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Risk of colorectal cancer for carriers of a germline mutation in *POLE* or *POLD1*

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Abstract

Background—Germline mutations in the exonuclease domains of the *POLE* and *POLD1* genes are associated with an as yet unquantified increased risk of colorectal cancer (CRC).

Methods—We identified families with *POLE* or *POLD1* variants by searching PubMed for relevant studies prior to October 2016 and by genotyping 669 population-based CRC cases diagnosed <60 years of age from the Australasian Colorectal Cancer Family Registry. We estimated the age-specific cumulative risks (penetrance) using a modified segregation analysis.

Results—We observed 67 CRCs (mean age at diagnosis=50.2 (standard deviation [SD]=13.8) years) among 364 first- and second- degree relatives from 41 *POLE* families and 6 CRCs (mean age at diagnosis=39.7 (SD=6.83) years) among 69 relatives from 9 *POLD1* families. We estimated risks of CRC to age 70 years (95% confidence interval [CI]) for males and females, respectively, to be: 40%(26%–57%) and 32%(20%–47%) for *POLE* mutation carriers; and 63%(15%–99%) and 52%(11%–99%) for *POLD1* mutation carriers.

Conclusion—CRC risks for *POLE* mutation carriers are sufficiently high warranting consideration of annual colonoscopy screening and management guidelines comparable to Lynch syndrome. Refinement of estimates of CRC risk for *POLD1* carriers is needed, however, clinical management recommendations could follow those suggested for *POLE* carriers.

Keywords

POLE; *POLD1*; Colorectal cancer; penetrance; polymerase proof reading associated polyposis

INTRODUCTION

Colorectal cancer (CRC) is a leading cause of cancer related mortality worldwide. Identifying people at high risk of developing CRC and optimising their screening can reduce the incidence of, and mortality from, CRC. Approximately 35% of CRC are estimated to be attributable to genetic factors [1], however, known hereditary CRC syndromes caused by high penetrance germline mutations account for only 3–5% of all CRCs [2]. In recent years, gene discovery efforts have identified several novel CRC susceptibility genes including rare germline variants within the polymerase proofreading domains of the *POLE* and *POLD1*

genes, which are reported to be associated with CRC and polyposis (referred to as polymerase proofreading-associated polyposis)[3–5]. These novel CRC susceptibility genes are now included on multigene sequencing panels for clinical testing but the age-specific cumulative risks (penetrance) of CRC for people who carry mutations in these genes have not yet been quantified, which is an impediment to optimising personalised clinical management. The aim of this study was to estimate the age-specific cumulative risks of CRC separately for male and female carriers of *POLE* and *POLD1* gene mutations.

METHODS

We searched in PubMed for relevant studies published prior to October 2016 that reported pedigree and cancer data for families with germline *POLE* or *POLD1* variants that were either novel or previously observed at population frequency of ≤0.002 according to the non-Finnish European population in the ExAC database[6], given recent evidence that shows low variant allele frequency is an important guide for determining disease causing variants[7]. Variants identified from the literature were re-annotated, for consistency, via *in silico* methods using Annovar[8] with default settings. We applied a criteria for predicting pathogenicity of missense variants in both genes as recommended by the American College of Medical Genetics and Genomics (ACMG),[9] namely using (i) multiple commonly used *in silico* tools (SIFT, PolyPhen2, MutationTaster, CADD, GERP, REVEL, and M-CAP (Table S1 for references)) and (ii) a high level of consensus between multiple *in silico* tools for prediction of deleterious effect. For this study, we applied the recommended or default thresholds for prediction of deleteriousness for each of the seven *in silico* tools (see Table S1 for thresholds). For each variant, the sum of *in silico* tools that reported the variant to be deleterious was calculated (maximum score of 7). A variant was considered to be likely pathogenic for this study where ≥4 out of 7 *in silico* tools predicted the variant to have a deleterious effect (Table S1). Families were excluded from the penetrance analysis if they were: (i) families of probands with variants not predicted to be pathogenic by <4 out of the 7 *in silico* tools used; (ii) discovery families that originally described the *POLE* c.1270C>G p.Leu424Val and *POLD1* c.1433G>A p.Ser478Asn variants[3]; (iii) families of carriers of *de novo* mutations; or (iv) uninformative due to missing information on sex or age at cancer diagnosis of probands. For those families included in the analysis, mutation carrier status, sex, cancer or polyp-affected status, age at cancer or polyp/polyposis diagnosis, last known age or death, and country of study of families were extracted, where possible, from identified studies.

We searched for *POLE* or *POLD1* mutation carrier families by genotyping 669 population-based probands diagnosed with CRC before 60 years of age from the Australasian Colorectal Cancer Family Registry (ACCFR)[10,11] (Table S2) for 17 rare germline variants within the exonuclease domains of the *POLE* and *POLD1* genes (Table S3 and Supplementary Materials and Methods). These 17 variants were selected based on multiple sources namely: 1) rare germline variants in the exonuclease domains of *POLE* and *POLD1* reported in the ExAC database (≤0.002 allele frequency), 2) variants identified from our in-house whole genome and whole exome sequencing studies of 100 multiple-case CRC-affected families from the clinic-based recruitment arm of the Australasian Colorectal Cancer Family Registry (ACCFR) that were either rare or novel variants according to ExAC

database (≤0.002 allele frequency), 3) were reported in the discovery paper by Palles et al[3], and 4) were predicted to be deleterious by ≥4 out of the 7 *in silico* tools.

Using data from both published studies and the ACCFR, we estimated the hazard ratio (HR) and corresponding 95% confidence interval (CI) of CRC for mutation carriers compared with the general population (based on age, sex- and country-specific incidences) and the age-specific cumulative risks (penetrance), using a modified segregation analysis that incorporated data of all family members whether genotyped or not, and whether affected or not. We properly adjusted for ascertainment of families in which each pedigree's data was conditioned on the proband's genotype, cancer status and age at diagnosis (for population-based families) or on the proband's genotype, and the cancer statuses and ages at diagnoses of all family members (for clinic-based families) to produce unbiased estimates (see details in Supplementary Materials and Methods). All statistical tests were two-sided, and *P*-values less than 0.05 were considered statistically significant.

RESULTS

From the literature, we identified 15 studies reporting 37 rare variants (MAF ≤0.002) within the exonuclease domains of *POLE* and *POLD1*. Of these 37 variants, 32 were predicted to be pathogenic by *in silico* criteria (Table S1). Of the 89 families with *POLE* (n=70) or *POLD1* (n=19) mutations, 42 were excluded (7 families with variants not predicted to be pathogenic, 3 families from Palles et al[3] study which initially reported the association of *POLE* and *POLD1* with CRC, 3 families of *de novo* mutation carriers, 29 families of probands without age or sex information). From the ACCFR, two unrelated carriers of the *POLE* c.861T>A p.Asp287Glu variant and one carrier of the *POLE* c.1336C>T p.Arg446Trp variant were identified (Pedigrees shown in Figure S1).

We included 47 families (38 *POLE* and 9 *POLD1*) from published studies, and 3 families with *POLE* mutations from the ACCFR (Figure S1), in the penetrance analysis. Of these, 28 (21 *POLE* and 7 *POLD1*) families were ascertained because they had a family history of cancer while 22 (20 *POLE* and 2 *POLD1*) were ascertained via population-based cancer registries regardless of family history. We observed 67 CRCs with a mean age at diagnosis of 50.2 (standard deviation [SD]=13.8) years among 364 first- and second- degree relatives (53% female) from 41 families with *POLE* mutations, and 6 CRCs with a mean age at diagnosis of 39.7 (SD=6.83) years among 69 first- and second- degree relatives (45% female) from 9 families with *POLD1* mutations (Table 1).

We estimated cumulative risks of CRC to age 70 years for males and females, respectively, to be: 28% (95% CI, 10%–42%) and 21% (95% CI, 7%–33%) for *POLE* mutation carriers; and 90% (95% CI, 33%–99%) and 82% (95% CI, 26%–99%) for *POLD1* mutation carriers (Figure 1). The CRC HR was estimated to be 12.2 (95% CI, 7.35–20.2) and 87.2 (95% CI, 15.3–495) for *POLE* and *POLD1* mutation carriers, respectively (Table 2). The HRs decreased with age, being 38.7 (95% CI, 17.5–85.4) for <50 years compared with 8.21 (95% CI, 4.24–15.9) for ≥50 years for *POLE* mutation carriers (P =0.003), and 201 (95% CI, 62.0–651) for <50 years compared with 3.34 (95% CI, 0.22–50.1) for ≥50 years for *POLD1*

mutation carriers (P =0.007; Table 2). There was no evidence for a difference in HRs by sex (all P >0.1).

The *POLE* c.1270C>G, p.Leu424Val mutation has been reported in 19 families. For these specific mutation carriers, the estimated cumulative risks of CRC to age 70 years were 97% (95% CI, 85%–99%) for males and 92% (95% CI, 75%–99%) for females. The corresponding HR was 131 (95% CI, 71.3–242) when both sexes were combined, and 75.0 (95% CI, 37.9–149) for males and 269 (95% CI, 111–650) for females. Results for penetrance and HR estimates were not materially different between analyses with and without imputing missing ages.

DISCUSSION

To our knowledge, this is the first report of both relative and cumulative risks of CRC for people who carry germline mutations within the exonuclease domains of the *POLE* or *POLD1* genes. Our current analysis included all of the reported rare germline variants within the exonuclease domains of *POLE* and *POLD1* predicted to be pathogenic by multiple commonly used *in silico* tools, however, it is possible that not all variants result in the same level of risk as evidenced by the recurring *POLE* c.1270C>G, p.Leu424Val mutation.

CRC has been the predominant cancer identified in *POLE* and *POLD1* mutation carriers to date (perhaps due to the way the families had been selected for genetic testing), however a broader extracolonic spectrum of cancers is being revealed as additional carrier families are identified. In addition to CRC, cancers of the endometrium, ovaries, pancreas, brain and small intestine have been reported for carriers, similar to what has been observed for DNA mismatch repair (MMR) gene mutation carriers (Lynch syndrome).[12] The presence of 10 to <100 adenomas and/or the presence of duodenal polyps could be a distinguishing feature of *POLE* or *POLD1* mutation carriers from MMR gene mutation carriers[5]. Interestingly, carriers of the *POLE* c.1270C>G, p.Leu424Val mutation showed no predilection for site and a mucinous adenocarcinoma histological type for a subset of tumors, suggesting variability in phenotype even for the same mutation, implicating potential environmental or genetic modifiers.

Additional phenotypic variability was observed with regards to tumor DNA mismatch repair status where the majority of CRCs from *POLE* and *POLD1* carriers have been MMR-proficient or microsatellite stable, however, a small subset of CRCs in *POLE* mutation carriers have shown tumor MMR-deficiency, without evidence of a germline MMR gene mutation [13,14]. Therefore, germline *POLE* exonuclease domain variants may account for a proportion of people with tumor MMR-deficient phenotype not explained by germline MMR gene mutations or acquired *MLH1* promoter hypermethylation (suspected Lynch syndrome)[15]. Furthermore, somatic *POLE* and *POLD1* mutations have been reported in both colorectal and endometrial cancers [16,17], supporting the hypothesis that loss of polymerase proofreading and the resultant hypermutation tumor phenotype can underlie inactivation of the MMR genes through somatic mutations.

This study has several limitations including the lack of detailed information on how cancer histories of family members in published studies were verified. A large proportion of families were excluded from the analysis due to missing information on age and sex of probands, thereby reducing the precision of our risk estimates. We used *in silico* predictions to assign pathogenicity for variant inclusion in the penetrance analysis, however, it has been shown that *in silico* tools and their algorithms for missense variant effect prediction are only 65–80% accurate when examining known disease causing missense variants[18]. The *POLE* and *POLD1* variants included in the analysis were predicted to be deleterious by multiple *in silico* variant effect prediction tools (predicted deleterious by at least four out of the seven tools used in this study), as recommended by the American College of Medical Genetics and Genomics,[9] and further selected based on a variant allele frequency filter of ≤0.002, adding confidence that our CRC risk estimates were based on only those variants likely to be pathogenic. We genotyped 17 *POLE* and *POLD1* rare, likely pathogenic variants to identify additional carriers, however, we cannot exclude the possibility that other *POLE* and *POLD1* variants outside of those genotyped may exist within the ACCFR CRC-affected individuals. Apart from CRC, we were unable to estimate risks of other cancers due to insufficient numbers of cancer diagnoses. Finally, our estimates might not necessarily be applicable to non-Caucasians.

In summary, the increased CRC risks for all carriers of a *POLE* pathogenic or likely pathogenic exonuclease domain variant, particularly for the recurrent *POLE* c.1270C>G, p.Leu424Val mutation, warrant consideration of annual colonoscopy screening and clinical management guidelines comparable to those currently recommended for people with Lynch syndrome or Familial Adenomatous Polyposis. As yet the risk of metachronous CRC is not known, but is likely to be similarly increased, raising consideration of subtotal colectomy rather than segmental resection for *POLE* mutation carriers. Functional studies to support variant classification may help to further refine the CRC risk estimates as will additional carrier families. For *POLD1* mutation carriers, refinement of penetrance estimates for CRC is needed, however, clinical management recommendations could follow those suggested for *POLE* mutation carriers.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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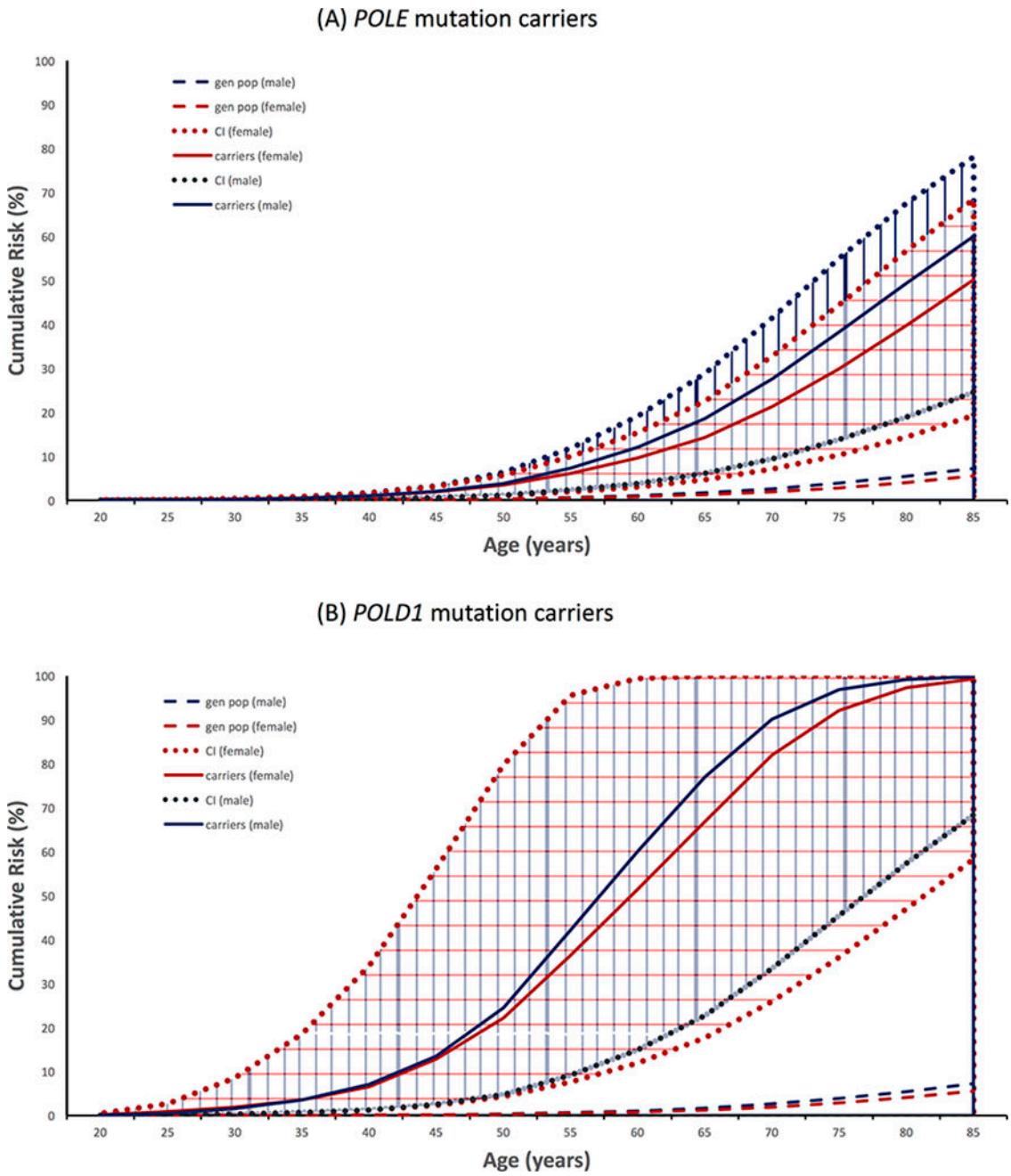

Figure 1.

Cumulative risks (unbroken lines) and corresponding 95% confidence intervals (dotted lines) of colorectal cancer for (**A**) *POLE* mutation carriers, (**B**) *POLD1* mutation carriers, and for the general population* (dashed lines). Blue and red represent males and females, respectively. *based on SEER (9 Registries): White (2003–2007) incidence data. SEER, Surveillance, Epidemiology and End Results database.

Table 1

Numbers and mean ages at diagnosis of cancers in the first- and second-degree male and female relatives of probands from *POLE* and *POLD1* mutation families.

	Male		Female	
Site of cancer	**N**	**Mean age (SD)**	**N**	**Mean age (SD)**
POLE		(n=172)		(n=192)
Colon/rectum	36	48.5 (14.9)	31	52.1 (12.5)
Cutaneous malignant melanoma	5	46.8 (29.9)*	11	54.4 (18.7)
Duodenum	1	45	0	—
Renal	1	86	0	—
Ureter	1	46	0	—
Oesophagus	1	85	1	77
Pancreas	1	46	1	78
Brain	1	69	2	68*
Bone	1	UK	0	—
Lung	2	61.0 (5.66)	1	92
Liver	0	—	1	UK
Leukaemia	2	74.0 (12.7)	0	—
Astrocytoma	3	50.7 (30.9)	0	—
Ewing's sarcoma	0	—	1	14
Intra-abdominal	0	—	1	UK
Head and neck	1	52	3	74.0 (2.65)
Breast	0	—	4	64.5 (21.4)
Endometrium	NR	NR	3	53.0 (9.85)
Ovary	NR	NR	4	43.8 (6.29)
Prostate	5	74.0 (14.2)*	NA	NA
POLD1		(n=38)		(n=31)
Colon/Rectum	4	42.3 (7.04)	2	34.5 (2.12)
Stomach	1	72	1	85
Renal	0	—	1	74
Urinary bladder	0	—	1	UK
Hodgkin lymphoma	0	—	1	30
Head and neck	1	56	0	—
Breast	0	—	3	58.3 (10.7)
Endometrium	NR	NR	3	55.0 (2.65)
Ovary	NR	NR	1	31

N, total number of affected relatives; SD, standard deviation; UK, unknown age at diagnosis; NR, not relevant; —, not applicable

*unknown age at diagnosis for one person

Table 2

Hazards Ratio (95% confidence interval) of colorectal cancer for carriers of a germline mutation in *POLE* or *POLD1*

	POLE	***POLD1***	***POLE* p.Leu424Val**
Overall HR (95%CI)	**12.2 (7.35–20.2)**	**87.2 (15.3–495)**	**131 (71.3–242)**
Sex			
Male	12.3 (5.35–28.1)	723 (102–5140)	75.0 (37.9–149)
Female	12.1 (5.64–16.1)	75.0 (19.2–292)	269 (111–651)
P-difference	0.9	0.1	0.03
Age			
<50 years	38.7 (17.5–85.4)	201 (62.0–651)	238 (95.6–593)
≥50 years	8.21 (4.24–15.9)	3.34 (0.22–50.1)	98.0 (44.1–218)
P-difference	0.003	0.007	0.2