Israeli Updated GI BRCA Guidelines « Colorectal Cancer

דר נעים אבו פריחה
מרכז רפואי סורוקה, כללית מחוז דרום
אסותא באר שבע

CRC screening group

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Background

- ✓ CRC is a common cancer in Israel
- ✓ 3 of 87 (3.5%) CRC Ashkenazi patients had Ashkenazi mutation
- ✓ Another study; 4/225 patients (1.78%)

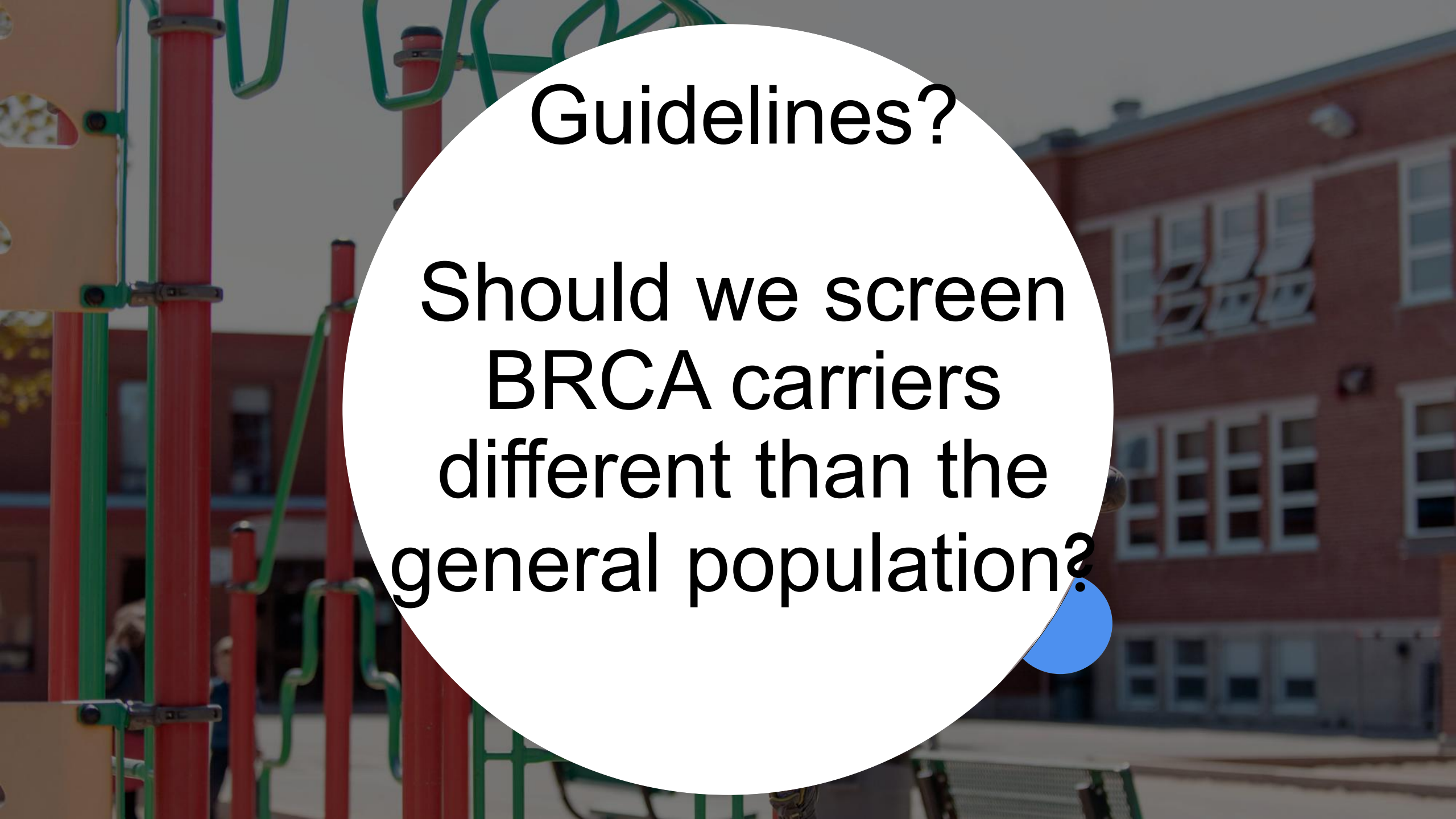
In Israel,

BRCA population screening for all Ashkenazi woman since 2020

Studies regarding CRC among BRCA mutation carriers' are scarce and conflicting

Drucker L, Stackievitz R, Shpitz B, Yarkoni S. Incidence of BRCA1 and BRCA2 mutations in Ashkenazi colorectal cancer patients: preliminary study. Anticancer Res. 2000 Jan-Feb;20(1B):559-61. PMID: 10769725.

Chen-Shtoyerman R et al. The frequency of the predominant Jewish mutations in BRCA1 and BRCA2 in unselected Ashkenazi colorectal cancer patients. Br J Cancer. 2001 Feb;84(4):475-7.


Guidelines?
Should we screen BRCA carriers different than the general population?

Methodology

Key words – BRCA1, BRCA2, gene, HEREDITARY BREAST AND OVARIAN CANCER together with one of: colon cancer, colorectal cancer, rectal cancer, colonoscopy

Limiting – HUMAN, English, Case reports, abstracts, starting with studies from 2000

Librarian literature search: Tal Kaminski, Technion medical library

Four data base search- Pubmed, Google Scolar, Embase, cochrain

1400 abstracts were reviewed on Rayyan by two separate independent reviewers

28 papers were reviewed

Results

- 14 observational studies were included
- 2 meta- analysis 2018, 2021
- One AGA clinical practice update 2020

OR for CRC in BRCA mutation carriers

Table 1. Odds Ratios of Colorectal Cancer Risk in *BRCA1* and *BRCA2* Carriers Included in a Meta-Analysis by Oh et al 2018[18]

	Study first author	Year	Study type (comparison)	Mutation type	Sample size	OR (95% CI)	Obs vs Exp CRCs
	BRCA1						
	Mersch[19]	2015	Cohort (general population)	NA	613	1.58 (0.44–5.76)	
*	Phelan[8]	2014	Cohort (general population)	NA	5481	0.92 (0.47–1.81)	16 17.4
	Thompson[3]	2002	Cohort (general population)	NA	2245	1.91 (0.78–4.67)	14
**	Kadouri[16]	2007	Cohort (noncarriers)	Ashkenazi Jewish founder	229	1.70 (0.63–4.87)	6 12
***	Brohet[20]	2013	Pedigree (general population)	NA	6585	1.76 (1.26–2.48)	93 53
	Moran[21]	2012	Pedigree (general population)	NA	1815	0.87 (0.41–1.83)	
	Brose[22]	2002	Pedigree (general population)	NA	483	2.04 (0.93–4.49)	11 11.4
	Ford[23]	1994	Pedigree (general population)	NA	464	3.19 (0.70–14.5)	
	Suchy[10]	2010	Case-control	Polish founder	2398 cases; 4570 controls	0.87 (0.41–1.83)	
	Niell[12]	2004	Case-control	Ashkenazi Jewish founder	999 cases; 1028 controls	1.26 (0.52–3.06)	
	Overall	—	—	—	—	1.49 (1.19–1.85)	
	BRCA2						
	Mersch[19]	2015	Cohort (general population)	NA	459	0.54 (0.10–3.02)	
	Phelan[8]	2014	Cohort (general population)	NA	1474	0.82 (0.25–2.68)	
	Kadouri[16]	2007	Cohort (noncarriers)	Ashkenazi Jewish founder	100	1.29 (0.28–5.84)	
	Moran[21]	2012	Pedigree (general population)	NA	1526	1.01 (0.43-2.40)	
	van Asperen[24]	2005	Pedigree (general population)	NA	1811	1.21 (0.63–2.34)	
	BCLC[4]	1999	Pedigree (general population)	NA	3728	1.22 (0.43–3.43)	
	Niell[12]	2004	Case-control	Ashkenazi Jewish founder	999 cases; 1028 controls	1.22 (0.54–2.74)	
	Overall	—	—	—	—	1.10 (0.77–1.58)	

*40% carriers prior breast cancer . SIR= 4.76 (2.2-9) for 30-49yrs in BRCA1 carriers age <50
**HR was 3.9 (1.3-12.1) for all irrespective of timing of breast\OC . HR =4 (1.1-15.2) for prior cancer
*** 20% prior breast/OC. RR for woman 2.2 (1.7-2.83, p<0.001)

Kupfer SS, Gastroenterology. 2020 Aug;159(2):760-764.

Cancer Risks Associated With *BRCA1* and *BRCA2* Pathogenic Variants

The Consortium Data

BRCA1/2 to estimate age-specific relative (RR) and absolute risks

22 first primary cancer types adjusting for family ascertainment.

RR calculated to age specific population incidence.

Results- BRCA1 carriers 8884, Non carriers 5870

BRCA2 carriers 6095, Non carriers 3435

Li S, Silvestri V et al. Cancer Risks Associated With *BRCA1* and *BRCA2* Pathogenic Variants. J Clin Oncol. 2022 May 10;40(14):1529-1541. doi: 10.1200/JCO.21.02112. Epub 2022 Jan 25. PMID: 35077220; PMCID: PMC9084432.

Number of CRC cancers and RR

TABLE 1. No. of First Primary Cancer Cases in the Informative *BRCA1* and *BRCA2* Families

	BRCA1 Families, No.							*BRCA2* Families, No.						
		Males			Females				Males			Females		
Cancer Site	Total	Carriers (n = 1,508)	Noncarriers (n = 1,716)	Untested (n = 44,396)	Carriers (n = 7,376)	Noncarriers (n = 4,154)	Untested (n = 40,801)	Total	Carriers (n = 1,063)	Noncarriers (n = 1,064)	Untested (n = 30,032)	Carriers (n = 5,032)	Noncarriers (n = 2,371)	Untested (n = 28,094)
Bladder	123	6	6	79	1	5	26	72	5	1	48	4	2	12
Brain and CNS	186	5	1	105	1	1	73	156	0	1	82	2	3	68
Breast	9,389	17	3	26	3,648	271	5,424	7,143	82	4	133	2,612	205	4,107
Cervix uteri	187	0	0	0	34	20	133	125	0	0	0	26	10	89
Colon-rectum	726	20	14	360	20	13	299	490	12	8	240	3	10	217

TABLE 2. Primary Cancer RRs and 95% CIs for *BRCA1* and *BRCA2* Carriers From the Main Analysis

		BRCA1 Carriers		*BRCA2* Carriers	
Cancer Site	Age, years	RR (95% CI)	*P*	RR (95% CI)	*P*
Bladder	40-79	0.88 (0.33 to 2.36)	.80	1.71 (0.75 to 3.89)	.20
Brain and CNS	20-79	1.15 (0.52 to 2.55)	.73	1.10 (0.42 to 2.87)	.85
Male breast	30-79	4.30 (1.09 to 16.96)	.04	44.03 (21.32 to 90.93)	< .001
Cervix uteri	20-79	1.45 (0.85 to 2.49)	.18	1.61 (0.86 to 3.04)	.14
Colon-rectum	30-79	1.48 (1.01 to 2.16)	.04	1.30 (0.80 to 2.11)	.29

stratified by age: 30-64yr 1.93 (1.23, 3.02)
30-49yr 1.25 (0.51, 3.06) NS
50-64yr 2.34 (1.4, 3.91)

Second primary after **Breast cancer** in BRCA1 and BRCA2

- ✓ 25,811 females and 480 males diagnosed with BC
- ✓ Tested for germline BRCA1/BRCA2 PVs in NHS Clinical Genetics centers in England between
- ✓ Between 1995 and 2019

- ✓ followed until SPC diagnosis, death, migration, contralateral breast/ovarian surgery

- ✓ Standardized incidence ratios (SIRs) using English population incidences,

Hazard ratios (HRs) comparing carriers to noncarriers using Cox regression, and Kaplan-Meier 10-year cumulative risks.

Allen I et al . Second Primary Cancer Risks After Breast Cancer in *BRCA1* and *BRCA2* Pathogenic Variant Carriers. J Clin Oncol. 2025 Feb 20;43(6):651-661.

Second primary after **Breast cancer** in BRCA1 and BRCA2

- ✓1840 BRCA1 carriers
- ✓1750 BRCA2 carriers
- ✓21,543 non carriers

Allen I et al . Second Primary Cancer Risks After Breast Cancer in *BRCA1* and *BRCA2* Pathogenic Variant Carriers. J Clin Oncol. 2025 Feb 20;43(6):651-661.

Table 2
SIRs for Second Primary Risks in Females

Compared with population incidences

SPC Site	*BRCA1* PV Carriers		*BRCA2* PV Carriers		*BRCA1/BRCA2* PV Noncarriers	
	SIR (95% CI)	Observed SPCs, No.	SIR (95% CI)	Observed SPCs, No.	SIR (95% CI)	Observed SPCs, No.
Entire cohort						
Contralateralbreast	15.6 (11.8 to 20.2)	57	7.70 (5.45 to 10.6)	38	3.03 (2.67 to 3.43)	257
Ovary	44.0 (31.4 to 59.9)	40	16.8 (10.3 to 26.0)	20	1.22 (0.82 to 1.74)	30
Nonbreast/ovarian	2.18 (1.59 to 2.92)	45	1.68 (1.24 to 2.23)	48	1.26 (1.14 to 1.38)	424
Colorectum	4.80 (2.62 to 8.05)	14	1.40 (0.51 to 3.05)	6	1.23 (0.95 to 1.58)	63

Standardized incidence ratios (SIRs)

Compared to non carriers, BRCA1 carriers had elevated colorectal (HR, 2.93 [95% CI, 1.53 to [5.62]

Additional studies since last meta analysis

Table 1. Odds Ratios of Colorectal Cancer Risk in *BRCA1* and *BRCA2* Carriers Included in a Meta-Analysis by Oh et al 2018[18]

Study first author	Year	Study type (comparison)	Mutation type	Sample size	CRCs	OR (95% CI)	Population
BRCA1							
Allen	2024	retrospective cohort (vs non carriers and population incidence)	NA	1840 Female	14(0.8%)	SIR, 4.80 [95% CI, 2.62 to 8.05] HR, 2.93 [95% CI, 1.53 to 5.62]	Mostly Women, Male (1.8%) After breast cancer, no data on ethnicity
Li	2022	retrospective cohort family pedigree (vs non carriers=population incidence)	NA	8884 (1508+7376)	40 (20 +20)	*RR= total 1.48 (1.01-2.26),p=0.04 RR 30-64yr 1.93 (1.23, 3.02) 50-64yr 2.34 (1.4, 3.91)	Women, male 1st primary , 4.7% Ashkenazi
BRCA2							
Allen	2024	retrospective cohort (vs non carriers and population incidence)	NA	1750 Female	6 (0.3%)	SIR= 1.40 (0.51 to 3.05)	Mostly Women, Male (1.8%) After breast cancer, no data on ethnicity
Li	2022	retrospective cohort family pedigree (vs non carriers=population incidence)	NA	6095 1063+5032	12+3	SIR= RR=1.3 (0.8-2.11),p=0.29	Women, male 1st primary , 4.7% Ashkenazi

Li S, JCO 40:1529-1541.2022 (*not robust on sensitivity analysis)
Allen I, JCO 2024 October 29; : JCO2401146. doi:10.1200/JCO.24.01146

Summary GI CRC groups

BRCA1

- RR, SIR among studies that found an association there is consistent small increased risk of CRC

BRCA2

- no increased risk compared to general population

Limitations:
Family History , retrospective studies, previous screening, Previous cancer

Recommendations*

BRCA1

Consider to screen as FDR especially in those with prior cancer

(regarding the age no consensus was achieved between age 40-45)

BRCA2

Same as general population

*Awaiting final data from prospective studies to be published in 2026

Thank you for your attention