

Supplementary Methods

Estimating the cumulative risk per 100,000 in a hypothetical cohort of individuals aged 60 to 79 in the general population and among screened individuals.

We estimate the average age-specific rate (for each gender) as follows:

- Rate at age 60 = 40% of observed rate at ages 55-59 and 60% of observed rate at ages 60-64
- Rate at age 61 = 20% of observed rate at ages 55-59 and 80% of observed rate at ages 60-64
- Rate at age 62 = observed rate at ages 60-64
- Rate at age 63 = 80% of observed rate at ages 60-64 and 20% of observed rate at ages 65-69
- Rate at age 64 = 60% of observed rate at ages 60-64 and 40% of observed rate at ages 65-69

The age-specific rates for both genders were averaged and used to estimate the cumulative risk from age 60 to 79 in the population.

To estimate rates in screened individuals, average age-specific population rates were multiplied by the weighted average of the odds ratios (ORs) within 12 months of a screening test for ages at which screening is offered (i.e., 60, 62, 64, etc. up to age 74, Table S4).

For the non-screening age groups (i.e., 61, 63, 65, etc. up to age 79), the average of the ORs for one year and for two or more years (i.e., 180-365 days and 2+ years respectively, as shown in Table S4) were used. These estimates were corrected for self-selection bias.

Estimation of risk ratios by Duke's stage

To estimate the rate of advanced (Dukes' stage D) CRC per 100,000 individuals in the population, the average gender-age specific rates were multiplied by the proportion of cases suspected to be Dukes' stage D among all unscreened cases in the study (33% for males and 32% for females) before averaging the risk. To obtain the risk among those screened we multiply the average risk in the population by the weighted average of the odds ratios for Dukes' stage D (see table below) as detailed above.

Supplementary Tables

Supplementary Table 1. Colorectal cancers diagnosed in the Nottingham RCT after a median follow-up of 19.5 years by stage at diagnosis, invitational and attendance status

Stage	Screened-invited		Invitational status		Not invited - unscreened		Risk ratio (Not screened-invited/ Not invited-unscreened) OR (95% CI)
	N	Rate per 1,000 population	N	Rate per 1,000 population	N	Rate per 1,000 population	
Dukes A	238	5.31	76	2.50	258	3.44	0.73
Dukes' B	398	8.88	321	10.55	735	9.80	1.08
Dukes' C	358	7.98	233	7.66	653	8.71	0.88
Dukes' D	224	5.00	228	7.50	468	6.24	1.20 (1.03, 1.41)
Dukes' B+	980	21.86	782	25.71	1856	24.75	1.04 (0.96, 1.13)
Dukes' C+	582	12.98	461	15.16	1121	14.95	1.01
Total cancers	1320	29.44	959	31.53	2354	31.39	1.00 (0.93, 1.08)
Total population in study	44838		30415		74998		

* Risk ratios in bold are used for self-selection correction. We use the same correction for Dukes' B or worse as for Dukes' C or worse

Supplementary Table 2. Number of Invitations by screening status among eligible individuals

Number of invitations	Invited - not screened		Invited – screened		Total	
	N	(%)	N	(%)	N	(%)
1	7941	49.2%	8199	50.8%	16140	100%
2	7101	39.0%	11084	61.0%	18185	100%
3	2499	27.6%	6556	72.4%	9055	100%
4	57	19.5%	235	80.5%	292	100%

Supplementary Table 3. Corrected odds ratio of bowel cancer by screening status and time since last screening test - results for the main analysis.

Invitational status - screening status	Controls		Cases		cOdds ratio (95% CI) ^a
	N	(%)	N	(%)	
All Stages					
Invited - unscreened	11695	(40.3)	5903	(40.3)	Reference
Invited - time since last test					
<30 days	806	(2.8)	2131	(14.6)	9.66 (8.17, 11.43)
30-60 days	1027	(3.5)	885	(6.0)	3.03 (2.56, 3.59)
60-90 days	947	(3.3)	301	(2.1)	0.89 (0.73, 1.08)
90-180 days	1696	(5.8)	468	(3.2)	0.52 (0.44, 0.63)
180-365 days	2683	(9.2)	895	(6.1)	0.53 (0.46, 0.62)
365-730 days	5776	(19.9)	2208	(15.1)	0.67 (0.58, 0.77)
2 years	2263	(7.8)	891	(6.1)	0.88 (0.75, 1.02)
3 or more years	2143	(7.4)	954	(6.5)	0.83 (0.71, 0.96)
Dukes stage B or worse					
Invited - unscreened	9082	(40.0)	5061	(44.2)	Reference
Invited - time since last test					
<30 days	565	(2.5)	1350	(11.8)	7.36 (6.08, 8.90)
30-60 days	721	(3.2)	550	(4.8)	2.30 (1.89, 2.80)
60-90 days	689	(3.0)	204	(1.8)	0.74 (0.59, 0.92)
90-180 days	1309	(5.8)	355	(3.1)	0.48 (0.40, 0.59)
180-365 days	2158	(9.5)	703	(6.1)	0.52 (0.43, 0.62)
365-730 days	4694	(20.7)	1757	(15.4)	0.65 (0.55, 0.76)
2 years	1713	(7.5)	697	(6.1)	0.85 (0.71, 1.02)

3 or more years	1771	(7.8)	764	(6.7)	0.79 (0.66, 0.94)
-----------------	------	-------	-----	-------	-------------------

Dukes stage C and D

Invited - unscreened	5626	(40.4)	3297	(47.0)	Reference
----------------------	------	--------	------	--------	-----------

Invited - time since last test

<30 days	318	(2.3)	706	(10.1)	6.18 (4.96, 7.69)
30-60 days	399	(2.9)	301	(4.3)	2.06 (1.64, 2.59)
60-90 days	413	(3.0)	115	(1.6)	0.62 (0.48, 0.81)
90-180 days	816	(5.9)	220	(3.1)	0.45 (0.36, 0.56)
180-365 days	1334	(9.6)	443	(6.3)	0.51 (0.42, 0.62)
365-730 days	2879	(20.7)	1074	(15.3)	0.62 (0.53, 0.74)
2 years	1032	(7.4)	405	(5.8)	0.75 (0.62, 0.92)
3 or more years	1092	(7.9)	453	(6.5)	0.72 (0.59, 0.87)

Dukes stage D

Invited - unscreened	2672	(40.4)	1926	(57.7)	Reference
----------------------	------	--------	------	--------	-----------

Invited - time since last test

<30 days	108	(1.6)	116	(3.5)	2.38 (1.57, 3.60)
30-60 days	125	(1.9)	84	(2.5)	1.46 (0.95, 2.24)
60-90 days	160	(2.4)	42	(1.3)	0.56 (0.35, 0.90)
90-180 days	398	(6.0)	102	(3.1)	0.46 (0.31, 0.68)
180-365 days	668	(10.1)	192	(5.7)	0.49 (0.34, 0.70)
365-730 days	1450	(21.9)	474	(14.2)	0.43 (0.37, 0.49)
2 years	466	(7.0)	183	(5.5)	0.56 (0.46, 0.69)
3 or more years	575	(8.7)	221	(6.6)	0.74 (0.52, 1.05)

^a Corrected for self-selection: 1.00 for all Stages, 1.04 up to Dukes' C or worse and 1.20 for Dukes' D.

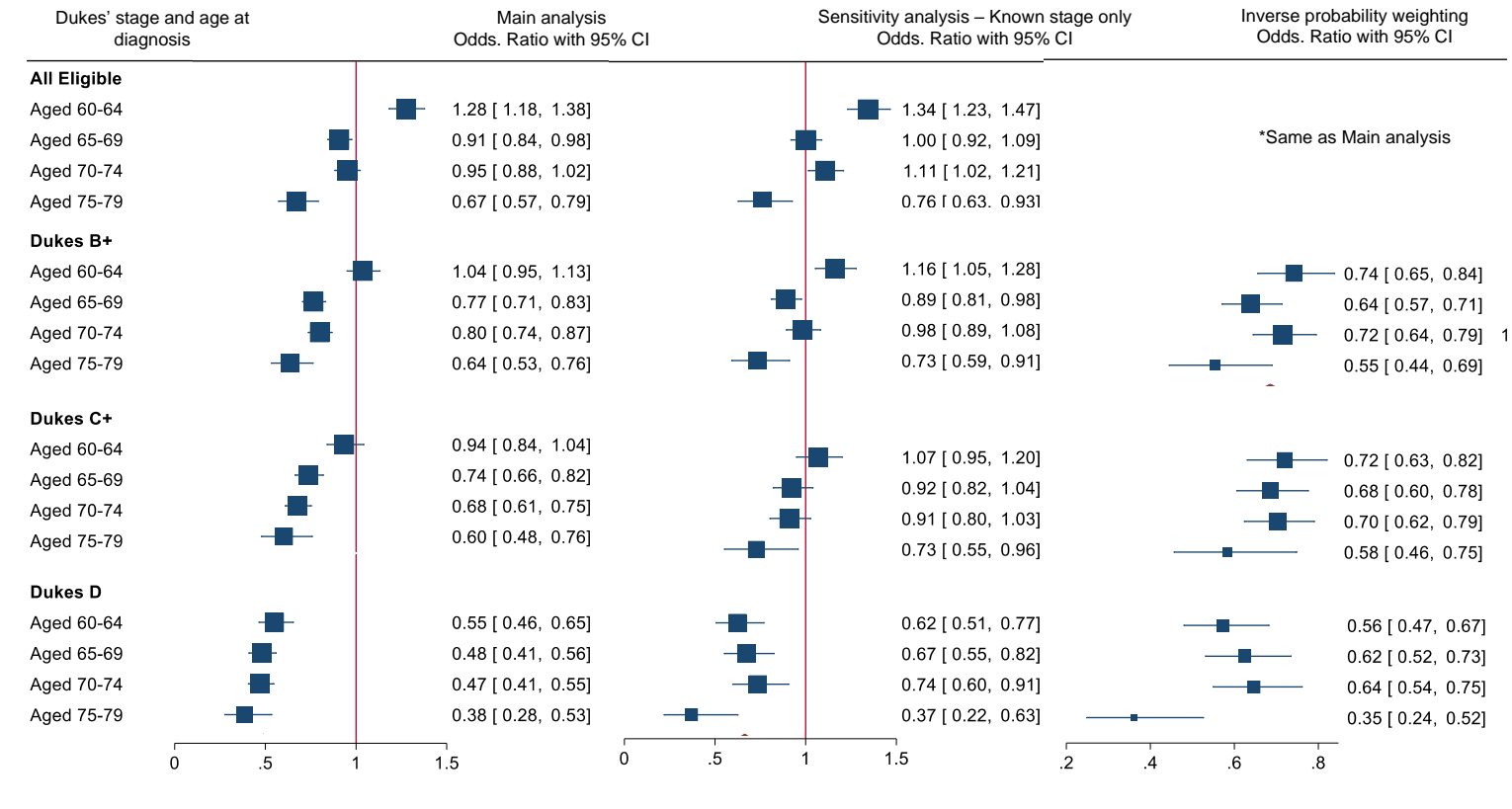
Supplementary Table 4. Odds ratios and corrected odds ratios (cOR) of being diagnosed with CRC by age and Duke's stage used to estimate the cumulative risk of CRC in a hypothetical cohort.

Invitational status - screening status	Controls (N)	Cases (N)	OR	Average crude OR	cOR (used in Figure 4)	Controls (N)	Cases (N)	OR	Average crude OR	cOR (used in Figure 4)
Age 60 to <62 years	All Stages					Stage D				
Invited - unscreened	2543	1024	1			470	299	1		
Invited - time since last test										
<30 days	244	593	12.31			24	25	2.21		
30-60 days	288	217	3.59			27	22	1.72		
60-90 days	225	55	0.81			33	6	0.36		
90-180 days	360	102	0.58			62	22	0.57		
180-365 days	435	166	0.65	1.86	1.88	101	27	0.34	0.67	0.93
365-730 days	738	311	0.79			186	59	0.45		
2 years+	222	75	1.09	0.94	0.95	29	10	0.54	0.50	0.69
Age 62 to <74years	All Stages					Stage D				
Invited - unscreened	8525	4383	1			1975	1433	1		
Invited - time since last test										
<30 days	581	1614	9.13			77	90	1.76		
30-60 days	712	666	3.00			93	65	1.06		
60-90 days	746	246	0.89			128	35	0.42		
90-180 days	1347	369	0.53			316	83	0.34		
180-365 days	2062	696	0.54	1.49	1.50	520	149	0.34	0.53	0.73
365-730 days	4693	1763	0.66			1175	392	0.44		
2 years+	1903	735	0.87	0.77	0.77	440	150	0.58	0.51	0.71

Aged 74 to 79 years	All Stages					Stage D				
Invited - unscreened	2882	1573	1			733	554	1		
Invited - time since last test										
<30 days	131	355	9.14			21	19	1.44		
30-60 days	209	147	2.25			21	15	1.10		
60-90 days	164	55	0.86			30	9	0.43		
90-180 days	294	80	0.47			90	18	0.23		
180-365 days	522	153	0.43	1.35	1.37	154	41	0.31	0.46	0.64
365-730 days	1081	411	0.62			276	85	0.36		
2 years+	631	282	0.84	0.73	0.74	153	58	0.51	0.43	0.60

Supplementary Figures

Supplementary Figure 1. Odds ratio of colorectal cancer among those screened by stage and age at diagnosis in the main and sensitivity analyses.



Supplementary Figure 2. Odds ratio of colorectal cancer among those screened by stage and gender in the main and sensitivity analysis.

