was available from 175 families with at least one member who had breast cancer and a germline loss-of-function mutation in *PALB2*. After adjustment for ascertainment, 154 families were eligible for analysis. These 154 families included 311 women with *PALB2* mutations, of whom 229 had breast cancer (Table 1), and 51 men with *PALB2* mutations, of whom 7 had breast cancer. Among the 154 families, there were 48 different loss-of-function mutations in *PALB2* (Fig. 1A, and Table S3 in the Supplementary Appendix).

**Table 1. Breast and Ovarian Cancer among Female *PALB2* Mutation Carriers and Noncarriers and Untested Females, According to Age at Diagnosis or Data Censoring.**

| Age Group | *PALB2* Mutation Carriers | | | Tested Noncarriers | | | Untested | | |
|---|---|---|---|---|---|---|---|---|---|
| | Unaffected | Breast Cancer | Ovarian Cancer* | Unaffected | Breast Cancer | Ovarian Cancer* | Unaffected | Breast Cancer | Ovarian Cancer* |
| | *number of women* | | | | | | | | |
| <20 yr | 1 | 0 | 0 | 1 | 0 | 0 | 172 | 0 | 0 |
| 20–29 yr | 4 | 7 | 0 | 6 | 0 | 0 | 170 | 8 | 0 |
| 30–39 yr | 2 | 50 | 0 | 24 | 5 | 0 | 218 | 32 | 1 |
| 40–49 yr | 15 | 84 | 1 | 22 | 10 | 3 | 235 | 81 | 3 |
| 50–59 yr | 23 | 55 | 4 | 30 | 10 | 3 | 321 | 62 | 8 |
| 60–69 yr | 14 | 24 | 1 | 18 | 6 | 0 | 364 | 61 | 6 |
| 70–79 yr | 12 | 7 | 2 | 11 | 1 | 0 | 315 | 34 | 7 |
| ≥80 yr | 11 | 2 | 0 | 13 | 0 | 0 | 436 | 3 | 0 |
| Total | 82 | 229 | 8 | 125 | 32 | 6 | 2231 | 281 | 25 |

* This category includes all diagnosed cases of ovarian cancer (including those diagnosed after a breast-cancer diagnosis).

### RISK OF CANCER CALCULATED UNDER DIFFERENT MODELS

The risk of breast cancer for *PALB2* mutation carriers was increased by a factor of 9.47 (95% CI, 7.16 to 12.57), as compared with the breast-cancer incidence in the general population of the United Kingdom between 1993 and 1997, under a single-gene model of constant relative risk across all ages (Table S4 in the Supplementary Appendix). The corresponding mean cumulative risk of breast cancer by 70 years of age was estimated to be 47.5% (95% CI, 38.6 to 57.4). It initially appeared that the relative risk of breast cancer among *PALB2* mutation carriers was higher at younger ages, with a relative risk of 17.6 for mutation carriers 20 to 39 years of age, as compared with a relative risk of 8.7 for those 40 to 79 years of age; however, models allowing for age-specific relative-risk parameters did not fit the data significantly better than the model with a constant relative risk ($P=0.07$).

Models that accounted for residual familial aggregation of breast cancer, in addition to the aggregation attributable to *PALB2* loss-of-function mutations, provided a better fit to the data (Table S5 in the Supplementary Appendix). Moreover, a model including a background effect of familial factors on *PALB2* mutation–associated risk provided a significantly better fit ($P=0.04$) than did a model without modification of this risk (see the Supplementary Appendix). Such familial factors could include genetic, environmental, or lifestyle variables that are correlated among relatives.

We fitted models in which parameters were expressed in terms of the risk for breast cancer in *PALB2* mutation carriers relative to the baseline incidence (i.e., for non–mutation carriers with no residual familial component) and were assumed either to be constant with age or to vary with each decade of age (Table S5 in the Supplementary Appendix). When this relative-risk parameter was constant, it was estimated to be 9.07 (95% CI, 5.72 to 14.39). This model provided the best fit to the data. A model in which the risk relative to the baseline incidence was allowed to vary with age did not provide a significant improvement over the model with a constant relative risk ($P=0.40$) (Table S5 in the Supplementary Appendix).

Age-specific estimates of risk among *PALB2* mutation carriers, over all background familial effects and risk ratios relative to population incidences under the best-fitting model, are summarized in Table 2. For *PALB2* mutation carriers, the annual breast-cancer incidence increased with age, from 0.01% per year at 20 to 24 years of age to 1.60% per year at 50 to 54 years of age, then leveled off at approximately 1.4% per year thereafter. The relative risk associated with *PALB2*, averaged over all mutation carriers, was 8 to 9 up

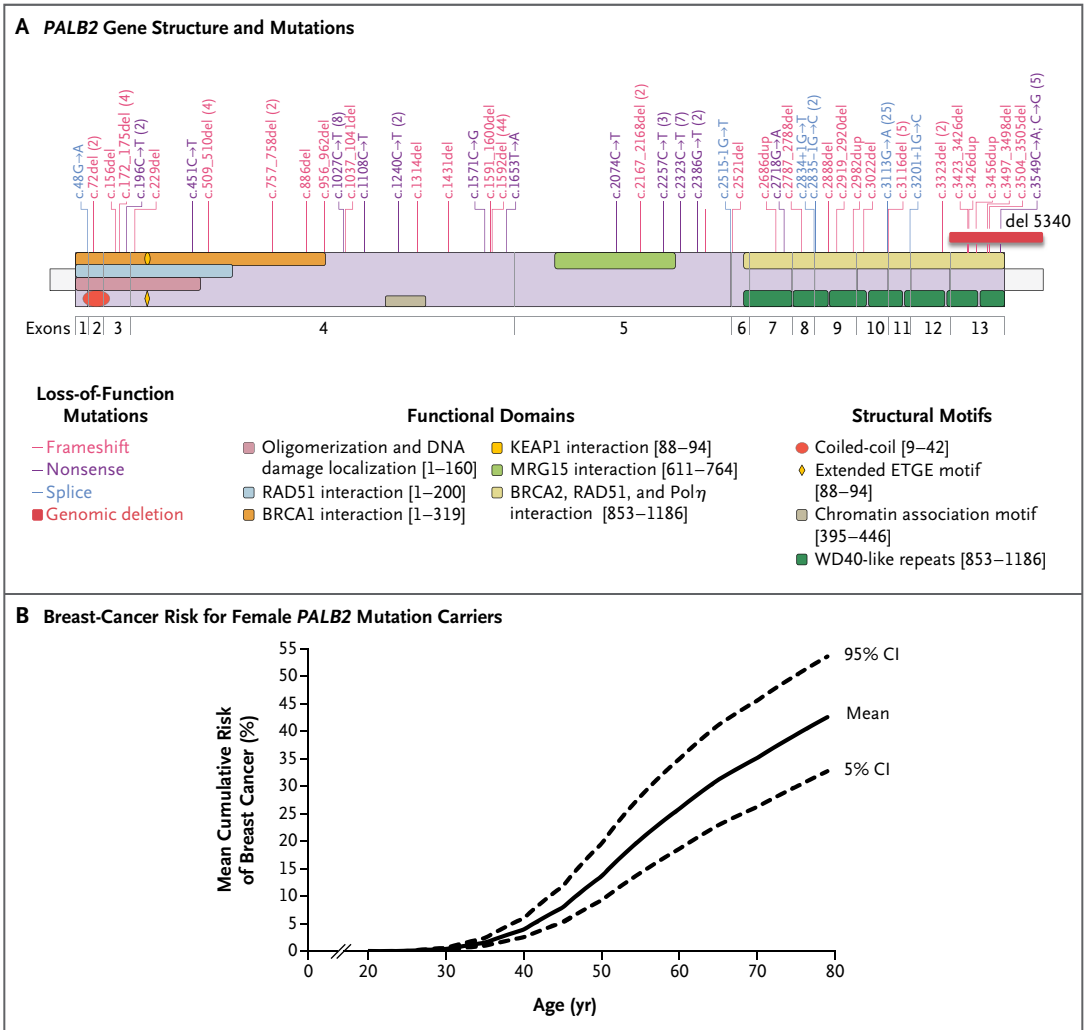


**Figure 1. Loss-of-Function *PALB2* Germline Mutations in Relation to Functional Domains and Structural Motifs of the PALB2 Protein, and Cumulative Breast-Cancer Risk for Female Mutation Carriers.**

Panel A is a schematic representation of the *PALB2* gene together with all deleterious variants reported in this study, superimposed on the exonic structure of the gene, with functional domains and structural motifs indicated. The number of families with a certain allele is shown in parentheses after the mutation; no such number is given for mutations present only in single families. Numbers in square brackets after functional domains and structural motifs denote amino acid positions. Note that the KEAP1 interaction functional domain is an extended ETGE motif. Panel B shows the mean cumulative risk of breast cancer for female *PALB2* mutation carriers and associated confidence intervals.

to 40 years of age, 6 to 8 between 40 and 60 years of age, and approximately 5 at 60 years of age or older (Table 2, and Fig. S1 in the Supplementary Appendix). The cumulative risk of breast cancer for female *PALB2* mutation carriers was estimated to be 14% (95% CI, 9 to 20) by 50 years of age and 35% (95% CI, 26 to 46) by 70 years of age (Fig. 1B).

Using the same approach, we estimated that the relative risk of ovarian cancer among *PALB2* mutation carriers was 2.31 (95% CI, 0.77 to 6.97; P=0.18). The relative risk of breast cancer for male *PALB2* mutation carriers, as compared with the male breast-cancer incidence in the general population, was estimated to be 8.30 (95% CI, 0.77 to 88.56; P=0.08). The risk of breast cancer

**Table 2. Estimated Age-Specific Relative Risk of Breast Cancer for Female *PALB2* Mutation Carriers under the Most Parsimonious Model.***

| Age Group | Annual Mean Breast-Cancer Incidence† | Mean Relative Risk (95% CI)‡ |
|---|---|---|
| | % | |
| 20–24 yr | 0.01 | 9.01 (5.70–14.16) |
| 25–29 yr | 0.07 | 8.97 (5.68–14.08) |
| 30–34 yr | 0.23 | 8.85 (5.63–13.78) |
| 35–39 yr | 0.50 | 8.54 (5.51–13.08) |
| 40–44 yr | 0.85 | 8.02 (5.29–11.95) |
| 45–49 yr | 1.27 | 7.31 (4.98–10.55) |
| 50–54 yr | 1.60 | 6.55 (4.60–9.18) |
| 55–59 yr | 1.45 | 5.92 (4.27–8.10) |
| 60–64 yr | 1.47 | 5.45 (4.00–7.33) |
| 65–69 yr | 1.19 | 5.10 (3.80–6.76) |
| 70–74 yr | 1.34 | 4.82 (3.63–6.33) |
| 75–79 yr | 1.34 | 4.56 (3.48–5.95) |

* The most parsimonious model allows for a constant risk ratio relative to the baseline breast-cancer incidence (applicable to those without a mutation and with no residual component) and equal residual and modifying variances.
† Values are the estimated mean breast-cancer incidence over all background familial effects.
‡ Relative risks are for the comparison of the mean breast-cancer incidence among *PALB2* mutation carriers (over all background familial effects) with the age-specific breast-cancer incidence in the U.K. population from 1993 to 1997.

among female *PALB2* mutation carriers was not significantly changed by including ovarian cancer or male breast cancer in the model.

### HORMONE-RECEPTOR AND HER2 STATUS

Breast-cancer estrogen-receptor status was available for 129 affected *PALB2* mutation carriers, and the tumors in 95 of the 129 (74%) were estrogen-receptor–positive; this frequency is similar to that seen among patients with *BRCA2* mutations[18] or with sporadic breast cancer. Additional information on progesterone-receptor and HER2 status was available for a total of 63 affected *PALB2* mutation carriers, 19 (30%) of whom had an estrogen-receptor–negative, progesterone-receptor–negative, and HER2-negative (triple-negative) phenotype, as compared with a frequency of triple-negative status that ranges from 12 to 17% among unselected patients with breast cancer.[19]

**Table 3. Estimated Relative Risk of Breast Cancer for Female *PALB2* Mutation Carriers in Earlier and Later Birth Cohorts.**

| Year of Birth | Relative Risk (95% Floated CI)* |
|---|---|
| Before 1940 | 1.00 (0.59–1.69) |
| 1940–1959 | 2.84 (1.64–4.93) |
| In 1960 or later | 6.29 (2.81–14.10) |

* Floated CIs allow for comparisons of the relative-risk estimates across all categories without the need to define a reference category. $P<0.001$ for heterogeneity, from the comparison of the model allowing for a single relative-risk parameter and the model with cohort-specific parameters.

### BIRTH COHORT AND COUNTRY OF RESIDENCE

We evaluated whether birth cohort or country of residence affected breast-cancer risk among *PALB2* mutation carriers. Carriers were divided into cohorts born before 1940, between 1940 and 1959, and in 1960 or later (Table 3). The relative risk of breast cancer among *PALB2* mutation carriers increased significantly as birth cohort became more recent ($P<0.001$). In contrast, we did not find evidence of differences in the relative-risk estimates for *PALB2* mutation carriers according to country of residence ($P=0.11$) (Table S6 in the Supplementary Appendix).

### FAMILIAL VARIANCE

In our analyses, we assumed that the total familial variance was approximately 1.66, on the basis of previous estimates from breast-cancer segregation analyses.[13,14] This is equivalent to a risk of breast cancer for first-degree relatives of patients with breast cancer that is approximately 2.3 times as high as that in the general population, in line with estimates from large epidemiologic studies.[20] When the total familial variance was assumed to be 1.2, equivalent to an approximate familial relative risk of 1.8 for first-degree relatives, the mean breast-cancer risk for female *PALB2* mutation carriers by 70 years of age was estimated to be 36.9%. When the familial variance was assumed to be 2.0, equivalent to an approximate familial relative risk of 2.7, the corresponding mean breast-cancer risk was estimated to be 34.3%. Therefore, the mean penetrance estimates were not sensitive to assumptions about the total familial variance, provided these were in line with observed patterns of familial relative risks of breast cancer.

**Table 4. Risk of Breast Cancer for Female *PALB2* Mutation Carriers, According to Family History of Breast Cancer.**

| Age | Cumulative Risk (95% CI) | | | | |
|---|---|---|---|---|---|
| | Mean Estimate without Family History Taken into Account | Mother Unaffected at 50 Yr of Age, Maternal Grandmother Unaffected at 70 Yr of Age* | Mother with Breast Cancer at 35 Yr of Age* | Sister and Mother with Breast Cancer at 50 Yr of Age* | Mother and Maternal Grandmother with Breast Cancer at 50 Yr of Age* |
| | | | *percent* | | |
| 30 yr | 0.4 (0.3–0.7) | 0.3 (0.2–0.6) | 0.8 (0.5–1.1) | 0.9 (0.6–1.2) | 0.7 (0.5–1.0) |
| 35 yr | 2 (1.0–2.4) | 1 (0.9–2.2) | 3 (2–4) | 3 (2–4) | 3 (2–4) |
| 40 yr | 4 (3–6) | 3 (2–5) | 7 (5–10) | 8 (6–11) | 7 (5–9) |
| 45 yr | 8 (5–12) | 7 (5–11) | 14 (9–20) | 16 (12–21) | 13 (10–18) |
| 50 yr | 14 (9–20) | 13 (8–18) | 23 (16–31) | 27 (21–33) | 22 (17–29) |
| 55 yr | 20 (14–28) | 19 (13–26) | 33 (24–43) | 38 (30–45) | 32 (25–40) |
| 60 yr | 26 (19–35) | 24 (18–33) | 40 (31–51) | 46 (38–54) | 40 (32–48) |
| 65 yr | 31 (23–42) | 29 (22–39) | 47 (37–58) | 53 (45–61) | 46 (38–55) |
| 70 yr | 35 (26–46) | 33 (25–44) | 52 (41–63) | 58 (50–66) | 51 (42–60) |
| 75 yr | 40 (30–51) | 38 (28–48) | 57 (46–68) | 63 (55–71) | 56 (47–65) |
| 80 yr | 44 (34–55) | 41 (32–53) | 61 (50–72) | 67 (59–75) | 61 (51–69) |

* Data are predicted breast-cancer risks obtained from the most parsimonious model, which allows for the residual familial aggregation effects in *PALB2* mutation carriers and noncarriers.

## DISCUSSION

As clinical genetic testing for breast-cancer risk increasingly includes other genes in addition to *BRCA1* and *BRCA2*, it is important to have robust risk estimates for women who carry loss-of-function mutations in genes such as *PALB2*. We estimated the risk of breast cancer for *PALB2* mutation carriers, using data from 154 families with 362 members who had loss-of-function mutations in this gene. Under the best-fitting model, which included a residual familial component, the mean risk of breast cancer for female *PALB2* mutation carriers by 70 years of age was estimated to be 35% (95% CI, 26 to 46). Models that allowed for a residual familial component influencing risk fit the data significantly better than did models without a modifying component, which suggests that breast-cancer risk for *PALB2* mutation carriers is modified by other genetic or environmental factors that cluster in families, as shown previously for *BRCA1* and *BRCA2*.[10,21-23] Thus, the results suggest that no single set of penetrance estimates applies to all *PALB2* mutation carriers; the risk of breast cancer associated with *PALB2* will also depend on genotypes at other modifying loci or on other familial factors.[24] Until such modifiers of risk are identified, our model allows for *PALB2*-associated breast-cancer risk to be computed on the basis of both genotype and family history.

The cumulative risk estimates for female *PALB2* mutation carriers, calculated with the use of different assumptions about family history of breast cancer, are shown in Table 4. By 70 years of age, breast-cancer risk ranged from 33% (95% CI, 25 to 44) for a female carrier with no affected relatives to 58% (95% CI, 50 to 66) for a female carrier with two first-degree relatives who had breast cancer diagnosed by 50 years of age. Such differences in risk are consistent with previous observations,[25] and it is possible that family history and *PALB2* genotype should be considered together in determining the risk level and appropriate management.

On the basis of our mean risk estimates and an assumed *PALB2* mutation carrier frequency of 0.08% (see the Supplementary Appendix), *PALB2* loss-of-function mutations are estimated to account for approximately 2.4% of the familial aggregation of breast cancer. However, this estimate is very imprecise, since it depends critically on the assumed *PALB2* mutation frequency, for which data are currently scarce. Moreover, *PALB2* mutation frequency, and therefore the contribution of

such mutations to familial aggregation, varies widely across populations.

In contrast, a consistent finding across populations is that breast-cancer risk among *PALB2* mutation carriers is significantly higher for women from more recent birth cohorts, a finding that has also been reported for carriers of loss-of-function mutations in *BRCA1* and *BRCA2*.[26-28] Even though we used calendar period–specific and cohort-specific incidences in our analyses, thus allowing for changes in breast-cancer incidence over time, this observation may be partly accounted for by changes in surveillance methods, specifically for women with a strong family history of breast cancer. Although it appeared that there were differences in the *PALB2*-associated relative risks of breast cancer according to country, these differences were not significant in the present sample. Future large studies of *PALB2* mutation carriers, ideally including prospective cohorts, will be needed to further characterize cancer risks conferred by *PALB2* mutations, to assess the role of factors such as lifestyle and hormone use on the breast-cancer risk of *PALB2* mutation carriers, and to investigate differences according to country of origin or specific *PALB2* mutations.

Our analysis included both families that were carefully selected through screening of families with multiple members who had breast cancer and families identified through population-based studies of patients with breast cancer. All our analyses were corrected for the methods of ascertainment, in order to preclude bias in risk estimates caused by the inclusion of families with multiple cases. We recognize the variation and uncertainty in modes of ascertainment of families among different centers. Modeling likelihood as conditional on family history will reduce bias but can reduce the precision of estimates. It is expected that inclusion of data from more carrier families over time will improve precision.

The large number of families and confirmed *PALB2* mutation carriers in our study offers additional precision in estimating breast-cancer risk. Loss-of-function mutations in *PALB2* confer a higher risk of breast cancer than do loss-of-function mutations in other genes for which there are good risk estimates, notably *CHEK2* 1100delC[29] and *ATM*.[30-32] On the basis of our estimates, the breast-cancer risk for a *PALB2* mutation carrier, even in the absence of a family history of breast cancer, would be classified as high according to various guidelines.[33,34] This level of risk may justify adding *PALB2* to genetic testing for *BRCA1* and *BRCA2*.

On the basis of our estimates of risk, women with loss-of-function mutations in *PALB2* should be studied to determine whether enhanced surveillance for breast cancer, in line with that offered to women with mutations in *BRCA2*, can influence outcomes. Risk-reducing surgical options could also be tested. We found a nonsignificant increase, by a factor of 2.3, in the risk of ovarian cancer for *PALB2* carriers. The question of whether loss-of-function mutations in *PALB2* confer a predisposition to ovarian cancer will require larger studies to address. We also estimated that the risk of breast cancer for male *PALB2* mutation carriers is increased by a factor of 8, which is consistent with previous reports,[7,35,36] but the confidence interval for this estimate was very large. *PALB2* loss-of-function mutations have been shown to confer a predisposition to pancreatic cancer,[37,38] but the lifetime risk in carriers has yet to be quantified.

Our study includes most of the reported families with *PALB2* mutation carriers, as well as many not previously reported, but it is still based on small numbers. Because of the widespread availability of multigene panels and whole-exome sequencing, screening for inherited loss-of-function mutations in *PALB2* has begun to enter clinical practice. As families with *PALB2* mutations are identified, it will be valuable to collect family history and other data for future analysis, in order to refine estimates of the cancer risks for *PALB2* mutation carriers.

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## APPENDIX

The authors' full names and academic degrees are as follows: Antonis C. Antoniou, Ph.D., Silvia Casadei, Ph.D., Tuomas Heikkinen, Ph.D., Daniel Barrowdale, B.Sc., Katri Pylkäs, Ph.D., Jonathan Roberts, B.Sc., Andrew Lee, Ph.D., Deepak Subramanian, M.B., B.Chir., Kim De Leeneer, Ph.D., Florentia Fostira, Ph.D., Eva Tomiak, M.D., Susan L. Neuhausen, Ph.D., Zhi L. Teo, Ph.D., Sofia Khan, Ph.D., Kristiina Aittomäki, M.D., Ph.D., Jukka S. Moilanen, M.D., Ph.D., Clare Turnbull, M.D., Ph.D., Sheila Seal, M.I.Biol., Arto Mannermaa, Ph.D., Anne Kallioniemi, M.D., Ph.D., Geoffrey J. Lindeman, F.R.A.C.P., Ph.D., Saundra S. Buys, M.D., Irene L. Andrulis, Ph.D., Paolo Radice, Ph.D., Carlo Tondini, M.D., Siranoush Manoukian, M.D., Amanda E. Toland, Ph.D., Penelope Miron, Ph.D., Jeffrey N. Weitzel, M.D., Susan M. Domchek, M.D., Bruce Poppe, M.D., Ph.D., Kathleen B.M. Claes, Ph.D., Drakoulis Yannoukakos, Ph.D., Patrick Concannon, Ph.D., Jonine L. Bernstein, Ph.D., Paul A. James, M.B., Ch.B., Ph.D., Douglas F. Easton, Ph.D., David E. Goldgar, Ph.D., John L. Hopper, Ph.D., Nazneen Rahman, M.D., Ph.D., Paolo Peterlongo, Ph.D., Heli Nevanlinna, Ph.D., Mary-Claire King, Ph.D., Fergus J. Couch, Ph.D., Melissa C. Southey, Ph.D., Robert Winqvist, Ph.D., William D. Foulkes, M.B., B.S., Ph.D., and Marc Tischkowitz, M.D., Ph.D.

The authors' affiliations are as follows: Departments of Public Health and Primary Care (A.C.A., D.B., A.L., D.F.E.) and Oncology (D.F.E.), Centre for Cancer Genetic Epidemiology, Department of Oncology (D.F.E.), and Department of Medical Genetics and National Institute for Health Research Cambridge Biomedical Research Centre (M.T.), University of Cambridge, and the Department of Clinical Genetics, East Anglian Regional Genetics Service, Addenbrooke's Hospital (J.R., D.S., M.T.), Cambridge, and the Oncogenetics Team, Institute of Cancer Research and Royal Marsden National Health Service Foundation Trust, London (C.T., S.S., N.R.) — all in the United Kingdom; the Division of Medical Genetics, Department of Medicine, University of Washington, Seattle (S.C., M.-C.K.); the Department of Obstetrics and Gynecology, University of Helsinki and Helsinki University Central Hospital (T.H., S.K., H.N.), and the Department of Clinical Genetics, Helsinki University Central Hospital (K.A.), Helsinki, the Laboratory of Cancer Genetics and Tumor Biology, Department of Clinical Chemistry and Biocenter Oulu, University of Oulu, and the Laboratory of Cancer Genetics and Tumor Biology, Northern Finland Laboratory Center NordLab, Oulu University Hospital (K.P., R.W.), and the Department of Clinical Genetics, University of Oulu and Oulu University Hospital (J.S.M.), Oulu, Biocenter Kuopio and Cancer Center of Eastern Finland, University of Eastern Finland, Kuopio (A.M.), and the Institute of Biomedical Technology–Cancer Genomics, University of Tampere, Tampere (A.K.) — all in Finland; the Center for Medical Genetics, Ghent University Hospital, Ghent, Belgium (K.D.L., B.P., K.B.M.C.); the Molecular Diagnostics Laboratory, Institute of Nuclear and Radiologic Sciences and Technology, Energy and Safety, National Center for Scientific Research Demokritos, Athens (F.F., D.Y.); the Department of Genetics, Eastern Ontario Regional Genetics Program, Children's Hospital of Eastern Ontario, Ottawa (E.T.), Samuel Lunenfeld Research Institute, Mount Sinai Hospital, Toronto (I.L.A.), and the Program in Cancer Genetics, Departments of Human Genetics and Oncology, Lady Davis Institute, and Research Institute, McGill University Health Centre, McGill University, Montreal (W.D.F.) — all in Canada; the Department of Population Sciences, Beckman Research Institute (S.L.N.), and the Division of Clinical Cancer Genetics (J.N.W.), City of Hope, Duarte, CA; the Genetic Epidemiology Laboratory, Department of Pathology, University of Melbourne (Z.L.T., M.C.S.), Familial Cancer Centre, Royal Melbourne Hospital (G.J.L.), and Stem Cells and Cancer Division, Walter and Eliza Hall Institute of Medical Research (G.J.L.), Parkville, and the Familial Cancer Centre, Peter MacCallum Cancer Centre (P.A.J.), and the Centre for Molecular, Environmental, Genetic and Analytic Epidemiology, University of Melbourne (J.L.H.), Melbourne — all in Australia; the Huntsman Cancer Institute, University of Utah School of Medicine, Salt Lake City (S.S.B., D.E.G.); the Unit of Molecular Bases of Genetic Risk and Genetic Testing (P.R.) and the Unit of Medical Genetics (S.M.), Department of Preventive and Predictive Medicine, Fondazione Istituto di Ricovero e Cura a Carattere Scientifico, Istituto Nazionale dei Tumori Milano, and Istituto di Oncologia Molecolare della Fondazione Italiana Ricerca sul Cancro (P.P.), Milan, and the Unit of Medical Oncology, Azienda Ospedaliera Papa Giovanni XXIII, Bergamo (C.T.) — all in Italy; the Department of Molecular Virology, Immunology and Medical Genetics, Ohio State University, Columbus (A.E.T.), and Department of Genetics and Genome Sciences, Case Western Reserve University Medical School, Cleveland (P.M.); Basser Research Center, Abramson Cancer Center, University of Pennsylvania, Philadelphia (S.M.D.); the Genetics Institute and Department of Pathology, Immunology and Laboratory Medicine, University of Florida, Gainesville (P.C.); the Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York (J.L.B.); and the Departments of Health Sciences Research and Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN (F.J.C.).

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