Determining risk of colorectal cancer and the effect of screening colonoscopy based on genetic risk score

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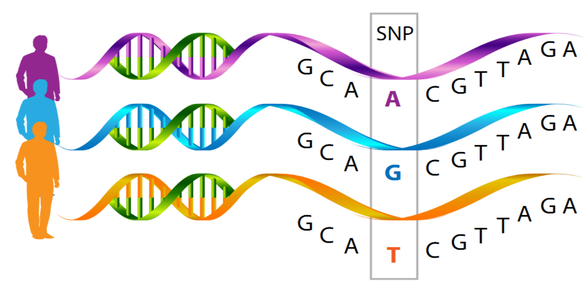
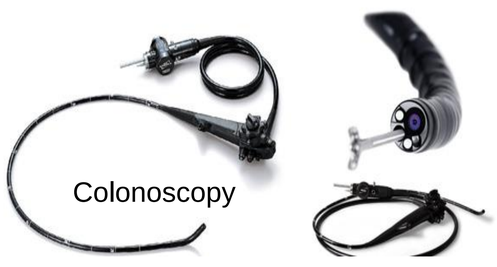
Research for a Life without Cancer

Background

- Previous studies showed that the genetic risk score (GRS), computed based on colorectal cancer (CRC) related single nucleotide polymorphisms (SNPs), could be relevant for risk stratification.
- In this study, we aimed to assess the association of the GRS with CRC incidence controlled by screening colonoscopy and also to evaluate whether the effect of screening colonoscopy differed with genetic variants.





Methods

- We obtained genetic data from 6600 participants in a German population-based cohort study (age range at baseline: 50-75).
- A total of 147 incident CRC cases were identified during a median follow-up of 14 years.
- We constructed the GRS based on 55 SNPs associated with CRC risk.
- Cox proportional hazard models were used to examine the association between the GRS and CRC risk.
- Time-varying Cox proportional hazard models were performed to evaluate whether screening colonoscopy effect differed with genetic risk.

Results

- Incorporating the GRS in the prediction model improved the discriminatory accuracy compared with only using family history and environmental factors **(Figure 1).**

- Model 1 includes age, sex and family history of CRC.
- Model 2 extends model 1 by additionally adding BMI, smoking status and alcohol consumption.
- Model 3 combines factors in model 1 and GRS.
- Model 4 combines factors in model 2 and GRS.
- *P*-value for comparison between model 1 and model 3 is 0.048 and between model 2 and model 4 is 0.039.

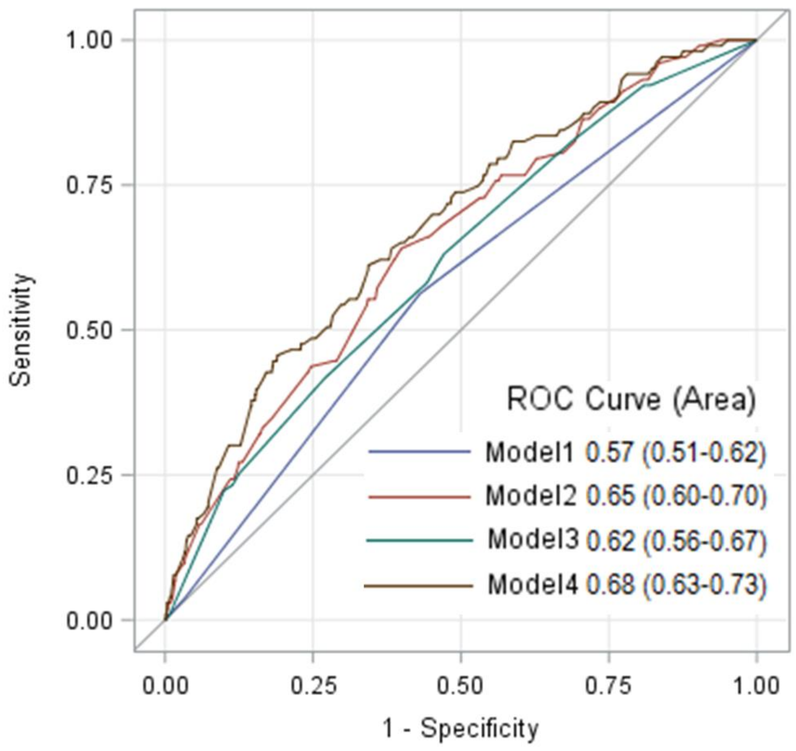


Figure 1. Receiver operating characteristic (ROC) curves for prediction of CRC among participants without previous screening colonoscopy

Results

- Overall, having a GRS in the medium and high tertile was associated with a 1.3- and 1.8-fold risk of CRC incidence, respectively.
- While increased GRS was strongly associated with CRC risk among participants without a previous colonoscopy, such associations were not noted among colonoscopy-screened population **(Table 1).**

Table 1. Hazard ratios of the GRS associated with CRC in the overall population and stratified by screening colonoscopy use*

GRS Level	Overall population (n=6600)		No screening colonoscopy (n=2940)		Ever screening colonoscopy (n=3660)	
	cases /controls	HR (95% CI)	cases /controls	HR (95% CI)	cases /controls	HR (95% CI)
Low	35/2004	reference	20/921	reference	15/1083	reference
Medium	56/2565	1.28 (0.84-1.96)	41/1111	1.87 (1.09-3.20)	15/1454	0.75 (0.36-1.53)
High	56/1884	1.76 (1.15-2.68)	42/805	2.59 (1.51-4.43)	14/1079	1.02 (0.47-2.03)
		p_{trend}=0.008		p_{trend}<0.001		p_{trend}=0.94

HR, hazard ratio; CI, confidence interval

- Compared with no screening colonoscopy, use of screening colonoscopy was associated with a 62% and 67% reduction in CRC incidence among people with medium and high GRS, respectively **(Table 2).**

Table 2. Association between screening colonoscopy and CRC in each GRS level using time-varying Cox-proportional hazard model*

GRS level	Screening colonoscopy	CRC cases	Person-years	Rate per 100,000 person-years	HR (95% CI)
Low (n=2039)	**None**	20	14,403	138.9	reference
	Ever	15	11,637	128.9	1.08 (0.54-2.18)
Medium (n=2621)	**None**	41	17,688	231.8	reference
	Ever	15	15,869	94.5	0.38 (0.21-0.70)
High (n=1940)	**None**	42	13,150	319.4	reference
	Ever	14	11,815	118.5	0.33 (0.18-0.61)

HR, hazard ratio; CI, confidence interval

Conclusion & Discussion

- In this study, we identified that the association between genetic predisposition and CRC risk was reduced among cohorts who had undergone screening colonoscopy.
- Our results show that at least 60% of CRC cases could be preventable by undergoing screening colonoscopy among individuals with a GRS threshold of 30% or more.
- Refinement of CRC screening guideline by incorporating genetic variants represents an important research direction, particularly in terms of acceptability and feasibility of GRS-based risk stratification in the community.

*Models in table 1 and 2 were adjusted for age, sex, education, body mass index (BMI), smoking, alcohol consumption, family history of CRC, physical activity, aspirin intake, red and processed meat consumption, and hormone replacement therapy.

Credit to the pictures in the introduction: http://cahartmanfiction.com & https://www.rosebudendoscopy.com.au/colonoscopy.html

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