

Clinically relevant combined effect of polygenic background, rare pathogenic germline variants, and family history on colorectal cancer incidence

Supplemental Figures

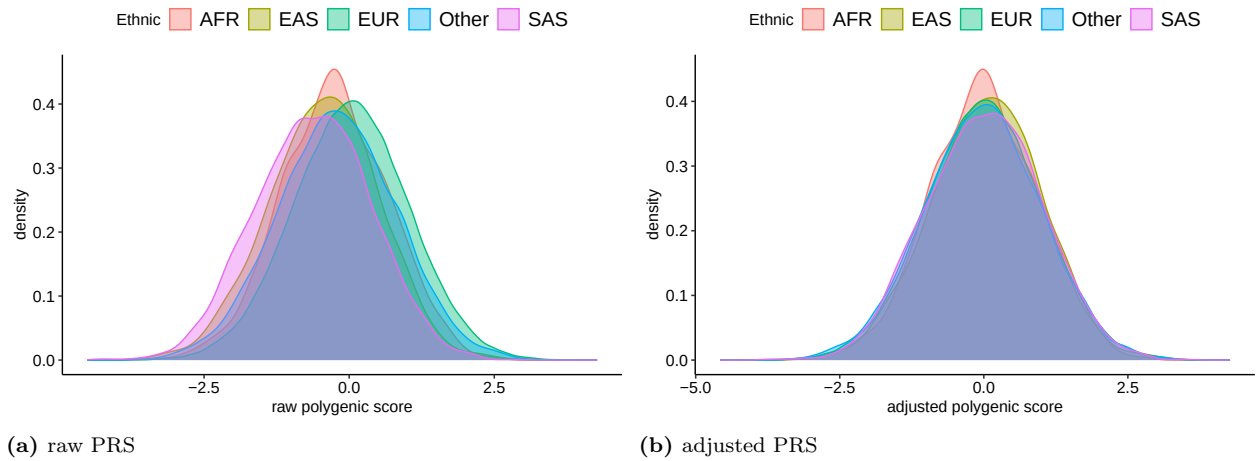


Figure S1: Distributions of the colorectal cancer (CRC) PRS across the estimated genetic ethnicities. Estimated genetic ethnicities were estimated by projecting the samples in the 1000 genome project (1KGP) principal component space while considering the five 1KGP superpopulations as reference (<https://github.com/privefl/paper-ancestry-matching/tree/master/code>). Distributions of: a) raw PRS; b) adjusted PRS.

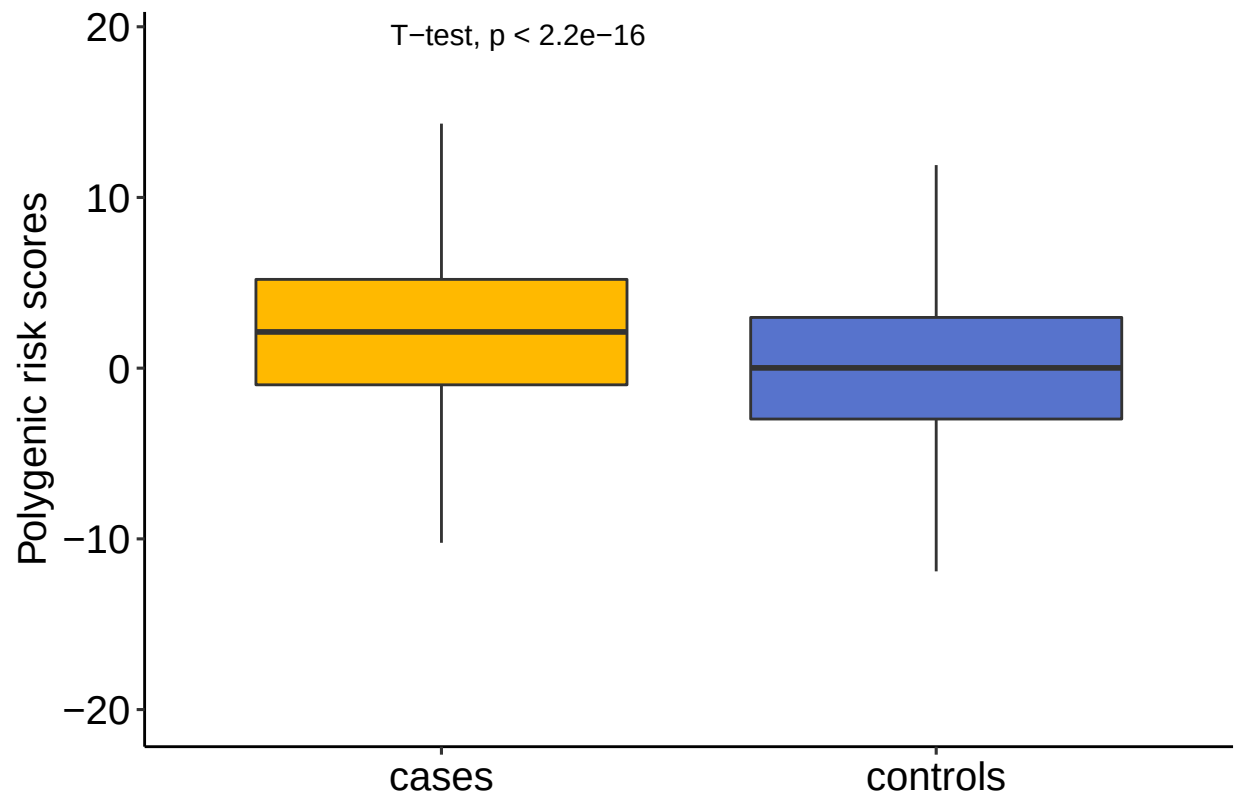


Figure S2: Adjusted PRS (aPRS) among CRC cases versus controls.

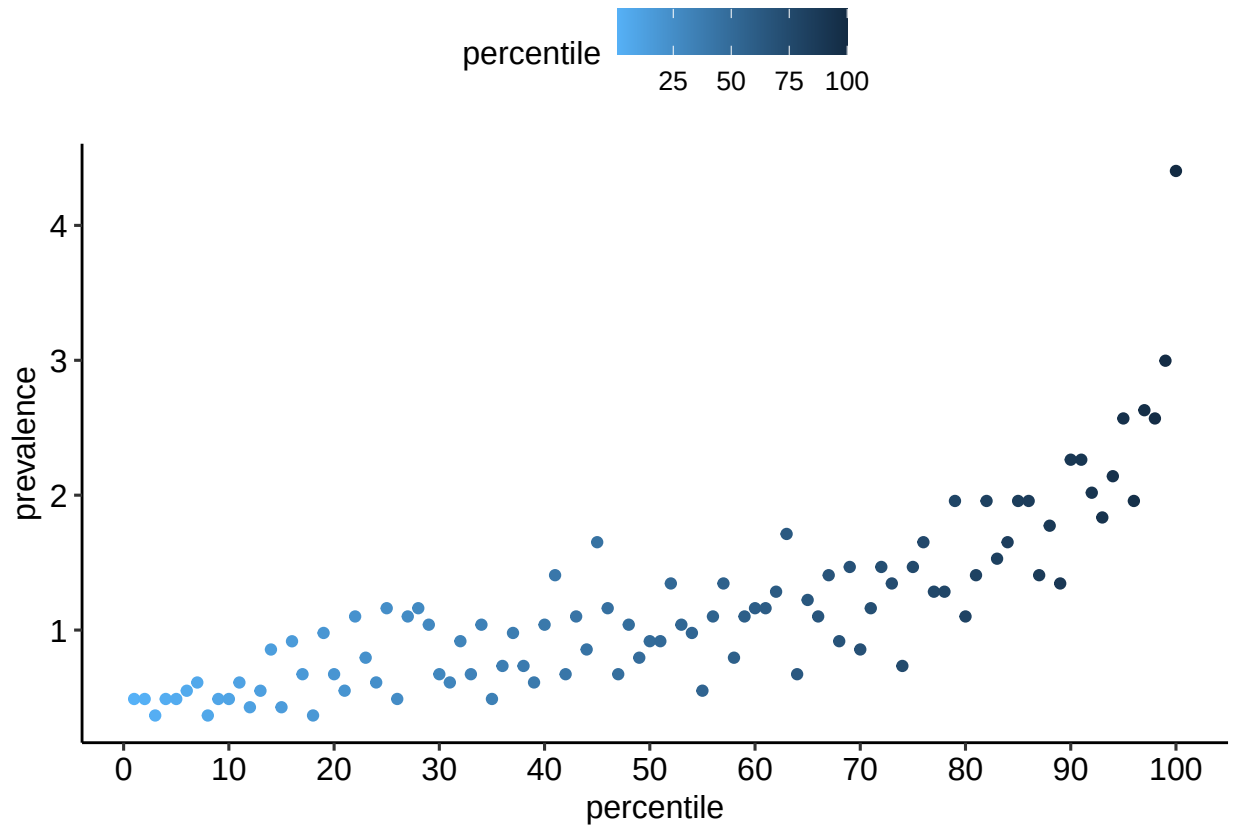
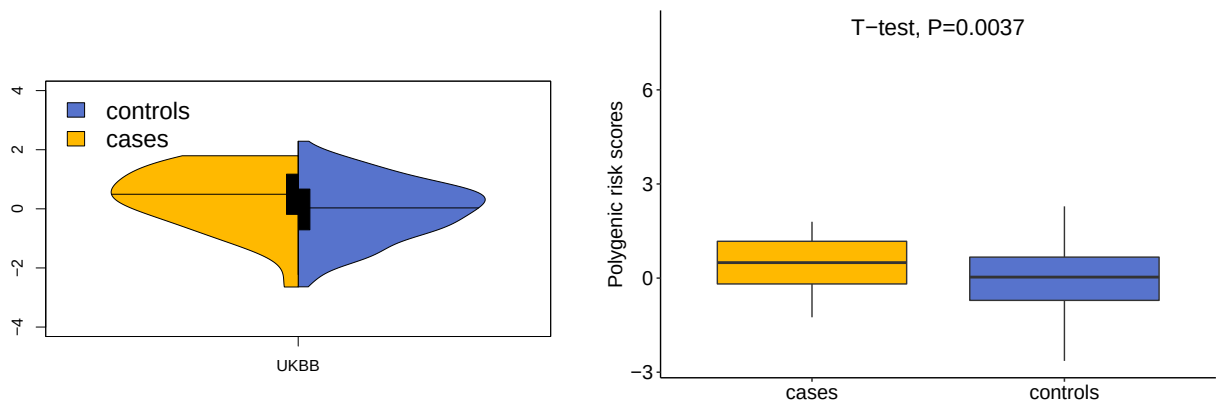


Figure S3: Prevalence of the colorectal cancer (CRC) according to polygenic risk score (PRS) percentiles.



(a) Density plot

(b) Box plot

Figure S4: PRS among CRC affected (cases) and unaffected (controls) carriers. Density (a) and box plots (b) show the PRS distribution among affected and unaffected carriers. Horizontal line indicates PRS mean in plot (a).

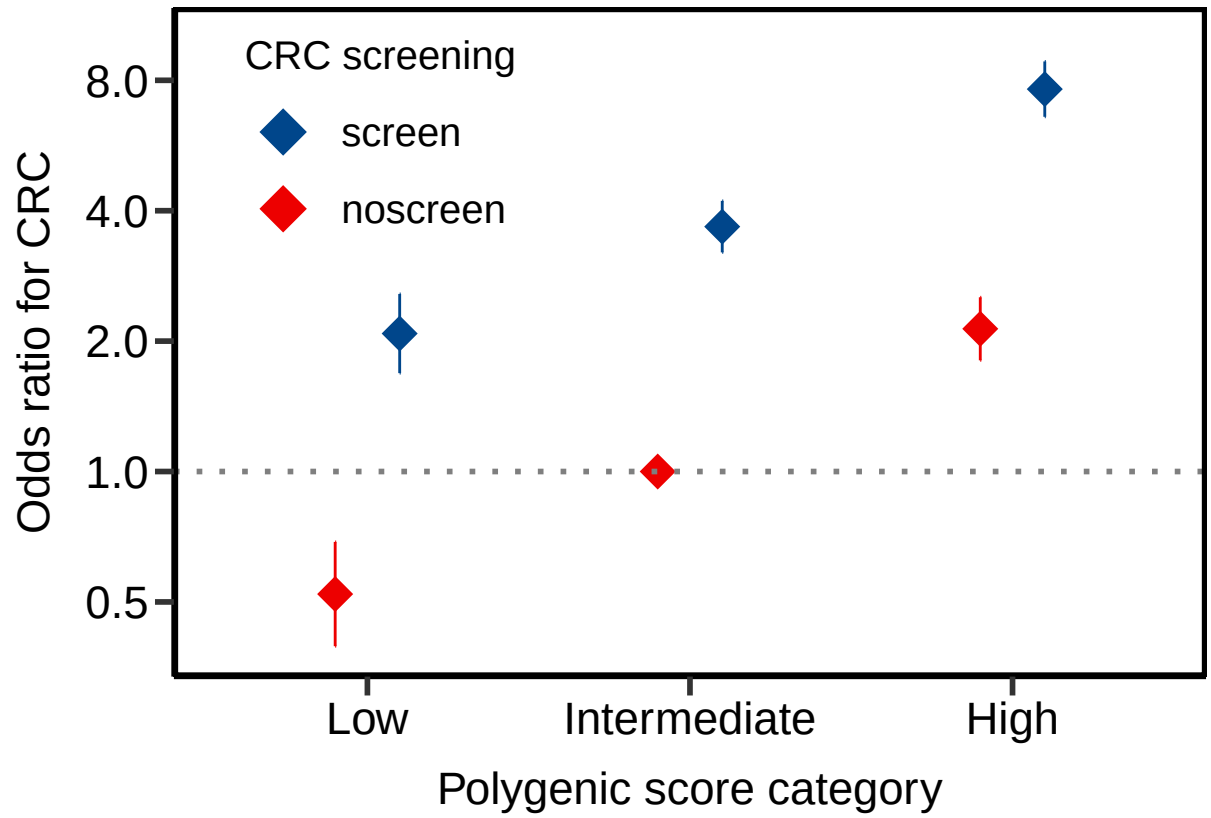


Figure S5: Colorectal cancer (CRC) odds ratio among individuals stratified for CRC screening status and PRS.

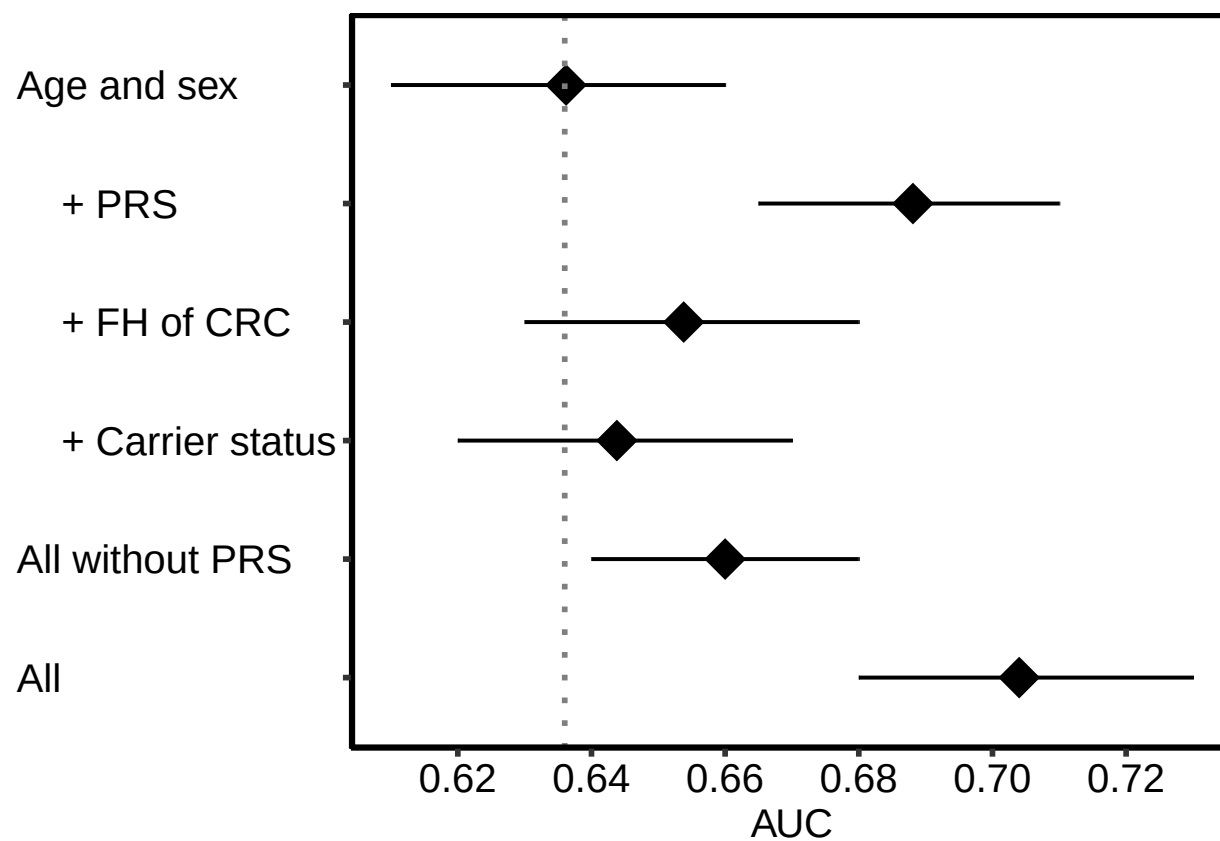


Figure S6: Model discrimination assessed for combinations of polygenic risk score (PRS), family history of CRC (FH) and carrier.

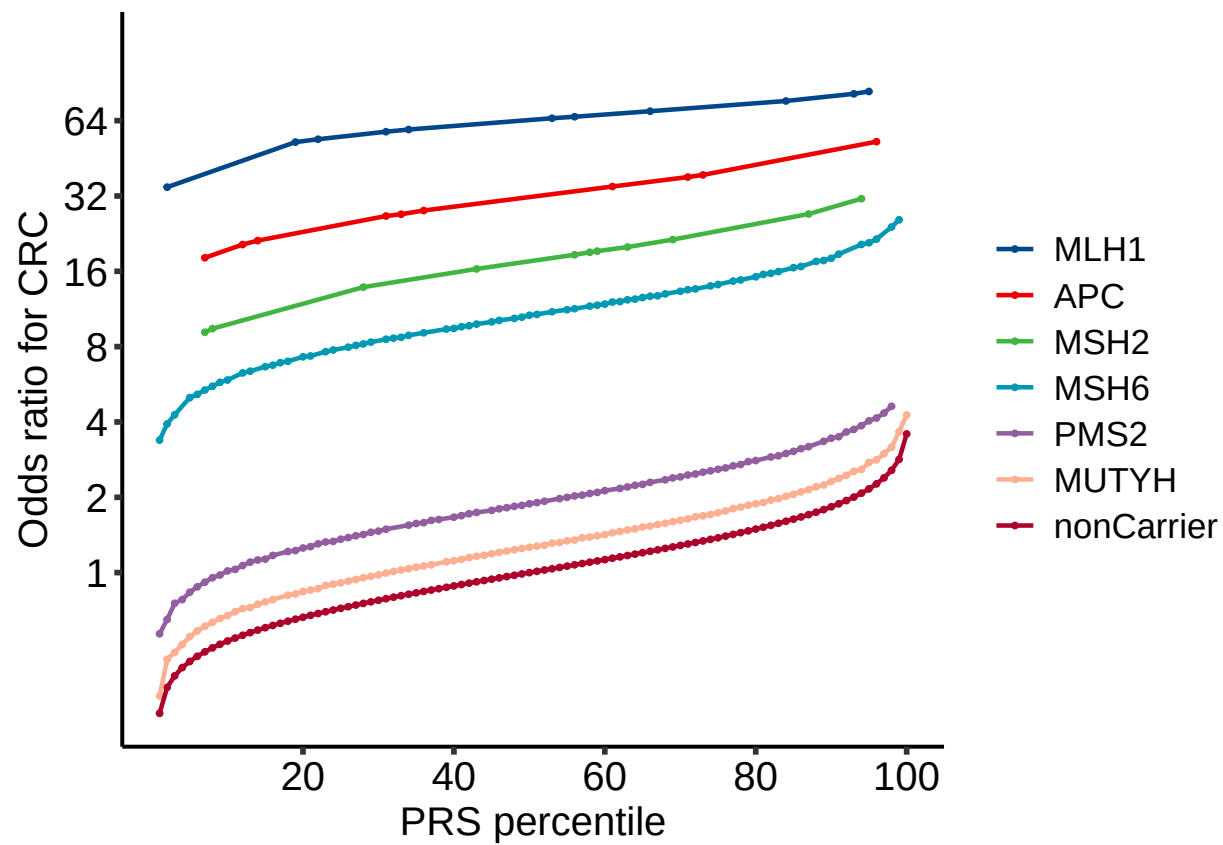


Figure S7: Interplay of heterozygous pathogenic variant (PV) carrier status, family history (FH), and polygenic risk score (PRS) in single genes.

Supplemental Tables

Table S1: Provided as excel file.

Table S2: Number of PV carriers separated by gene and clinical status.

gene	Cases	Controls	Total
APC	3	8	11
MLH1	6	5	11
MSH2	2	11	13
MSH6	14	121	135
PMS2	5	224	229
Total	30	369	399
MUTYH*	5	365	370

Note:

* MUTYH variants were included only in the single gene analysis to compare the effect size with the other genes.

Table S3: Interplay of PV, and PRS in CRC.

prs	Carrier				nonCarrier			
	CI	HR	OR	p.value	CI	HR	OR	p.value
High	74	11.5 (6.3-20.8)	17.5 (9.0-32.4)	1.6e-17	22	2.08 (1.9-2.3)	2.08 (1.9-2.3)	7.5e-49
Intermediate	51	6 (3.7-9.8)	7 (4.2-11.7)	1.1e-13	11	1	1	
Low	40	4.3 (1.4-13.2)	3.9 (1.2-12.3)	2.2e-02	6	0.55 (0.47-0.65)	0.54 (0.46-0.64)	3.6e-14

Note:

CI = Cumulative incidence; HR = Hazard ratio; OR = Odds ratio.

Table S4: Interplay of PV, and FH in CRC.

prs	History				nonHistory			
	CI	HR	OR	p.value	CI	HR	OR	p.value
High	26	2.8 (2.3-3.3)	3.1 (2.6-3.8)	1.4e-33	21	2.1 (1.9-2.4)	2.1(1.9-2.4)	3.1e-44
Intermediate	16	1.7 (1.4-1.9)	1.9 (1.6-2.18)	2.1e-15	11	1	1	
Low	8	0.7 (0.5-1.1)	0.9 (0.58-1.25)	4.2e-01	6	0.55 (0.49-0.69)	0.6 (0.47-0.67)	1.1e-10

Note:

CI = Cumulative incidence; HR = Hazard ratio; OR = Odds ratio.

Table S5: Interplay of PV, FH, and PRS in CRC.

prs	history	Carrier				nonCarrier			
		CI	HR	OR	p.value	CI	HR	OR	p.value
High	History	97.8	36.3 (13.6-97.1)	39.9 (12.69-125.41)	3e-10	25.5	2.7 (2.24-3.25)	3.08 (2.55-3.71)	<2e-16
High	nonHistory	62.1	8.97 (4.25-18.9)	14.56 (6.48-32.73)	9e-11	21	2.16 (1.94-2.41)	2.16 (1.94-2.41)	<2e-16
Intermediate	History	66.4	10.1 (4.80-21.3)	15.63 (6.95-35.17)	3e-11	16.3	1.63 (1.39-1.90)	1.83 (1.56-2.14)	4e-14
Intermediate	nonHistory	42.5	5.08 (2.63-9.80)	5.56 (2.82-10.94)	7e-07	10.4	1	1	
Low	History	50.	6.40 (0.901-45.5)	5.78 (0.76-43.95)	9e-02	7.6	0.73 (0.49-1.08)	0.83 (0.56-1.24)	0.4
Low	nonHistory	35.5	4.03 (1.01-16.1)	3.74 (0.91-15.43)	7e-02	6.2	0.58 (0.49-0.69)	0.57 (0.48-0.68)	1e-10

Note:

CI = Cumulative incidence; HR = Hazard ratio; OR = Odds ratio.

Table S6: Interplay of PV, PRS and FH in single genes.

gene	history	Low	Intermediate	High
nonCarrier	nonHistory	0.51 (0.46-0.57)	1 (1-1)	1.93 (1.8-2.07)
	History	0.85 (0.74-0.98)	1.66 (1.49-1.85)	3.18 (2.84-3.56)
MUTYH	nonHistory	0.65 (0.27-1.57)	1.25 (0.52-3)	2.37 (0.99-5.61)
	History	1.07 (0.44-2.59)	1.96 (0.81-4.67)	3.93 (1.64-9.16)
PMS2	nonHistory	0.94 (0.38-2.27)	1.89 (0.78-4.51)	3.3 (1.37-7.76)
	History	1.59 (0.65-3.84)	3.09 (1.28-7.29)	5.43 (2.28-12.49)
MSH6	nonHistory	5.35 (3.12-9.03)	9.8 (5.84-16.05)	17.7 (10.85-27.75)
	History	8.32 (4.89-13.87)	16.6 (10.12-26.22)	24.75 (15.56-37.4)
MSH2	nonHistory	7.78 (1.76-29.15)	14.95 (3.58-47.42)	NA
	History	NA	25.45 (6.61-66.02)	36.18 (10.28-79.15)
APC	nonHistory	20.45 (5.9-53.63)	34.63 (11.16-73.4)	54.2 (20.76-90.91)
	History	NA	40.87 (13.84-79.99)	NA
MLH1	nonHistory	NA	59.25 (28.03-90.24)	71.46 (37.96-98.14)
	History	49.7 (21.67-82.75)	66.19 (33.48-94.86)	90.37 (59.45-107.65)

Note:

OR = Odds ratio.; NA = represents missing data