Breast, Colorectal, and Pancreatic Cancer Mortality With Pathogenic Variants in *ATM*, *CHEK2*, or *PALB2*

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ABSTRACT

PURPOSE Oncologists encounter patients with pathogenic variants (PVs) in *ATM*, *CHEK2*, or *PALB2*, but little is known about their cancer mortality.

METHODS Patients who were 20 years or older, diagnosed in 2013-2019 with breast, colorectal, or pancreatic cancer, and reported to SEER registries in California and Georgia were linked to germline genetic testing results from four clinical laboratories and followed through 2021. Multivariable models of cancer mortality were fit; for each cancer, the reference group was the average hazard across all genetically tested patients with that diagnosis. Each cancer was modeled separately, followed by a single model that interacted the cancer type with all covariates. In addition to fixed effects models, random effects models were used as a regularization approach to reduce overfitting.

RESULTS A total of 70,272 tested patients with breast (48,473 estrogen receptor–/progesterone receptor–positive, human epidermal growth factor receptor 2 (HER2)–negative; 9,957 HER2-positive; 11,842 triple-negative) cancer, 5,822 with colorectal cancer, and 1,861 with pancreatic cancer were analyzed; the mean follow-up was 3.9 years. Patients with *ATM*, *CHEK2*, or *PALB2* PVs had no differences in breast, colorectal, or pancreatic cancer mortality. Patients with *ATM* PVs in triple-negative breast cancer appeared to have higher mortality in fixed effects models (hazard ratio [HR], 3.7 [95% CI, 1.8 to 7.8]), but not in random effects models (HR, 1.2 [95% CI, 0.8 to 1.6]) that reduce overfitting. Patients with *BRCA1/2* PVs had lower triple-negative breast cancer mortality in both models (fixed HR, 0.6 [95% CI, 0.5 to 0.9], random HR, 0.7 [95% CI, 0.6 to 0.8]). Patients with Lynch syndrome gene PVs had lower colorectal cancer mortality in both models (fixed HR, 0.5 [95% CI, 0.4 to 0.8], random HR, 0.7 [95% CI, 0.5 to 0.9]).

CONCLUSION Patients with *ATM*, *CHEK2*, or *PALB2* PVs had similar breast, colorectal, and pancreatic cancer mortality to the average genetically tested patient with their cancer type.

ACCOMPANYING CONTENT

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INTRODUCTION

Germline genetic testing is increasingly important for cancer management and includes many cancer-associated genes.[1-3] Inherited pathogenic variants (PVs) inform cancer treatment, surveillance, and testing of relatives. Patients want to know whether a PV increases their chance of cancer death and clinicians need to know how to counsel them. This is particularly urgent for PVs in less well-characterized genes.

Three genes in which PVs are often detected are *ATM*, increasing risk of breast, pancreatic, and potentially colorectal cancers; *CHEK2*, increasing risk of breast and potentially other cancers; and *PALB2*, increasing risks of breast, pancreatic, and potentially other cancers.[4-7] While *CHEK2* PVs were associated with colorectal cancer risk in previous studies, recent studies have questioned this association and consensus is lacking.[8] *ATM*, *CHEK2*, or *PALB2* PVs account for approximately 3% of breast cancer cases, representing nearly half of clinically meaningful PVs detected on germline testing.[9] Yet, little is known about cancer mortality with these PVs. Although previous studies demonstrated lower breast, ovarian, and pancreatic cancer mortality with *BRCA1/2* PVs[10-12] and lower colorectal cancer mortality with Lynch syndrome gene PVs,[13] studies of *CHEK2* PV-associated breast cancer mortality had mixed results.[14,15]

CONTEXT

Key Objective

Do patients with germline pathogenic variants (PVs) in *ATM*, *CHEK2*, or *PALB2* have higher mortality from breast, colorectal, or pancreatic cancer?

Knowledge Generated

In a population-based sample of 77,955 patients with genetically tested cancer, those with *ATM, CHEK2*, or *PALB2* PVs had no worse mortality from breast, colorectal, or pancreatic cancer than the average genetically tested patient with each cancer type.

Relevance *(S.B. Wheeler)*

Although mortality after breast, colorectal, and pancreatic cancer was similar among people with examined PVs, results apply only to the tested population in the two states examined, and given the known selection in genetic testing, caution is needed in inferring generalizability across all populations.

*Relevance section written by *JCO* Associate Editor Stephanie B. Wheeler, PhD, MPH.

We studied cancer-specific mortality in a population-based cohort of all adults diagnosed in 2013-2019 with breast, colorectal, or pancreatic cancer in Georgia or California who had germline testing results from one of four participating laboratories. Our hypothesis was that patients with *ATM*, *CHEK2*, or *PALB2* PVs have no difference in cancer-specific mortality compared with the average risk for genetically tested patients with each cancer type.

METHODS

All adults diagnosed with stage 0-IV breast, colorectal, or pancreatic cancer from January 1, 2013, to December 31, 2019, and reported to SEER registries in California (Los Angeles Cancer Surveillance Program, Greater Bay Area Cancer Registry, and Cancer Registry of Greater California) and Georgia (Georgia Cancer Registry) were linked to germline testing results from four laboratories (Ambry Genetics, Aliso Viejo, CA; GeneDx, Gaithersburg, MD; Invitae, San Francisco, CA; Myriad Genetics, Salt Lake City, UT) that performed most such testing.[1,2,10] Results were provided at the gene level, per the interpretation sent to the ordering clinician: PV or likely PV (categorized as positive), variant of uncertain significance, and benign or likely benign (categorized as negative). A list of tested genes was published previously[2] (Table 1). Genes considered were *ATM*, *CHEK2*, and *PALB2* and, for comparison, *BRCA1/2* (combined for primary analysis) and Lynch syndrome genes (*MLH1*, *MSH2*, *MSH6*, *PMS2*, and *EPCAM*); PVs in any other gene were combined as other. Lynch syndrome genes were analyzed together because while *MLH1* and *MSH2* PVs are associated with greater risk of developing and earlier age of onset of colorectal cancer compared with *MSH6* and *PMS2* PVs, there is no evidence that the genes have a differential impact on colorectal cancer subtype or tumor biology. Exclusion criteria were age <20 years, >1 primary cancer, or diagnosed on death certificate; patients tested >6 months postdiagnosis were excluded to avoid immortal time bias. The analytic data set combined genetic testing results from 2012 through the first quarter of 2021 with SEER variables and was stripped of protected health information, as previously described.[1,2,10] Institutional review boards associated with the SEER registries granted a complete waiver of Health Insurance Portability and Accountability Act authorization and informed consent and approved the study.

Covariates were selected on the basis of known relationships to cancer mortality, including social determinants of health, tumor biologic features, and treatments (additional information about variable selection and other details of the analysis are available at a GitHub repository).[16] Registries provided age, race, ethnicity, census tract poverty, insurance, marital status, tumor stage and grade, breast cancer subtype defined by estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) expression (ER-/PR-positive, HER2-negative, HER2-positive, or triple-negative), and colon or rectum site. Registries provided first-course treatment including surgery, chemotherapy, radiotherapy, and HER2-directed therapy. SEER data on overall, cancer-specific, and other-cause mortality were available through December 31, 2021; patients alive then and patients who died of other cancer or noncancer causes were censored.

Separate models were estimated for five cancer types (three breast cancer subtypes, colorectal and pancreatic cancers). Given multiple comparisons and heterogeneity in PV group sizes, we presented gene group estimates as fixed effects (dummy variables) and empirical Bayes estimates from a gamma frailty model.[17] This frailty model proposes that gene groups are drawn from a population of genes whose mortality effects follow a gamma distribution. This strategy obtains more stable predictions and reduces overfitting. Both fixed and random coefficients are centered around zero: hazard ratios (HRs) represent a comparison with a

TABLE 1. Patient Genetic and Demographic Characteristics

Characteristic	Breast Cancer, Triple-Negative, No. (%)	Breast Cancer, HER2-Positive, No. (%)	Breast Cancer, ER/PR-Positive, HER2-Negative, No. (%)	Colorectal Cancer, No. (%)	Pancreatic Cancer, No. (%)
Genetic testing result					
Negative	7,751 (65.5)	6,832 (68.6)	33,616 (69.4)	3,467 (59.6)	1,032 (55.5)
ATM PV	36 (0.3)	108 (1.1)	397 (0.8)	46 (0.8)	49 (2.6)
CHEK2 PV	67 (0.6)	208 (2.1)	722 (1.5)	48 (0.8)	23 (1.2)
PALB2 PV	128 (1.1)	45 (0.5)	344 (0.7)	9 (0.2)	15 (0.8)
BRCA1 PV	922 (7.8)	141 (1.4)	646 (1.3)	11 (1.1)	23 (1.7)
BRCA2 PV	432 (3.4)	210 (2.1)	1,333 (2.8)	4 (0.4)	66 (4.9)
Lynch syndrome[a] PV	47 (0.4)	25 (0.3)	208 (0.4)	661 (11.4)	15 (0.8)
Other gene[b] PV	381 (3.2)	300 (3.0)	1,401 (2.9)	309 (5.3)	152 (8.2)
VUS only	2,110 (17.8)	2,090 (21.0)	9,811 (20.2)	1,194 (20.5)	473 (25.4)
Sex					
Female	11,842 (100.0)	9,957 (100.0)	48,473 (100.0)	3,146 (54.0)	1,004 (54.0)
Male	0 (0.0)	0 (0.0)	0 (0.0)	2,675 (46.0)	857 (46.1)
Race and ethnicity					
Non-Hispanic White	6,060 (51.2)	5,454 (54.8)	29,728 (61.3)	3,397 (58.3)	1,226 (65.9)
Black	2,083 (17.6)	1,154 (11.6)	4,712 (9.7)	535 (9.2)	139 (7.5)
Asian	1,105 (9.3)	1,343 (13.5)	5,817 (12.0)	587 (10.1)	226 (12.1)
Hispanic	2,415 (20.4)	1,924 (19.3)	7,746 (16.0)	1,243 (21.4)	261 (14.0)
Other	181 (1.5)	81 (0.8)	470 (1.0)	60 (1.0)	10 (0.5)
Age at diagnosis, years					
<45	3,532 (29.8)	4,300 (43.2)	14,028 (28.9)	2,101 (36.1)	173 (9.3)
46-55	3,672 (31.0)	2,791 (28.0)	14,009 (28.9)	1,620 (27.8)	276 (14.8)
56-65	2,834 (23.9)	1,727 (17.3)	10,553 (21.8)	965 (16.6)	532 (28.6)
≥66	1,804 (15.2)	1,139 (11.4)	9,879 (20.4)	1,136 (19.5)	881 (47.3)
Census tract poverty level					
Low (<10%)	8,108 (68.5)	7,019 (70.5)	34,988 (72.2)	3,919 (67.3)	1,372 (73.7)
Medium (10%-19%)	2,534 (21.4)	2,048 (20.6)	9,656 (19.9)	1,312 (22.5)	343 (18.4)
High (≥20%)	1,200 (10.1)	890 (8.9)	3,829 (7.9)	591 (10.2)	147 (7.9)
Urban or rural					
Urban	11,053 (93.3)	9,346 (93.9)	45,739 (94.4)	5,424 (93.2)	1,729 (92.9)
Rural	787 (6.7)	611 (6.1)	2,734 (5.6)	398 (6.8)	132 (7.1)
Marital status					
Not married	4,865 (41.1)	3,710 (37.3)	17,790 (36.7)	2,290 (39.3)	591 (31.8)
Married or partnered	6,977 (58.9)	6,247 (62.7)	30,683 (63.3)	3,532 (60.7)	1,270 (68.2)

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TABLE 1. Patient Genetic and Demographic Characteristics (continued)

Characteristic	Breast Cancer, Triple-Negative, No. (%)	Breast Cancer, HER2-Positive, No. (%)	Breast Cancer, ER/PR-Positive, HER2-Negative, No. (%)	Colorectal Cancer, No. (%)	Pancreatic Cancer, No. (%)
State					
California	8,621 (72.8)	7,381 (74.1)	36,810 (75.9)	4,473 (76.8)	1,515 (81.4)
Georgia	3,221 (27.2)	2,576 (25.9)	11,663 (24.1)	1,349 (23.2)	346 (18.6)

NOTE. Includes characteristics of 77,955 patients diagnosed with breast, colorectal, or pancreatic cancer and linked to germline genetic testing results, Georgia and California, 2013-2019.
Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PR, progesterone receptor; SD, standard deviation; PV, pathogenic variant; VUS, variants of uncertain significance in any tested gene.

[a]Lynch syndrome genes: *MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM*.

[b]Other genes clinically tested in patients and reported by participating laboratories, in alphabetical order: *AIP*, *AKT1*, *ALK*, *APC*, *AXIN2*, *BAP1*, *BARD1*, *BLM*, *BMPR1A*, *BUB1B*, *BRIP1*, *CASR*, *CDC73*, *CDH1*, *CDK4*, *CDKN1B*, *CDKN1C*, *CDKN2A*, *CEBPA*, *CFTR*, *CPA1*, *CTC*, *CTNNA1*, *CTR9*, *CTRC*, *DICER1*, *DISL3*, *DKC1*, *EGFR*, *EGLN1*, *FAM175A*, *FANCC*, *FANCM*, *FH*, *FLCN*, *GALNT12*, *GATA2*, *GREM1*, *HOXB13*, *KIF1B*, *KIT*, *LZTR1*, *MAX*, *MEN1*, *MET*, *MITF*, *MLH3*, *MRE11A*, *MSH3*, *MUTYH*, *NBN*, *NF1*, *NF2*, *NTHL1*, *PALLD*, *PDGFRA*, *PHOX2B*, *POLD1*, *POLE*, *POT1*, *PRKAR1A*, *PRSS1*, *PTCH1*, *PTEN*, *RAD50*, *RAD51C*, *RAD51D*, *RB1*, *RECQL*, *RET*, *RINT1*, *RNF43*, *RPS20*, *RTEL1*, *RUNX1*, *SDHA*, *SDHAF1*, *SDHB*, *SDHC*, *SDHD*, *SMAD4*, *SMARCA4*, *SMARCB1*, *SMARCE1*, *SPINK1*, *SPRED1*, *STK11*, *SUFU*, *TERC*, *TERT*, *TMEM127*, *TP53*, *TSC1*, *TSC2*, *VHL*, *WT1*, *XRCC2*.

hypothetical person with the average hazard across all observed genetic testing results, holding other covariates constant. The Commenges-Anderson score test of homogeneity gave similar results (additional details are available at GitHub).[16] Fixed effects estimates were similar in supplemental analyses: (1) using multiple imputation, because of missing data >5% for some variables (notably grade); (2) assuming other-cause death represented a competing risk rather than a censoring event; (3) using a time-varying covariate for survival after March 2020, when the COVID-19 pandemic might have altered the cause of death reporting; and (4) using patients who tested negative as the comparator group (Data Supplement, Table S1, online only).

RESULTS

A total of 70,272 patients with breast cancer (11,842 triple-negative, 9,957 HER2-positive, and 48,473 ER-/PR-positive, HER2-negative), 5,822 with colorectal cancer (4,147 colon, 1,675 rectum), and 1,861 with pancreatic cancer met inclusion criteria. Table 1 shows genetic and demographic features and survival by cancer type. Table 2 shows tumor features and treatment and survival by cancer type.

HRs with 95% CIs for cancer-specific mortality with likelihood ratio tests for heterogeneity are shown in Figure 1. In random effects models, patients with *ATM*, *CHEK2*, or *PALB2* PVs had no difference in mortality hazard (relative to the average hazard across patients with all observed genetic testing results) for triple-negative, HER2-positive, ER-/PR-positive, HER2-negative breast cancer; colorectal cancer; or pancreatic cancer. The impact of estimate regularization to reduce overfitting is seen with *ATM* PVs in triple-negative breast cancer, where the hazard ratio (HR) was 3.7 (95% CI, 1.8 to 7.8) in the fixed effects model, but only 1.2 (95% CI, 0.8 to 1.6) in the random effects model. The fixed effects estimate was based on few observations (n = 36) and likely reflects overfitting. The only PVs with HRs different from the average hazard were in *BRCA1/2* (analyzed separately as *BRCA1* and *BRCA2*, Data Supplement, Table S2) in triple-negative breast cancer (HR, 0.6 [95% CI, 0.5 to 0.9]) and Lynch syndrome genes in colorectal cancer (HR, 0.5 [95% CI, 0.4 to 0.8]). *BRCA1/2* and Lynch syndrome gene PVs had similar estimates in fixed and random effects models.

DISCUSSION

To our knowledge, this is the first population-based study of cancer mortality in patients with *ATM, CHEK2*, or *PALB2* PVs across breast, colorectal, and pancreatic cancers. The results suggest that people with *ATM*, *CHEK2*, or *PALB2* PVs have similar breast, colorectal, and pancreatic cancer mortality hazard when compared with the overall hazard for patients with those cancer types.

Previous studies of the best-known cancer susceptibility syndromes—hereditary breast and ovarian cancer, because of *BRCA1/2* PVs, and Lynch syndrome—reported lower mortality in PV carriers.[10,11,13] For *BRCA1/2* PVs, this is attributed to chemosensitivity, initially thought to be platinum-specific, but shown in the INFORM trial to encompass doxorubicin and cyclophosphamide.[18] For Lynch syndrome, this has been attributed to superior tumor-associated immune response.[13] Our findings support the previous work. We observed lower HRs for patients with triple-negative breast cancer and *BRCA1/2* PVs and with colorectal cancer and Lynch syndrome gene PVs, compared with the average hazards for patients with these diagnoses. By contrast, there was little evidence for HRs different from 1.0 for *ATM, CHEK2*, or *PALB2* PVs, suggesting similar biology to sporadic tumors for the cancers investigated; however, longer follow-up time will enable further characterization.

The current findings also illustrate the value of using robust statistical methods that identify and attempt to reduce overfitting. We observed higher triple-negative breast cancer mortality with *ATM* PVs in a fixed effects model, but not in a random effects model that offered more stable estimates, as one of several statistical approaches labeled as regularization methods. Overfitting is recognized in genome-wide association studies[19] and is also relevant in more targeted investigations of gene-outcome relationships. Accordingly, overfitting may explain some associations reported by previous studies between PVs and cancer-specific mortality.

The present results should be viewed in the context of survival rates for the cancers investigated. Five-year survival rates for breast cancer are 31% for metastatic versus 86%-99% for nonmetastatic disease.[20] Metastatic recurrence and death are more common during the 5 years postdiagnosis with triple-negative and HER2-positive than with ER/PR-positive, HER2-negative breast cancer, for which recurrence risk extends decades after diagnosis.[21] Five-year survival rates for colorectal cancer are 14% for metastatic versus 73%-91% for nonmetastatic disease, and those for pancreatic cancer are 3% for metastatic versus 16%-44% for nonmetastatic disease.[20] Fewer than 6% of patients with breast cancer in this study had de novo metastatic disease, versus 21% with colorectal cancer and 44% with pancreatic cancer.

This study has limitations. Results were from two states. Survival was censored after 2021, yielding shorter follow-up time for patients with more recent diagnoses. Because of concerns about patient identifiability, sequence data were not included in the genetic results provided by participating laboratories. Data regarding microsatellite instability and mismatch repair status were not available. As in all studies of gene-outcome relationships, there are potential selection effects in terms of who received genetic testing. As we previously reported using the statewide population-based cancer registries of Georgia and California, genetic testing rates vary by cancer type, race, and ethnicity.[2] The current results are predictive comparisons that apply to the tested

TABLE 2. Tumor and Treatment Characteristics

Characteristic	Breast Cancer, Triple-Negative, No. (%)	Breast Cancer, HER2-Positive, No. (%)	Breast Cancer, ER/PR-Positive, HER2-Negative, No. (%)	Colorectal Cancer, No. (%)	Pancreatic Cancer, No. (%)
Year of diagnosis					
2013	1,346 (11.4)	1,065 (10.7)	4,809 (9.9)	365 (6.3)	50 (2.7)
2014	1,428 (12.1)	1,182 (11.9)	5,327 (11.0)	508 (8.7)	65 (3.5)
2015	1,606 (13.6)	1,435 (14.4)	6,040 (12.5)	640 (11.0)	98 (5.3)
2016	1,531 (12.9)	1,443 (14.5)	6,326 (13.1)	787 (13.5)	172 (9.2)
2017	1,666 (14.1)	1,479 (14.9)	6,825 (14.1)	943 (16.2)	200 (10.7)
2018	1,972 (16.7)	1,554 (15.6)	8,376 (17.3)	1,104 (19.0)	395 (21.2)
2019	2,293 (19.4)	1,799 (18.1)	10,766 (22.2)	1,475 (25.3)	882 (47.4)
Stage					
0	1,839 (15.5)	290 (2.9)	8,260 (17.0)	153 (2.6)	NR (NR)
I	3,286 (27.7)	4,184 (42.0)	25,179 (51.9)	1,159 (19.9)	303 (16.3)
II	4,430 (37.4)	3,682 (37.0)	10,362 (21.4)	1,448 (24.9)	403 (21.6)
III	1,832 (15.5)	1,230 (12.4)	3,461 (7.1)	1,861 (32.0)	337 (18.1)
IV	455 (3.8)	572 (5.7)	1,210 (2.5)	1,202 (20.6)	815 (43.8)
Grade					
1	384 (3.2)	477 (4.8)	12,625 (26.0)	792 (13.6)	394 (21.2)
2	2,103 (17.8)	3,824 (38.4)	24,047 (49.6)	3,955 (67.9)	864 (46.4)
3	9,237 (78.0)	5,619 (56.4)	11,586 (23.9)	963 (16.5)	600 (32.2)
4	118 (1.0)	38 (0.4)	215 (0.4)	113 (1.9)	NR (NR)
Colorectal primary site					
Colon	—	—	—	4,147 (71.2)	—
Rectum	—	—	—	1,675 (28.8)	—
Surgery (breast)					
Lumpectomy	4,085 (34.5)	3,146 (31.6)	23,189 (47.8)	—	—
Unilateral mastectomy	1,804 (15.2)	1,675 (16.8)	8,400 (17.3)	—	—
Bilateral mastectomy	2,016 (17.0)	1,879 (18.9)	8,740 (18.0)	—	—
Other	745 (6.3)	658 (6.6)	3,781 (7.8)	—	—
No surgery	3,194 (27.0)	2,598 (26.1)	4,358 (9.0)	—	—
Surgery (other)					
No	—	—	—	1,025 (17.6)	1,355 (72.8)
Yes	—	—	—	4,797 (82.4)	506 (27.2)
Chemotherapy					
No	3,544 (29.9)	1,639 (16.5)	33,126 (68.3)	2,480 (42.6)	236 (12.7)
Yes	8,298 (70.1)	8,318 (83.5)	15,347 (31.7)	3,342 (57.4)	1,625 (87.3)

(continued on following page)

TABLE 2. Tumor and Treatment Characteristics (continued)

Characteristic	Breast Cancer, Triple-Negative, No. (%)	Breast Cancer, HER2-Positive, No. (%)	Breast Cancer, ER/PR-Positive, HER2-Negative, No. (%)	Colorectal Cancer, No. (%)	Pancreatic Cancer, No. (%)
Radiation therapy					
No	10,356 (87.5)	8,937 (89.8)	32,273 (66.6)	4,988 (85.7)	1,684 (90.5)
Yes	1,486 (12.6)	1,020 (10.2)	16,200 (33.4)	834 (14.3)	177 (9.5)
HER2-directed therapy					
No	11,523 (97.3)	2,869 (28.8)	47,727 (98.5)	5,250 (90.2)	1,826 (98.1)
Yes	319 (2.7)	7,088 (71.2)	746 (1.5)	572 (9.8)	35 (1.9)
Died from cancer	1,436 (12.1)	482 (4.8)	1,727 (3.6)	952 (16.3)	1,085 (58.2)
Mean follow-up, days	1,406.4 (813.7)	1,522.9 (771.7)	1,481.5 (767.5)	1,210.9 (736.4)	510.3 (470.5)
2-year survival	10,735 (90.5)	9,734 (97.5)	47,462 (97.8)	4,034 (86.3)	630 (33.8)

NOTE. Includes characteristics of 77,955 patients diagnosed with breast, colorectal, or pancreatic cancer and linked to germline genetic testing results, Georgia and California, 2013-2019.
Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; NR, not reported because of small cell size, per SEER rules to reduce identifiability; PR, progesterone receptor; SD, standard deviation; PV, pathogenic variant; VUS, variants of uncertain significance in any tested gene.

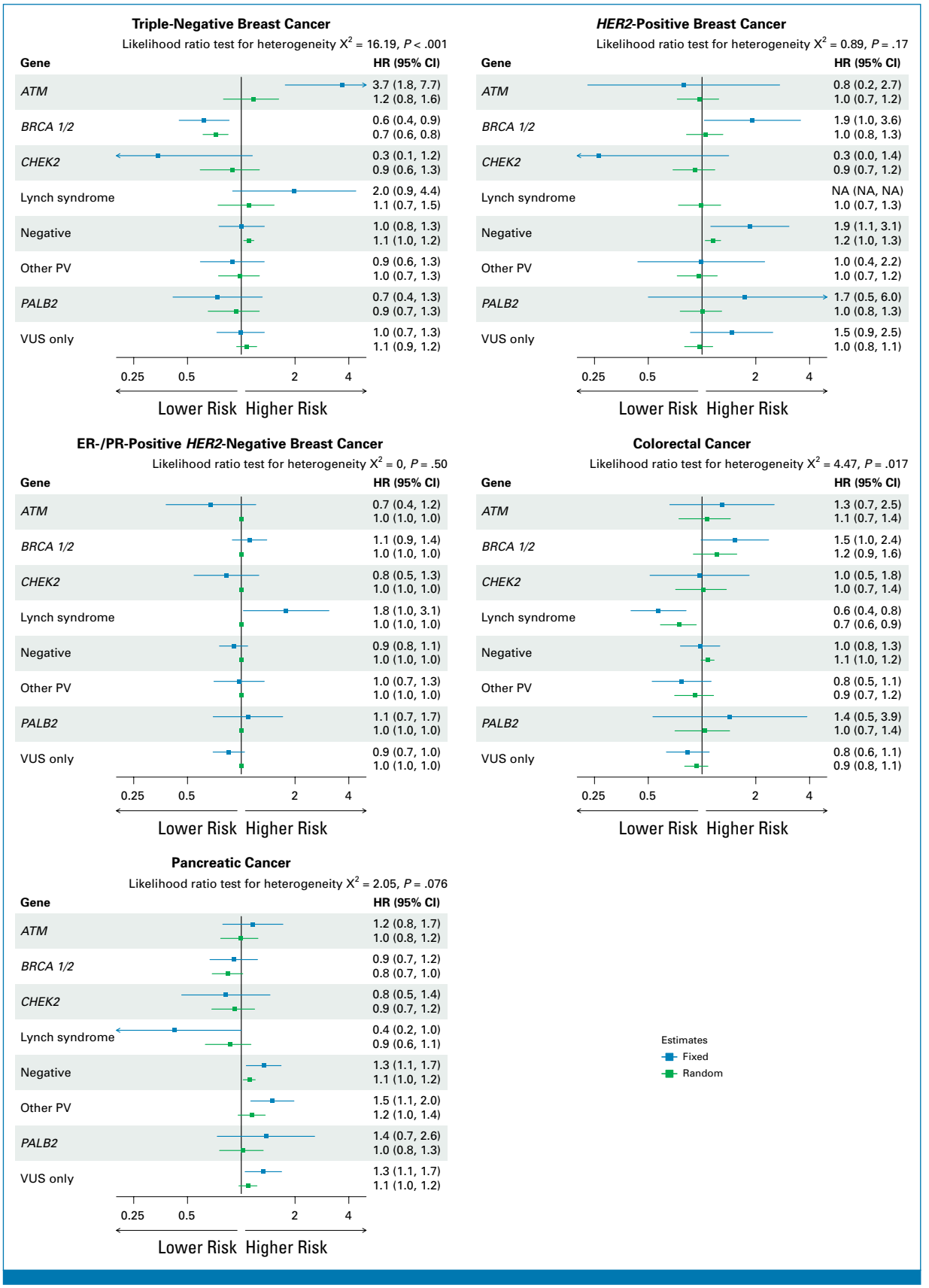

FIG 1. HRs for cancer-specific mortality by genetic testing results. Separate models were run for each cancer type (breast cancer: triple-negative, HER2-positive, and ER- and/or PR-positive and HER2-negative; colorectal cancer; and pancreatic cancer). Genetic testing results were (1) PVs in *ATM, CHEK2, PALB2, BRCA1, BRCA2* (*BRCA1/2*), Lynch syndrome genes (*MLH1, MSH2, MSH6, PMS2, EPCAM*), or other tested genes; (2) VUS in any tested gene; or (3) no PV or VUS in any tested gene. A gamma frailty model was used to

FIG 1. (Continued). estimate random and fixed coefficients, both of which were centered around zero; HRs for each cancer type represent comparison with a hypothetical person with that diagnosis and with the average hazard across all observed genetic testing results in the study population, holding other model covariates constant. For the random effects models, a likelihood ratio test of whether the gene group coefficients differ overall from the average hazard for each cancer is given at the top of the figure. ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; PV, pathogenic variant; VUS, variants of unknown significance.

population, and one should be cautious in generalizing beyond that population or if the tested population changes substantially.

This study's limitations are counterbalanced by considerable strengths: a diverse, contemporary, population-based sample representing a catchment area of 50 million people and the most complete population-based sample of genetically tested patients that exists to date; lifetime passive and active follow-up by SEER registries; and genetic data directly from testing laboratories. The results may reassure patients and inform clinical discussions about prognosis.

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DISCLAIMER

The National Cancer Institute, the US Centers for Disease Control and Prevention, and the California Department of Public Health had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.
The ideas and opinions expressed herein are those of the authors and do not necessarily reflect the opinions of the States of California or Georgia, the California or Georgia Departments of Public Health, the National Cancer Institute, and the US Centers for Disease Control and Prevention or their Contractors and Subcontractors.

EQUAL CONTRIBUTION

T.P.H. and A.W.K. contributed equally to this work.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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DATA SHARING STATEMENT

The GeneLink Study data set is under data use agreements between test industry partners and the University of Michigan that restrict access at this time to the participating scientists. The data set used for this study has been made available to the National Cancer Institute (NCI) and is available for request from the NCI's SEER Program website, following appropriate approvals.

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