Results from the DIRECT-study with ClinicalTrials.gov Identifier NCT04197856

Introduction

In our paper, *Direct letters to relatives at risk of hereditary cancer – A randomised trial on healthcare-assisted versus family-mediated risk disclosure*, published in European Journal of Human Genetics, we present results from the DIRECT study for the families with HBOC (hereditary breast and ovarian cancer syndrome) and Lynch syndrome. The study also included families with the diagnosis Familial breast cancer and Familial colorectal cancer. The outcome data including also these groups are presented in this file.

On the criteria-based diagnoses of "Familial breast cancer" and "Familial colorectal cancer"

Probands with negative genetic screening of BRCA1, BRCA2, PALB2, MLH1, MSH2, MSH6 or PMS2, was included in the study if belonging to a family fulfilling clinical criteria for familial breast cancer or familial colorectal cancer and having at least one at-risk relative (ARR) deemed to be eligible for mammography or colonoscopy surveillance within a year. The relatives who were eligible as "at-risk" was those who - according to the involved HCP - were in the age-interval to be offered clinical surveillance with yearly mammography or regular colonoscopy screening.

Figure 1. Inclusion of probands over time

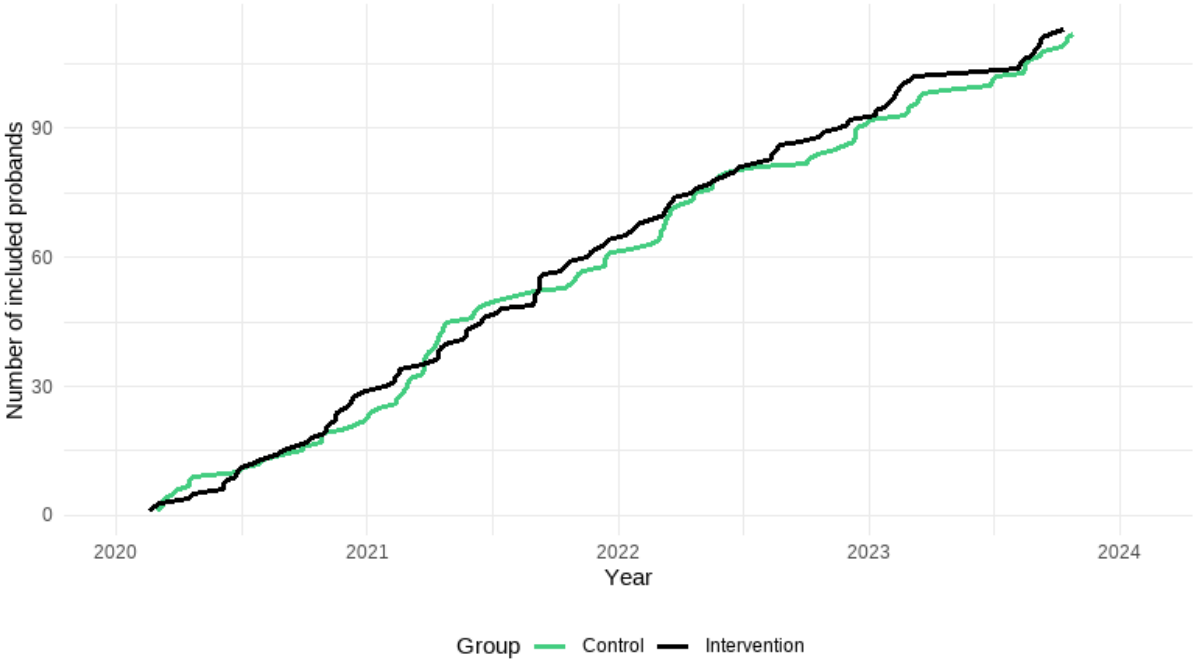

Table 1. Characteristics of all allocated probands. ARR, at-risk relative, HBOC, hereditary breast and ovarian cancer syndrome, BC, breast cancer, CRC, colorectal cancer. HBOC, hereditary breast and ovarian cancer syndrome, BC, breast cancer, CRC, colorectal cancer.

	Total (n=225)	**Intervention (n=113)**	**Control (n=112)**
Patient age median (min-max)		56 (21-90)	59 (29-83)
ARR per proband median (min-max)		3 (1-26)	3 (1-17)
Probands sex, No. (%)			
female	177	90 (80%)	87 (78%)
male	48	23 (20%)	25 (22%)
Probands age, No. (%)			
< 50 years	65	45 (40%)	20 (18%)
≥ 50 years	160	68 (60%)	92 (82%)
Study site, No. (%)			
A	97	54 (48%)	43 (38%)
B	72	29 (26%)	43 (38%)
C	56	30 (27 %)	26 (23%)
Referral reason, No. (%)			
Genetic screening	178	92 (81%)	86 (77%)
Predictive testing	47	21 (19%)	26 (23%)
Family diagnosis, No. (%)			
HBOC	124	66 (58%)	58 (52%)
Lynch syndrome	41	20 (18%)	21 (19%)
Familial breast cancer	45	20 (18%)	25 (22%)
Familial colorectal cancer	15	7 (6%)	8 (7%)
Educational attainment, No. (%)			
< 9 years	10	3 (3%)	7 (6%)
Compulsory (9 years)	28	16 (14%)	12 (11%)
Upper secondary (12 years)	37	22 (19%)	15 (13%)
University ≥ 1 year	44	16 (14%)	28 (25%)
University degree	75	40 (35%)	35 (31%)
NA	31	16 (14 %)	15 (13%)

Figure 2. Number of ARRs per family with family diagnosis HBOC, Lynch syndrome, familial BC or familial CRC, who contacted (dark blue) and did not contact (light blue) a cancer genetics clinic within a year. ARR, at-risk relative, HBOC, hereditary breast and ovarian cancer syndrome, BC, breast cancer, CRC, colorectal cancer.

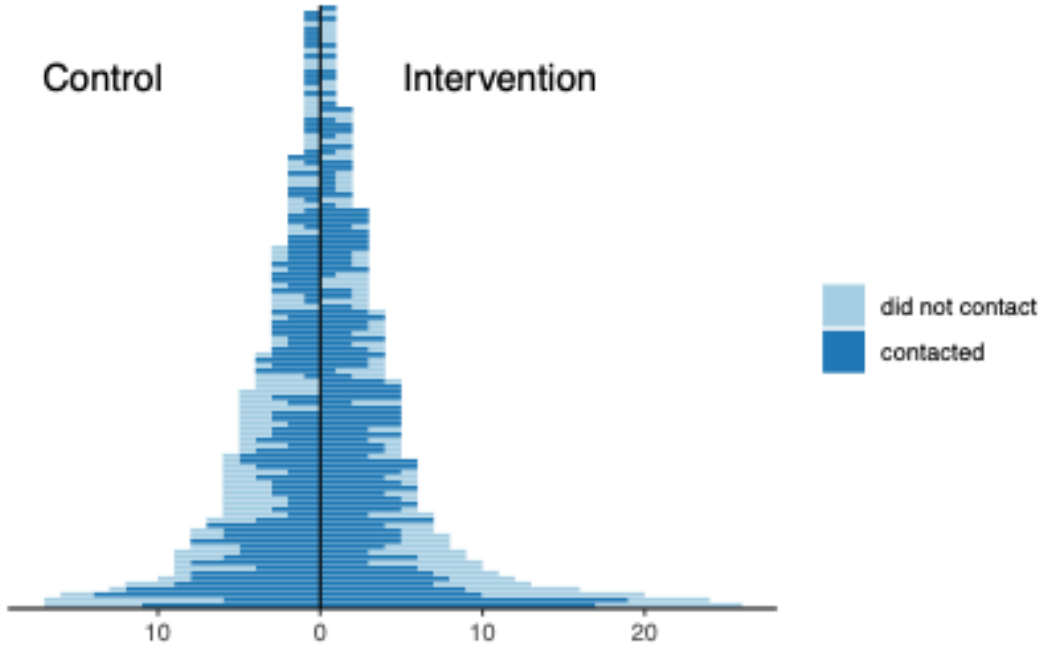

Table 2. Crude uptake of genetic counselling (GC) in different subgroups.

HBOC, hereditary breast and ovarian cancer syndrome, ARR, at-risk relative.

	Intervention *n ARRs contacting a cancer genetics clinic / n eligible ARRs (%)*	**Control** *n ARRs contacting a cancer genetics clinic / n eligible ARRs (%)*	chi^2-test ***P***
Total	349/513 (68%)	289/457 (63%)	.13
Probands sex			
female	264/374 (71%)	235/368 (64%)	.06
male	85/139 (61%)	54/89 (61%)	1
Probands age			
< 50	112/162 (69%)	30/45 (67%)	.89
≥ 50	237/351 (68%)	259/412 (63%)	.20
Study site			
A	185/274 (68%)	83/137 (61%)	.20
B	74/112 (66%)	115/182 (63%)	.71
C	90/127 (71%)	91/138 (66%)	.47
Family diagnosis			
HBOC	239/316 (76%)	188/266 (71%)	.21
Lynch syndrome	86/141 (61%)	66/113 (58%)	.77
Familial breast cancer	20/40 (50%)	25/49 (51%)	1
Familial colorectal cancer	4/16 (25%)	10/29 (34%)	.75
ARR sex			
female	216/282 (77%)	189/264 (72%)	.22
male	133/231 (58%)	100/193 (52%)	.28
Degree of kinship			
First-degree	218/287 (76%)	182/262 (69%)	.11
≥ Second-degree	131/226 (58%)	107/195 (55%)	.59

Figure 3. Odds ratios and 95% confidence intervals from the multivariable generalised linear mixed model for the uptake of GC. Reference levels used in the model: Allocation: control group, Probands sex: male, Probands age group: <50, Study site: A, Family diagnosis: HBOC, ARR sex: male, Kinship: 1st degree relative. GC, genetic counselling, ARR, at-risk relative, HBOC, hereditary breast and ovarian cancer syndrome, BC, breast cancer, CRC, colorectal cancer.

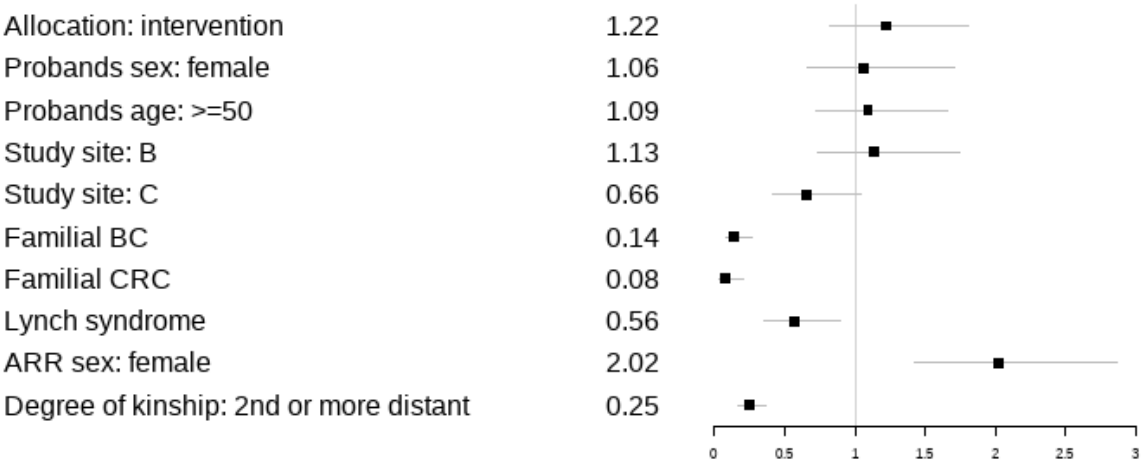

Table 3. Odds ratios with 95% CI and p-values of uptake of genetic counselling in ARRs at risk of HBOC, Lynch syndrome, familial BC or familial CRC, generated from univariable and multivariable generalised linear mixed model (GLMM) of different sociodemographic and clinical predictors. ARRs, at-risk relatives, HBOC, hereditary breast and ovarian cancer syndrome, BC, breast cancer, CRC, colorectal cancer.

		Univariable				**Multivariable**		
		OR	**95% CI**	***P***		**OR**	**95% CI**	***P***
Exposure	Control	1				1		
	Intervention	1.29	0.88-1.90	.19		1.22	0.82-1.81	.33
Probands sex	male	1				1		
	female	1.35	0.88-2.07	.16		1.06	0.66-1.69	.81
Probands age	< 50	1				1		
	≥ 50	0.76	0.49-1.18	.22		1.09	0.72-1.66	.69
Study site	A	1				1		
	B	0.94	0.60-1.46	.77		1.13	0.74-1.74	.57
	C	1.17	0.75-1.82	.50		0.66	0.42-1.04	.08
Family diagnosis	HBOC	1				1		
	Lynch syndrome	0.53	0.36-0.78	.001		0.56	0.36-0.89	.01
	Familial BC	0.34	0.20-0.57	< .001		0.14	0.08-0.26	< .001
	Familial CRC	0.13	0.06-0.29	< .001		0.08	0.03-0.20	< .001
ARR sex	male	1				1		
	female	2.79	2.03-3.82	< .001		2.02	1.42-2.88	< .001
Degree of kinship	First-degree	1				1		
	≥ Second-degree	0.20	0.14-0.30	< .001		0.25	0.17-0.37	< .001

Figure 4. Distribution of direct letters to ARRs at risk of HBOC, Lynch syndrome, familial breast cancer or familial colorectal cancer. ARRs, at-risk relatives, HBOC, hereditary breast and ovarian cancer syndrome.

[a] In one family the proband approved letter to all eligible ARRs but reported that one of the ARRs did not want to receive such direct letter.