

Supplementary Tables:

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Supplementary Table 1. Comparison of clinical characteristics of interval and screen detected CRCs

Characteristics	Screen detected	PLCO	NHS/HPFS
		OR (95% CI) Interval	OR (95% CI) Interval
Age at diagnosis			
10-year increase	ref	4.15 (3.00, 5.74)	1.38 (1.20, 1.58)
Year of diagnosis			
5-year increase	ref	7.12 (7.11, 7.13)	1.31 (1.20, 1.43)
Sex			
Female vs. male	ref	1.88 (1.26, 2.79)	0.94 (0.73, 1.20)
Family history of CRC			
Yes vs. no	ref	1.03 (0.59, 1.79)	0.83 (0.63, 1.11)
Tumor location			
Distal vs. proximal	ref	1.82 (1.01, 3.29)	1.11 (0.85, 1.43)
Stage			
Stage II/III vs I	ref	3.80 (2.45, 5.92)	1.51 (1.11, 2.04)
Stage IV vs I	ref	10.12 (4.36, 23.52)	2.42 (1.45, 4.05)
Tumor differentiation			
Poor/undifferentiated vs. well/moderate differentiated	ref	2.14 (1.21, 3.79)	1.40 (0.72, 2.72)

Notes: Univariate OR (95% CI) was computed for the comparison between interval and screen detected cancers. Abbreviations: CI, confidence interval; OR, odds ratio; CRC, colorectal cancer; PLCO, Prostate, Lung, Colorectal and Ovarian cancer screening trial; NHS, Nurses' Health Study; HPFS, Health Professionals Follow-up Study.

Supplementary Table 2. CRC-specific and overall mortality of interval CRCs according to cancer stage in PLCO and NHS/HPFS

	CRC-specific mortality				Overall mortality		
	No. of cases	No. of events	Crude HR (95% CI)	Multivariable adjusted HR (95% CI)	No. of events	Crude HR (95% CI)	Multivariable adjusted HR (95% CI)
All							
Screen detected	740	195	reference	reference	378	reference	reference
Interval	696	249	1.66 (1.33, 2.07)	1.47 (1.21, 1.78)	367	1.48 (1.16, 1.89)	1.27 (1.09, 1.47)
Others	3400	1808	2.47 (2.13, 2.86)	2.00 (1.71, 2.33)	2278	1.92 (1.64, 2.25)	1.65 (1.46, 1.86)
Stage I							
Screen detected	305	44	reference	reference	136	reference	reference
Interval	167	30	1.10 (0.36, 3.32)	0.87 (0.30, 2.50)	61	1.13 (0.83, 1.54)	0.89 (0.64, 1.22)
Others	642	169	1.57 (1.11, 2.22)	1.23 (0.80, 1.89)	288	1.32 (0.76, 2.30)	1.02 (0.80, 1.31)
Stage II/III							
Screen detected	282	98	reference	reference	152	reference	reference
Interval	327	102	1.13 (0.85, 1.49)	1.09 (0.82, 1.44)	156	1.20 (0.96, 1.50)	1.05 (0.83, 1.32)
Others	1570	721	1.54 (1.25, 1.90)	1.68 (1.35, 2.09)	936	1.42 (1.19, 1.69)	1.48 (1.23, 1.78)
Stage IV							
Screen detected	37	31	reference	reference	32	reference	reference
Interval	80	72	2.01 (1.32, 3.08)	2.06 (1.33, 3.18)	76	2.07 (1.36, 3.14)	2.08 (1.36, 3.19)
Others	627	585	1.98 (1.38, 2.85)	2.06 (1.41, 3.02)	597	1.98 (1.39, 2.83)	2.03 (1.40, 2.95)

Notes: Multivariable-adjusted HRs (95% CIs) were adjusted for age at diagnosis, year of diagnosis, sex, family history of CRC, tumor location, grade, and stage. Results of NHS/HPFS and PLCO were pooled using random-effects meta-analysis (P for heterogeneity > .05).

Supplementary Table 3. Characteristics of CRC patients with WES data in PLCO and NHS/HPFS

Characteristics	PLCO			NHS/HPFS		
	Screen detected (n=54)	Interval (n=20)	Others (n=73)	Screen detected (n=129)	Interval (n=97)	Others (n=570)
Age at diagnosis	64.8 ± 6.1	69.2 ± 6.8	72.6 ± 6.7	71.4 ± 7.7	73.0 ± 8.1	69.9 ± 8.8
Female	22 (40.7)	11 (55.0)	33 (45.2)	69 (53.5)	53 (54.6)	365 (64.0)
Family history of CRC	9 (16.7)	4 (20.0)	12 (16.4)	28 (21.7)	24 (24.7)	106 (18.6)
Tumor location						
Cecum	4 (7.4)	0 (0.0)	23 (31.5)	22 (17.1)	16 (16.5)	107 (18.8)
Ascending to transverse colon	5 (9.3)	4 (20.0)	39 (53.4)	45 (34.9)	34 (35.1)	177 (31.1)
Splenic flexure to sigmoid	28 (51.9)	12 (60.0)	6 (8.2)	37 (28.7)	27 (27.8)	162 (28.4)
Rectosigmoid and rectum	17 (31.5)	4 (20.0)	5 (6.8)	25 (19.4)	20 (20.6)	123 (21.6)
Stage						
Stage I	29 (53.7)	5 (25.0)	20 (27.4)	41 (31.8)	24 (26.4)	126 (24.0)
Stage II	13 (24.1)	8 (40.0)	21 (28.8)	39 (30.2)	30 (33.0)	170 (32.3)
Stage III	10 (18.5)	5 (25.0)	19 (26.0)	32 (24.8)	31 (32.0)	156 (29.7)
Stage IV	2 (3.7)	2 (10.0)	13 (17.8)	8 (6.2)	6 (6.6)	74 (14.0)
Tumor differentiation						
Well or moderately differentiated	49 (90.7)	15 (75.0)	50 (68.5)	114 (91.2)	81 (86.2)	507 (92.2)
Poorly differentiated or undifferentiated	4 (7.4)	5 (25.0)	23 (31.5)	11 (8.8)	13 (13.8)	43 (7.8)
Year of diagnosis						
≤ 2000	40 (74.1)	6 (30.0)	9 (12.3)	58 (45.0)	31 (32.0)	315 (55.3)
> 2000	14 (25.9)	14 (70.0)	64 (87.7)	71 (55.0)	66 (68.0)	255 (44.7)

Notes: Abbreviation: CRC, colorectal cancer; PLCO, Prostate, Lung, Colorectal and Ovarian cancer screening trial; NHS, Nurses' Health Study; HPFS, Health Professionals Follow-up Study. Continuous variables were presented as mean (standard deviation) and categorical variables were presented as number (percentage). Percentages were calculated among non-missing data.

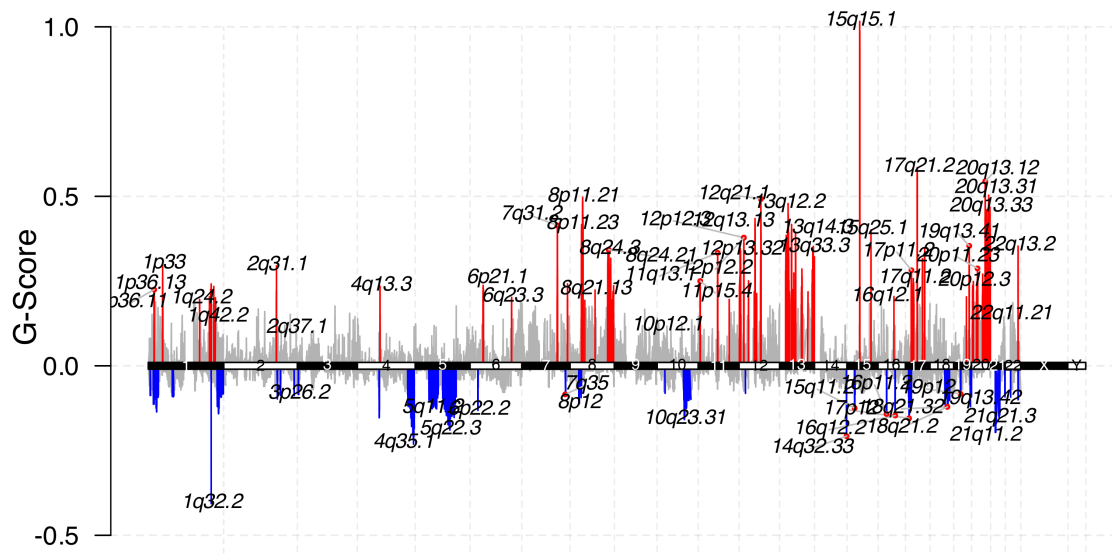
Supplementary Table 4: Comparison of mutational characteristics of interval and screen detected CRCs

Gene name*	Interval (n=117)	Screen detected (n=183)	OR (95% CI)	False Discovery Rate adjusted <i>P</i> values
BRAF	31	25	2.26 (1.20, 4.27)	.23
APC	59	115	0.59 (0.36, 0.98)	.26
ACVR2A	25	20	2.20 (1.10, 4.42)	.26
TP53	55	101	0.71 (0.43, 1.16)	.49
KRAS	24	59	0.54 (0.30, 0.96)	.26
SYNE1	33	26	2.35 (1.27, 4.39)	.18
TTN	41	72	0.82 (0.49, 1.37)	.78
MUC16	22	37	0.91 (0.48, 1.69)	.92
PIK3CA	22	31	1.13 (0.58, 2.15)	.92
OBSCN	21	28	1.20 (0.48, 1.69)	.86

Note: *ORs (95% CIs) were calculated for ten most frequently mutated genes (i.e., genes listed in Figure S1B) in PLCO and NHS/HPFS.

Supplementary Table 5: Comparison of mutational characteristics of interval and screen detected CRC according to stage of cancer

	Top differentially mutated gene	Interval cancer [mutation/total case]	Screen detected cancer [mutation/total case]	False Discovery Rate adjusted <i>P</i> values
Stage 1	HERC1	7/29	3/69	.052
Stage 2 and 3	AKAP9	8/74	2/94	.42
Stage 4	TP53	5/8	9/10	.37

A**B**